Management of Diabetes 2014: A Patient-centered Approach

John B. Buse, MD, PhD
Verne S. Caviness Distinguished Professor
Director, Diabetes Care Center
Chief, Division of Endocrinology
Executive Associate Dean, Clinical Research
University of North Carolina School of Medicine
Chapel Hill, NC U.S.A.

jbuse@med.unc.edu

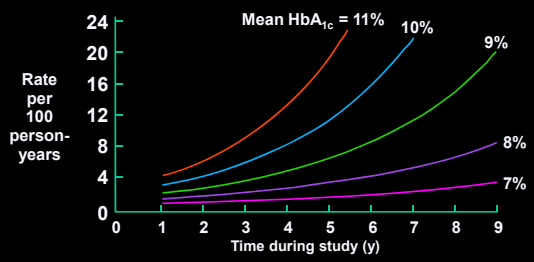
UNC SCHOOL OF MEDICINE

Disclosures

I have been an investigator and/or consultant without any direct financial benefit under contracts between his employer (the University of North Carolina) and the following companies: Amylin Pharmaceuticals, Inc., Andromeda, AstraZeneca, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, Dance Biopharm, Elcelyx Therapeutics Inc., Eli Lilly and Company, GI Dynamics, GlaxoSmithKline, Halozyme Therapeutics, F. Hoffmann-La Roche Ltd., Intarcia Therapeutics, Johnson & Johnson, Lexicon, LipoScience, Medtronic, Merck, Metavention, Novo Nordisk, Orexigen Therapeutics Inc., Osiris Therapeutics Inc., Pfizer Inc., PhaseBio Pharmaceuticals Inc, Quest Diagnostics, Sanofi, Santarus, Scion NeuroStim, Takeda, ToleRx and TransTech Pharma.

I am a consultant to PhaseBio Pharmaceuticals, Inc. and has received payments, reimbursement for travel and stock options for that effort.

DCCT: Absolute Risk of Sustained Retinopathy Progression by HbA_{1c} and Years of Follow-up



DCCT Research Group. *Diabetes*. 1995;44:968-983.

Microvascular Complications: Screening and Care

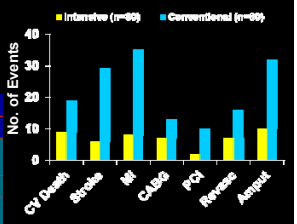
- Retinopathy
  - Screen: Annual dilated eye exam by eye care professional or fundus photography; perhaps longer intervals if totally normal
  - Care: Glycemic control, ophthalmology intervention
- Nephropathy
  - Screen: Annual spot urine microalbumin to creatinine ratio, serum creatinine (+/- potassium)
  - Care: Glycemic control, blood pressure management, ACE/ARB (consider referral to nephrology)
- Neuropathy
  - Screen: History/physical, foot exam, 10-g filament, 128-Hz tuning fork
  - Care: Glycemic control, screen for other causes, education, podiatry referral, extra depth shoes w molded inserts

Buse J, et al. In: *Williams Textbook of Endocrinology*, 12th ed . 2012

Steno-2: Risk Factor Management in Diabetes

- Intensive vs. conventional therapy for glucose, BP, lipids
- 7.8 y treatment, 13.3 y follow-up

	Baseline		Post Interv.	
	INT	CONV	INT	CONV
BP—Systolic	146	149	131	146
Diastolic	85	86	73	78
A1C, %	8.4	8.8	7.9	9.0
Lipids (mg/dL)				
TC	210	233	159	216
LDL-C	133	137	83	126
HDL-C	40	39	47	45
TGs	159	205	115	159

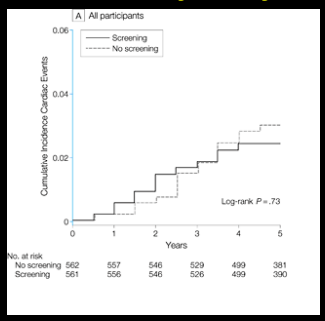


Deaths in 13.3 y follow-up:

- 24 vs. 40 patients for intensive vs. conventional
- Absolute Risk Reduction=20%, *P*=0.02
- HR 0.54, 95% CI: 0.32-0.89; *P*=0.02

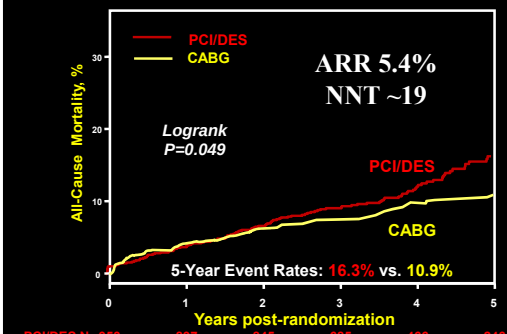
Gaede P, et al. *N Engl J Med*. 2008;358:580-591.

DIAD: Nuclear Stress Cardiac Imaging in Type 2 Diabetes Without Symptomatic or Previously Diagnosed Coronary Artery Disease



Young, L. H. et al. JAMA 2009;301:1547-1555.

FREEDOM Trial: ALL-CAUSE MORTALITY



Farkouh ME, et al. *Am Heart J.* 2008; 155:215-23. Farkouh ME, et al. *N Engl J Med.* 2012; 367:2375-84. Farkouh ME, et al. *J Am Coll Cardiol.* 2013; 61:1607-15. Magnuson EA, et al. *Circulation.* 2013; 127:820-31. Bansilal S, et al. *Am Heart J.* 2012; 164:591-9.

