Diabetes Care: Creating Clarity in a Sea of Confusion

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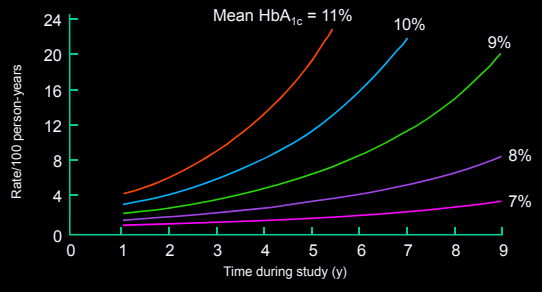
Disclosures

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; Astellas; Astra-Zeneca; Bayhill Therapeutics, Inc.; Boehringer Ingelheim; Bristol-Myers Squibb Company; Catabasis; Cebix, Inc.; CureDM; Diartis Pharmaceuticals; Elcelyx Therapeutics, Inc.; Eli Lilly and Company; Exsulin; Genentech; GI Dynamics; GlaxoSmithKline; Halozyme Therapeutics; F. Hoffmann-La Roche, Ltd.; Intarcia Therapeutics; Johnson & Johnson; Lexicon; LipoScience; Macrogenics; Medtronic MiniMed; Merck; Metabolic Solutions Development Co.; Metabolon, Inc.; Metavention; Novan; Novo Nordisk A/S; Novella Clinical; Orexigen Therapeutics, Inc.; Osiris Therapeutics, Inc.; Pfizer, Inc.; PhaseBio Pharmaceuticals Inc; Quest Diagnostics; Rhythm Pharmaceuticals; Sanofi; Spherix, Inc.; Takeda; Tolerx; Transpharma Medical Ltd.; TransTech Pharma; Veritas; Verva.

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.

UKPDS: "Legacy Effect" of Insulin/Sulfonylurea Therapy

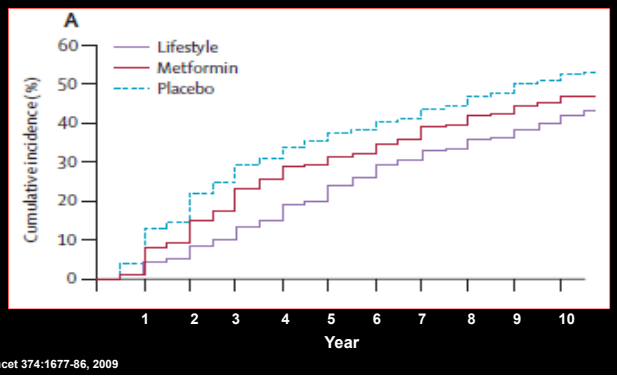
After median 8.8 years post-trial follow-up

Aggregate Endpoint		1997	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

Results Of The DPP Study



Lancet 374:1677-86, 2009

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

Study	Microvascular	CVD	Mortality
UKPDS	↓ ↓	↔ ↓	↔ ↓
DCCT / EDIC*	↓ ↓	↔ ↓	↔ ↔
ACCORD	↓	↔	↑
ADVANCE	↓	↔	↔
VADT	↓	↔	↔

*In T1DM Initial Trial Long-term Follow-up

↓ = Decreased rate ↔ =No effect ↑ =Increased rate

Adapted from Bergenstal R, et al. *Am J Med.* 2010;123:374e9-374e18.

UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837-853; Holman RR, et al. *N Engl J Med.* 2008;359:1577-1589. DCCT Research Group. *N Engl J Med.* 1993;329:977-986; Nathan DM, *et al. N Engl J Med.* 2005;353:2643-2653; Gerstein HC, et al. *N Engl J Med.* 2008;358:2545-2559; Patel A, et al. *N Engl J Med.* 