Summary 1:

- End-stage microvascular complications are largely preventable.
- Multiple risk factor management of cardiovascular risk factor is associated with benefits.
- Screening with stress imaging does not identify a high risk population among those without symptoms or findings.
- Thus, current approach is to manage CVD risk factors expectantly in patients with diabetes.
- In the setting of multivessel coronary disease, coronary artery bypass surgery is preferable to percutaneous intervention.

UKPDS: "Legacy Effect" of Insulin/Sulfonylurea Therapy

Remember: New-onset patients with A1C ~9%

Aggregate Endpoint		End RCT 1997	10-yr F/U 2007
Any diabetes related endpoint	*RRR:*	12%	9%
	P:	0.029	0.040
Microvascular disease	*RRR:*	25%	24%
	P:	0.009	0.001
Myocardial infarction	*RRR:*	16%	15%
	P:	0.052	0.014
All-cause mortality	*RRR:*	6%	13%
	P:	0.44	0.007

RRR = Relative Risk Reduction P = Log Rank

Holman RR, et al. *New England Journal of Medicine* 2008; 359:1577-1589

Comparison of Recent Glycemia Trials

Characteristic	ACCORD	ADVANCE	VADT
N	10,251	11,140	1,791
Mean Age	62	66	60.4
Duration of T2DM	10 yr	8 yr	11.5 yr
History of CVD	35%	32%	40%
BMI	32	28	31
Baseline A1C	8.3%	7.5%	9.4%
A1C Achieved	6.4% vs. 7.5%	6.5% vs. 7.3%	6.9% vs. 8.4%
RRR CVD Events	0.90 (0.78 – 1.04)	0.94 (0.84 – 1.06)	0.88 (0.74 – 1.05)
RRR Mortality	1.22 (1.01 – 1.46)*	0.93 (0.83 – 1.06)	1.07 (0.80 – 1.42)

ACCORD Study Group. *N Engl J Med.* 2008;358:2545-59.
ADVANCE Collaborative Group. N Engl J Med 358:2560-72, 2008.
Duckworth W for VADT. N Engl J Med 2009;360:129-39

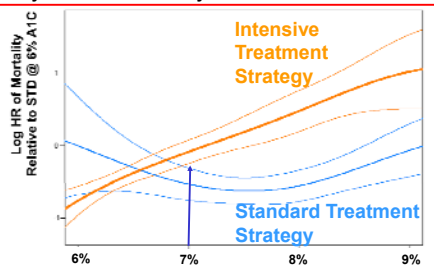
ACCORD: Exploring Lower Targets

Three randomizations	Three results
A1C: <6% vs. 7-8%	More intensive glycemic control •microvascular benefit •no CVD benefit •increased mortality
SBP: <120 mmHg vs. 130-140 mmHg	More intensive BP control •no CVD benefit •less stroke
Statin to get LDL to goal + fenofibrate or placebo	Fibrate plus statin •no CVD benefit •microvascular benefit

N Engl J Med. 363(3):233-244, 2010. The Lancet, 376 (9739):41930, 2010. *N Engl J Med.* 358:2545-59, 2008. *N Engl J Med.* 362(17):1575-85, 2010. *N Engl J Med.* 362(17):1563-74, 2010.

ACCORD Mortality as a Function of On-Trial A1C

Steady increase of mortality from 6% to 9% A1C in INT strategy



Excess risk with INT vs STD above A1C 7%

Riddle M, et al. *Diabetes Care* 33(5):983-90, 2010.

Present Landscape of CVD Outcomes Trials in Type 2 DM

Trial	Drug	Sample Size	Stage
TECOS	Sitagliptin	14,000	Started 12/2008
ACE	Acarbose	7500	Started 2/2009
EXAMINE	Alogliptin	5,400	Started 09/2009
CANVAS	Canagliflozin	4500	Started 11/2009
SAVOR TIMI-53	Saxagliptin	16,500	Started 4/2010
ELIXA	Lixisenatide	6000	Started 6/2010
EXSCEL	Exenatide LAR	12,000	Started 6/2010
C-SCADE 8	Empagliflozin	12,500	Started 7/2010
CAROLINA	Linagliptin	6000	Started 10/2010
LEADER	Liraglutide	8723	Started 8/2010
REWIND	Dulaglutide	9622	Started 7/2011

CLASS	TOTAL #
DPP-4i	~42,000+
GLP-1ra	~47,000+
SGLT-2i	~17,000+

http://www.clinicaltrials.gov

Summary 2:

- CVD outcome trials exploring more intensive management strategies suggest comprehensive management of CVD risk factors have major benefits:
  - *A1C target: Aim for lowest achievable A1C without requiring heroic effort and without producing severe hypoglycemia or other adverse effects of therapy (particularly in earlier disease and in the absence of CVD)*
  - *Blood pressure: <140 mmHg and DBP <80 mmHg* [ESC-ESH 140/85, AHA/ACC 140/90]
  - *Lipids: Use a potent statin at a substantial dose (and hopefully get to an LDLc < 100 mg/dl)*

Look-AHEAD: Intensive Lifestyle Intervention Has Broad Benefits

- BMI, CVD risk factors and A1C, despite less medication[1]
- Increased rates of partial diabetes remission[2]
- Urinary incontinence in women[3]
- Sleep apnea[4]
- Depression symptoms[5]
- Quality of life[6]
- Physical function[7]
- Mobility[8]
- Reduced NAFLD[9]
- Biomarkers[10]
- Sexual dysfunction in women[11]
- NO BENEFIT ON CVD[12]

1. Look AHEAD Research Group. *Arch Intern Med* 2010; 170:1566-1575.
2. Gregg EW, et al. *JAMA* 2012; 308:2489-96.
3. Phelan S, et al. *J Urol* 2012; 187:939-44.
4. Kuna ST, et al. *Sleep* 2013; 36:641-9.
5. Rubin RR, et al. *Diabetes Care* 2013; 36:1088-94.
6. Williamson DA, et al. *Arch Intern Med* 2009; 169:163-71.
7. Foy CG, et al. *Obesity (Silver Spring)* 2011; 19:83-93.
8. Rejeski WJ, et al. *N Engl J Med* 2012; 366:1209-17.
9. Lazo M, et al. *Diabetes Care*. 2010 Oct;33(10):2156-63.
10. McCaffery JM, et al. Int J Obes (Lond). 2013 Apr 3. [Epub ahead of print]
11. Wing RR, et al. *Diabetes Care*. 2013 Jun 11. [Epub ahead of print].
12. Look AHEAD. *N Engl J Med*. 2013; 369:145-154.

Mediterranean Diet . . . More of:

Food	Goal
Olive Oil (extra virgin olive oil) (1 tbsp = 14 gms)	≥ 4 tbsp/day
Tree nuts and peanuts (30g, 15g walnuts, 7.5g almonds, 7.5g hazelnuts)	≥ 3 servings/wk
Fresh fruits	≥ 3 servings/day
Vegetables	≥ 2 servings/day
Fish (especially fatty fish), seafood	≥ 3 servings/wk
Legumes	≥ 3 servings/wk
Sofrito (sauce made w/ tomatoes & onions, often including garlic and herbs simmered slowly w olive oil)	≥ 2 servings/wk
White meat	Instead of red meat
Wine with meals (optional, only for habitual drinkers)	≥ 7 glasses/wk

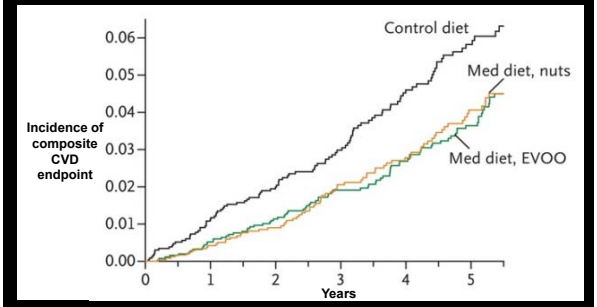
Estruch R, et al. *N Engl J Med.* 2013; 368:1279-90.

Mediterranean Diet . . . Less of:

Food	Goal
Soda Drinks	< 1 drink/day
Commercial bakery goods, sweets, and pastries	< 3 servings/wk
Spread Fats	< 1 servings/day
Red and processed meats	< 1 servings/day

Estruch R, et al. *N Engl J Med.* 2013; 368:1279-90.

PREDIMED Trial: Primary Endpoint



Estruch R, et al. *N Engl J Med.* 2013; 368:1279-90.

Summary 3:

- CVD outcome trials exploring lifestyle interventions suggest:
  - *Intensive lifestyle efforts targeting weight loss have broad based benefits, though no benefit for CVD*
    - Perhaps benefits in those without CVD?
  - *Diet composition or quality, specifically the "Mediterranean Diet" does appear to reduce CVD.*

What Are the Remaining Opportunities?

- Screen for diabetes with earlier treatment aimed at prevention of diabetes and CVD (lifestyle, glycemic/BP intervention, statins, aspirin in high risk individuals)
- Novel treatments are promising but require study, e.g. GLP-1 receptor agonists, SGLT-2 inhibitors and DPP-4 inhibitors as well as agents under development
- Individualized, multidisciplinary (e.g. non-physician providers), opportunistic targeting of CVD risk factors based on assessment of global risk
  - *Shared decision making*
  - *Peer support*
  - *Holistic approach*

In hopes of promoting adherence

Screening

Screening For Diabetes and Prediabetes

Testing at least every 3 years starting at age 45

Test	Prediabetes	Diabetes
FPG	100-125 mg/dL	≥126 mg/dL
OGTT	140-199 mg/dL	≥200 mg/dL
A1C	5.7-6.4%	≥6.5%

American Diabetes Association. *Diabetes Care.* 2013:306, S11-66..

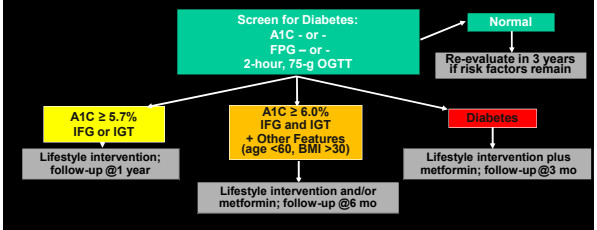
Younger/More Frequent Testing

If patient is overweight or obese (BMI ≥ 25 kg/m^2) and has one or more of the following risk factors (or two if not overweight):

- **First degree relative with diabetes**
- **Physically inactive**
- **High risk race/ethnicity**
- **A1C≥ 5.7%, IFG or IGT on previous test**
- **Hypertension (140/90 mmHg)**
- **HDL cholesterol (<35 mg/dL and/or a triglyceride level >250 mg/dL)**
- **History of GDM or delivering baby weighing >9 lbs**
- **Polycystic ovary syndrome (PCOS)**

American Diabetes Association. *Diabetes Care.* 2013:306, S11-66..

Intervention and Follow-Up

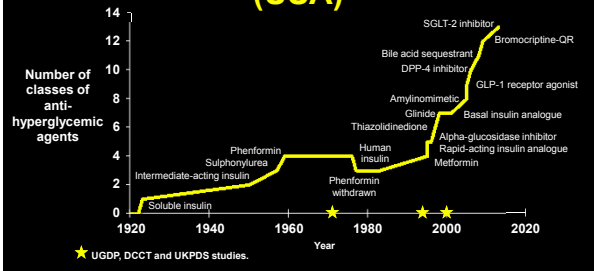


METFORMIN IS NOT FDA APPROVED FOR PREVENTION

Adapted from the American Diabetes Association. *Diabetes Care.* 2013:306, S11-66..

Glucose Management

100-year History of Antihyperglycaemic Therapeutics (USA)



Buse, JB ©

Optimizing Outcomes for Patients With Chronic Diseases

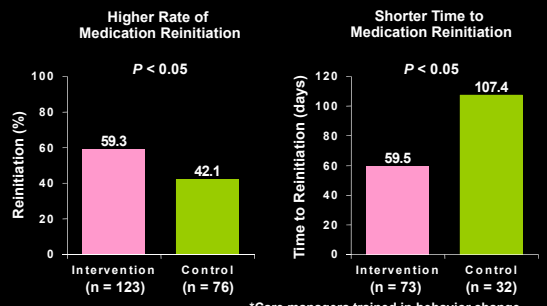
- Medication adherence rates in chronic care: 50%
  - Must have engaged, informed, motivated patient
  - Shared decision-making in a setting of mutual respect, open communication, cultural/socioeconomic sensitivity
  - Leverage opportunities to change/improve lifestyle behaviors

Factors Affecting Patient Adherence to Diabetes Medications

Patient Belief/Concern	Odds Ratio for Poor Adherence	Confidence Interval
Feeling medicines are hard to take	14.0	4.4–44.6
Belief that they have diabetes only when sugar is high	7.4	2–27.2
No need to take medicine when glucose level was normal	3.5	0.9–13.7
Worry about side effects	3.3	1.3–8.7
Lack of self-confidence in controlling diabetes	2.8	1.1–7.1

Mann DM et al. *J Behav Med*. 2009;32(3):278–284.

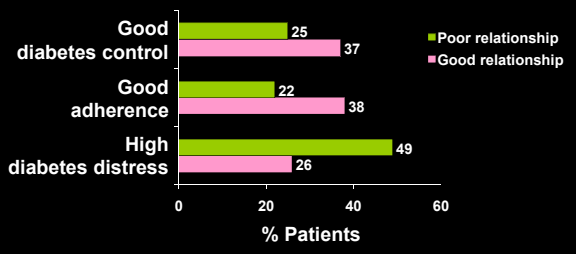
Communication* Intervention Improves Medication Use



*Care managers trained in behavior change, patient readiness to change, motivational interviewing, and active listening

Lawrence DB, et al. *Dis Manag*. 2008;11:141-144.

Relationship With Provider Predicts Diabetes Outcomes



Peyrot M, et al. *Diabetes Care*. 2005;28(11):2673-2679.

Antihyperglycemic Agents in Type 2 Diabetes

Class	Generic or Brand	A1C Reduction	Usual Dosing (times/day)	Injected or Oral	Severe Hypo-glycemia	Weight Change	Other Safety Concerns (beyond hypoglycemia and weight gain)
R, Lispro, Aspart, Glulisine	Brand	1.5 - 2.5	2-4	Injected	Yes	Gain	Breast Cancer
NPH, Glargine, Detemir	Brand	1.5 - 2.5	1	Injected	Yes	Gain	
Glipizide ER, Glimepiride	Generic	1.5	1	Oral	Yes	Gain	CVD
Repaglinide	Brand	1 - 1.5	3	Oral	Yes	Gain	
Nateglinide	Generic	0.5 - 0.8	3	Oral	Rare	Gain	
Metformin	Generic	1.5	1-2	Oral	No	Neutral	B12 deficiency, lactic acidosis
Acarbose, Miglitol	Generic	0.5 - 0.8	3	Oral	No	Neutral	
Pioglitazone	Brand	0.5 - 1.4	1	Oral	No	Gain	CHF, Bone fx, Bladder Ca
Pramlintide	Brand	0.5 – 0.9	3	Injected	No	Loss	
Exenatide	Brand	0.7 - 1.0	2	Injected	No	Loss	ARF, Pancreatitis, PancCa
Liraglutide	Brand	0.9 - 1.4	1	Injected	No	Loss	ARF, Pancreatitis, MTC, PancCa
Exenatide OW, albiglutide	Brand	0.9 - 1.6	Every 7d	Injected	No	Loss	ARF, Pancreatitis, MTC, PancCa
Sita-, saxa-, lina-, alo- gliptin	Brand	0.6 - 0.8	1	Oral	No	Neutral	Pancreatitis, PancCa
Colesevelam	Brand	~0.5	1-2	Oral	No	Neutral	Hypertriglyceridemia
Bromocriptine QR	Brand	~0.6	1	Oral	No	Neutral	Various in PI
Cana-, dapa-, empa- gliflozin	Brand	0.6 – 1.2	1	Oral	No	Loss	LDL, ARF, Genital infections, K

Adapted from: Nathan DM, et al. *Diabetes Care*. 2009; 32:193-203. ADA. *Diabetes Care*. 2010;33:S11-S61. Buse J, et al. In: *Williams Textbook of Endocrinology*, 12th ed . 2012. Individual agents prescribing information.

"Everything else": The Mainstay of Medical Care

"Dr. [Ted] Kaptchuk [Harvard] describes placebos as not just the traditional sugar pill, but also "everything that surrounds a medical treatment": how caregivers describe the medication, how they administer it, the expectations they have for the medicine, their tone of voice, their strength of eye contact. In short, everything that doctors and nurses do in an interaction with a patient.

This is not especially surprising. Healers and shamans have known intuitively about the importance of this interaction since the dawn of time. Before we had developed treatments that could significantly impact the pathology of disease — antibiotics, chemotherapy, stents, organ transplants, transfusions — the 'everything else' was the mainstay of medical care."

http://well.blogs.nytimes.com/2013/08/15/a-powerful-tool-in-the-doctors-toolkit/?ref=health&_r=0

Figure 2. T2DM Antihyperglycemic Therapy: General Recommendations

Inzucchi SE, et al. *Diabetes Care* 2012;35:1364–1379.

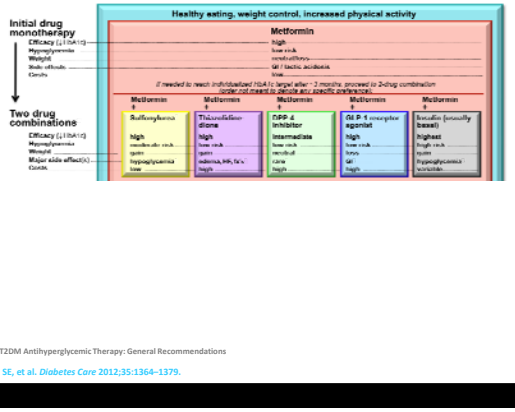


Figure 2. T2DM Antihyperglycemic Therapy: General Recommendations

Inzucchi SE, et al. *Diabetes Care* 2012;35:1364–1379.

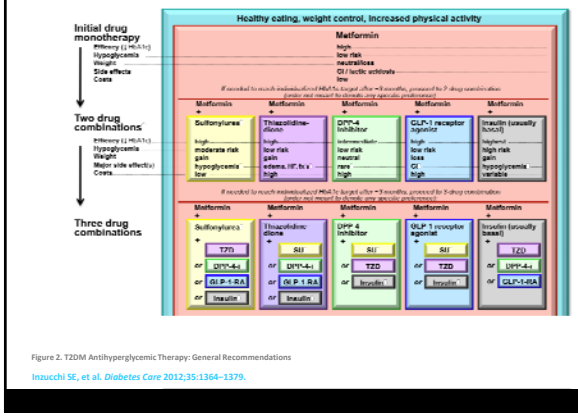
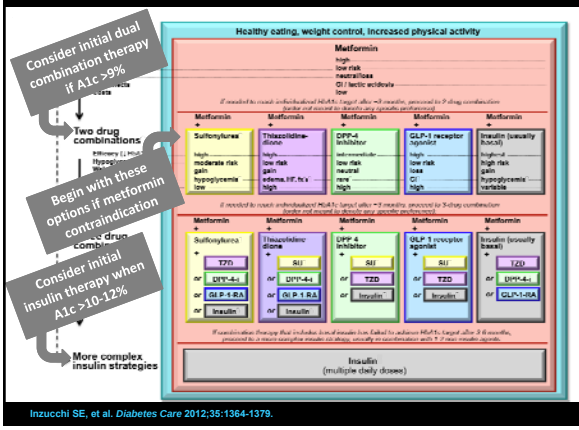


Figure 2. T2DM Antihyperglycemic Therapy: General Recommendations

Inzucchi SE, et al. *Diabetes Care* 2012;35:1364–1379.

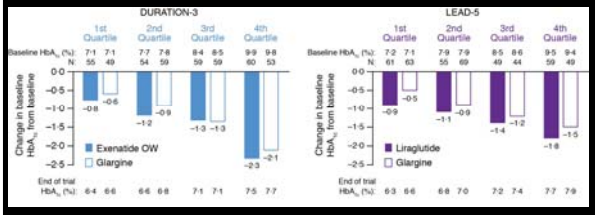


Inzucchi SE, et al. *Diabetes Care* 2012;35:1364-1379.

Where are we going from here?

GLP-1 Receptor Antagonists

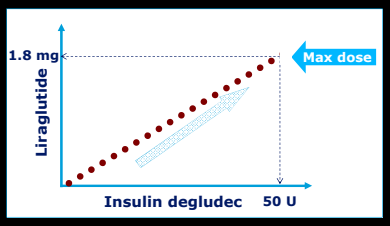
Is Insulin the Most Effective Injectable Antihyperglycemic Therapy?



Buse J, et al. *Diabetes Obesity Metabolism*, in press.

IDegLira*

Fixed-ratio Combination of Insulin Degludec* and Liraglutide

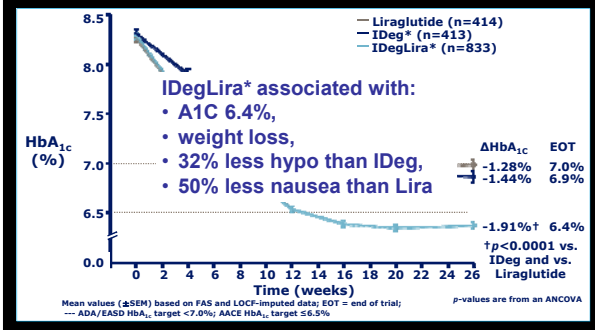


One dose step = 1 U insulin degludec and 0.036 mg liraglutide

Buse J et al. Diabetes Care. 2014 Aug 11. pii: DC_140785. [Epub ahead of print]

*Not FDA approved

DUAL-1 Study: HbA_{1c} over time



Gough S et al. *Lancet Diabetes & Endocrinology*, in press.

*Not FDA approved

AWARD-4: Dulaglutide† vs Glargine

(on background of premeal lispro ± metformin)

- T2 diabetes. Age >18y. A1C 7-11%. BMI 23-45. On 1-2 shots of any kind of insulin at baseline.
  - *Mean: age 59; duration 13; total insulin 56 units; A1C 8.5%.*
- 9 week run-in to stop OAD's except metformin and adjust insulin. Randomized to glargine at bedtime or one of two doses of dulaglutide once weekly (0.75 mg or 1.5 mg)
- At randomization, lispro insulin at total dose of 50% of end of run-in total (and in glargine arm, 50% as glargine)

	@	DULA 1.5	DULA 0.75	Glargine
A1C change (%)	26 wk	-1.6*	-1.6*	-1.4*
Lispro dose (units)	26 wk	93	97	68
Glargine dose (units)	26 wk	0	0	65
Weight change (kg)	52 wk	-0.35	0.9	2.9
Symptomatic hypo (events/p-y)	52 wk	31	35	40
Severe hypo (N)	52 wk	11	15	22
Nausea (%)	52 wk	26	18	3

Jendle J, et al. EASD abstract #42. Available on-line at http://www.easdvirtualmeeting.org/resources/15089.

†Not FDA approved

SGLT-2 Inhibitors

Summary of Observed Efficacy of SGLT2 Inhibitors

- Similar to other oral antihyperglycemic agents in A1C reduction
  - Reduces both FPG and PPG
- Modest weight loss
  - ~3 kg at 26 weeks vs placebo
  - Slightly greater weight loss at 52 weeks
  - Weight loss vs placebo sustained at 102 weeks
- Modest blood pressure reduction
  - 2-7 mm Hg vs placebo
- Minimal improvements in TG and HDL

*Abnormally frequent urination

Hasan FM, Alsahli M, Gerich JE. Diabetes Res Clin Pract. 2014 Jun;104(3):297-322.
Tahrani AA, Barnett AH, Bailey CJ. Lancet Diabetes Endocrinol. 2013 Oct;1(2):140-51.

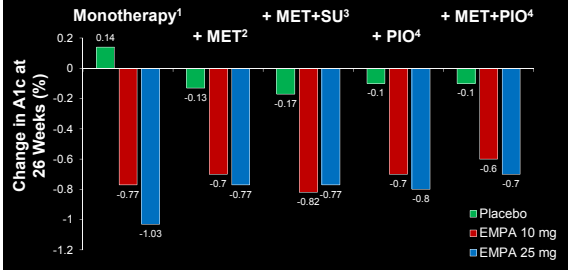
Summary of Adverse Effects of SGLT2 Inhibitors

- Genital mycotic infections
- Pollakiuria*
- Genital infections
- Warnings:
  - *Hypotension:* Before initiating SGLT-2i assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.
  - *Impairment in renal function:* Monitor renal function during therapy.
  - *Increased LDL-c*

*Abnormally frequent urination

Hasan FM, Alsahli M, Gerich JE. Diabetes Res Clin Pract. 2014 Jun;104(3):297-322.
Tahrani AA, Barnett AH, Bailey CJ. Lancet Diabetes Endocrinol. 2013 Oct;1(2):140-51.

Empagliflozin as an Exemplar of Broad Efficacy

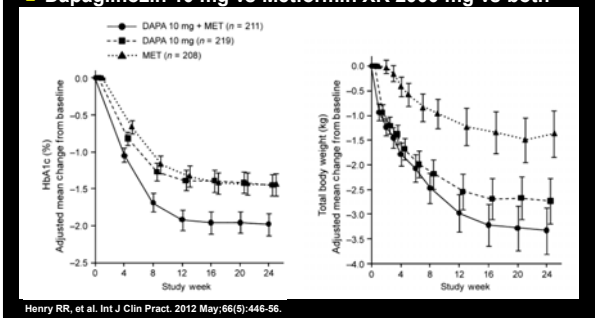


MET, metformin; SU, sulfonylurea; PIO, pioglitazone

1. Roden M, et al. Lancet Diabetes Endocrinol. 2013;1:208-219.
2. Haring, H. U., et al. *Diabetes Care*. 2014.
3. Haring HU, et al. Diabetes Care. 2013;36:3396-3404.
4. Kovacs CS, et al. Diabetes Obes Metab. 2013. Epub ahead of print.

Dapagliflozin vs. Metformin vs. Both

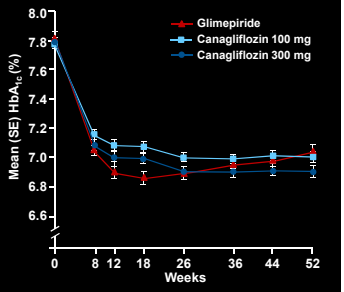
- Double blind 24 week study in treatment naïve participants with A1C 7.5-12%
- Dapagliflozin 10 mg vs Metformin XR 2000 mg vs both



Henry RR, et al. Int J Clin Pract. 2012 May;66(5):446-56.

Canagliflozin vs. Glimepiride

- Patient population:
  - Receiving metformin
  - 18-80 years
  - A1c = 7.0%-9.5%
  - N=1450
- Treatment groups:
  - CANA – 100 or 300 mg qd
  - Glimepiride titrated to 6 or 8 mg qd
- Duration of study:
  - 52 weeks

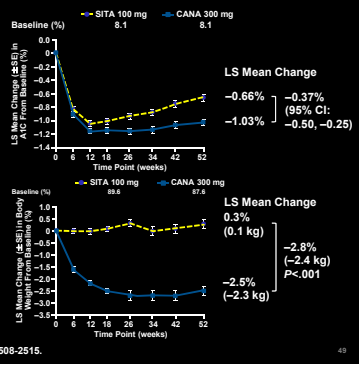


Drug	Change in weight (SE)
Canagliflozin 100 mg	-4.4 kg (0.6)
Canagliflozin 300 mg	-4.2 kg (0.7)
Glimepiride	0.8 kg (0.7)

Cefalu WT, et al. *Lancet*. 2013;382:941-950.

Canagliflozin vs. Sitagliptin

- Patient population:
  - Receiving metformin + SU
  - N=755
- Treatment groups:
  - CANA – 300 mg qd
  - SITA – 100 mg qd
- Duration of study:
  - 52 weeks



Schernthaner G, et al. *Diabetes Care*. 2013;36:2508-2515.

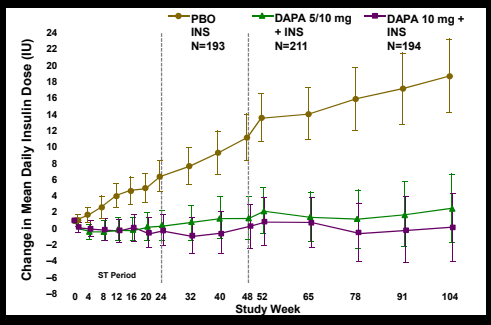
49

Dapagliflozin in Patients on High Doses of Insulin

- Patient population:
  - N=808 T2DM patients 18-80 years of age
  - Receiving insulin ≥30 IU/day (mean baseline=74 IU/day) ±1-2 oral antidiabetic drugs
  - A1c: 7.5%-10.5% (mean baseline=8.5%)
- Treatment groups:
  - DAPA 2.5, 5, or 10 mg qd
  - Placebo
- Duration of study:
  - 24 weeks[1]/104-week extension[2]

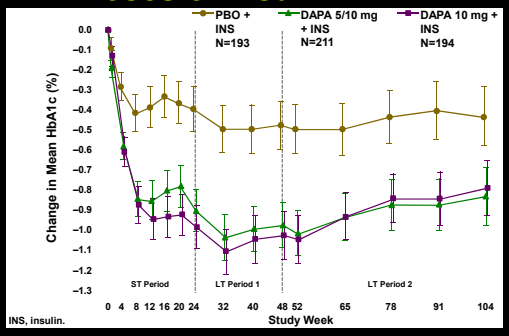
1. Wilding JP, et al. *Ann Intern Med*. 2012;156(6):405-415.
2. Wilding JP, et al. *Diabetes Obes Metab*. 2014;16:124-136.

Dapagliflozin in Patients on High Doses of Insulin - Dose



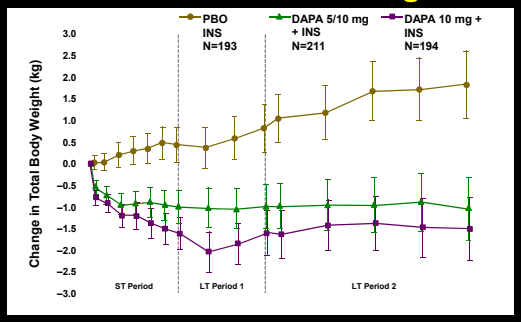
Data for the 2.5 mg dose of DAPA is available in the original publication
Wilding JP, et al. *Diabetes Obes Metab*. 2014;16:124-136.

Dapagliflozin in Patients on High Doses of Insulin – A1C



Data for the 2.5 mg dose of DAPA is available in the original publication
Wilding JP, et al. *Diabetes Obes Metab*. 2014;16:124-136.

Dapagliflozin in Patients on High Doses of Insulin - Weight



Data for the 2.5 mg dose of DAPA is available in the original publication
Wilding JP, et al. *Diabetes Obes Metab*. 2014;16:124-136.

SGLT-2 Inhibitor Dosing Recommendations

Canagliflozin (100 or 300 mg qd)	• Therapy should not be initiated if **eGFR <45 mL/min/1.73m²** • Patients should be initiated at 100 mg qd • Dose may be increased to 300 mg qd for patients requiring better glycemic control if well tolerated and **eGFR >60 mL/min/1.73m²** • Patients should be discontinued if **eGFR falls below 45 mL/min/1.73m²**
Dapagliflozin (5 or 10 mg qd)	• Therapy should not be initiated if **eGFR <60 mL/min/1.73m²** • Patients should be initiated at 5 mg qd and may be increased to 10 mg qd for patients requiring better glycemic control if well tolerated • Patients should be discontinued if **eGFR falls persistently below 60 mL/min/1.73m²**
Empagliflozin (10 or 25 mg qd)	• Therapy should not be initiated if **eGFR <45 mL/min/1.73m²** • Patients should be initiated at 10 mg qd. The dose may be increased to 25 mg qd if well tolerated • Patients should be discontinued if **eGFR falls persistently below 45 mL/min/1.73m²**

Prescribing information. Yang XP, et al. Eur J Clin Pharmacol. 2014 Aug 16. [Epub ahead of print]. Aylsworth A, et al. Ann Pharmacother. 2014 Jun 20;48(9):1202-1208. Neumiller JJ. Drugs Context. 2014 Jun 11;3:212262. doi: 10.7573/dic.212262. eCollection 2014.

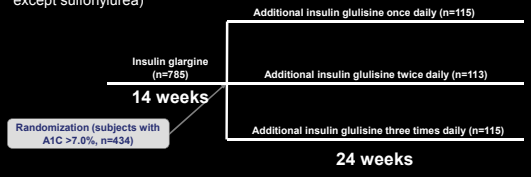
54

Insulin

1.2.3 Study: Glargine Plus 1, 2 or 3 Doses of Glulisine

Subjects:

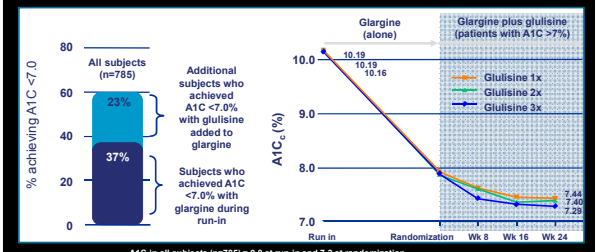
- Insulin naïve (785 entered study, 343 randomized) with type 2 diabetes (A1C ≥8.0%)
- Receiving 2 or 3 OHAs for ≥3 months (OHAs continued except sulfonylurea)



Davidson M *et al. Endocr Pract* 2011;Feb 16:1-9 (E-pub).

1.2.3 Study: Glargine Plus 1, 2 or 3 Doses of Glulisine

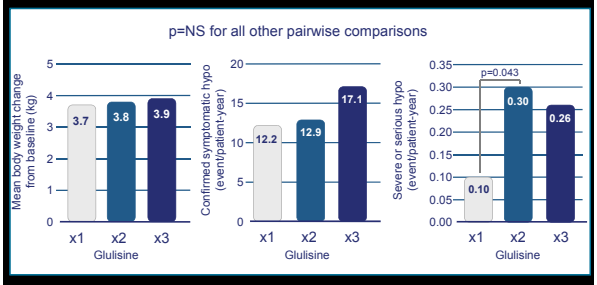
Responders in the whole population (n=785) | Evolution of A1C in the randomized population (n=343)



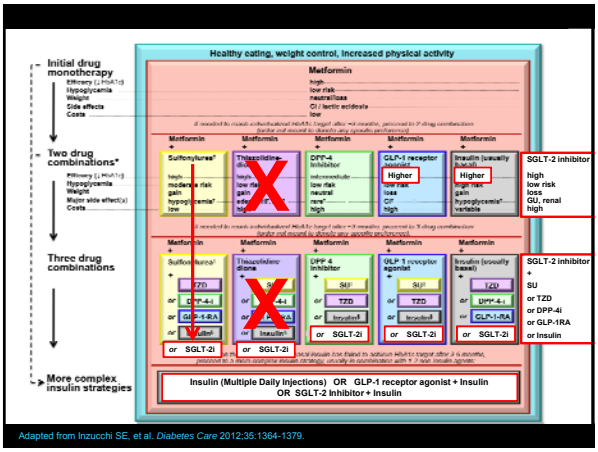
A1C in all subjects (n=785) = 9.8 at run-in and 7.3 at randomization

Davidson M *et al. Endocr Pract* 2011;Feb 16:1-9 (E-pub).

1.2.3 Study: Glargine Plus 1, 2 or 3 Doses of Glulisine



Davidson M *et al. Endocr Pract* 2011;Feb 16:1-9 (E-pub).



Adapted from Inzucchi SE, et al. *Diabetes Care* 2012;35:1364-1379.

Opportunities to Tailor Therapies to Meet Mutually Agreeable Goals

- **Low cost:**
  - Metformin – SU – TZD – Reli-On NPH insulin*
- **Weight loss:**
  - Metformin – GLP-1RA – SGLT-2i
  - Weight loss medications or surgery
- **Hypoglycemia avoidance**
  - Metformin – TZD – DPP-4i – GLP-1RA – SGLT-2i
- **Ease of use**
  - TZD – DPP-4i – GLP-1RA – SGLT-2i

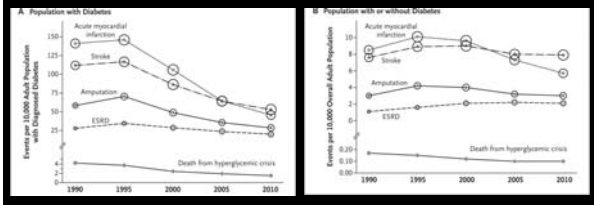
Adapted from Inzucchi SE, et al. *Diabetes Care* 2012;35:1364–1379.

*WalMart store brand

Summary

- Screen for case finding; individualize treatment
- Multiple drug choices provide many options
- Shared decision-making and patient-centered goals are important tools to improve adherence
- Most safety issues are concerns, not demonstrated problems
  - Hypoglycemia and weight gain with secretagogues and insulin
  - B12 deficiency with metformin
  - Weight gain, edema/CHF and bone fractures with glitazones
  - Dehydration with GLP-1ra
  - Genital infections and dehydration with SGLT-2 inhibitors
- Cancer is a serious problem for patients with diabetes, but there is little evidence that diabetes drugs materially affect cancer rates in humans

Trends in Age-Standardized Rates of Diabetes-Related Complications among U.S. Adults with and without Diagnosed Diabetes, 1990–2010.

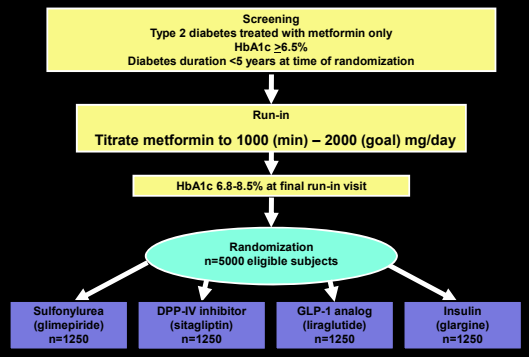


Gregg EW et al. N Engl J Med 2014;370:1514-1523.

The Diabetes Care Center Clinical Trials Team

Missing: Dawn Culmer, Jill Cunnup, Jean Dostou, LaToya Gray, Beth Harris, Jeff Kerr, Sue Kirkman

http://uncdiabetes.org/



First patient, first visit June 2013.
Last patient last visit 2020.
Nathan D, et al. *Diabetes Care. 2013*; 36(8):2254-61.

GRADE

Contact me anytime!

- jbuse@med.unc.edu
- www.UNCdiabetes.org
- Office (Jill): 919-966-0134
- Cell: 919-923-6963 (text message)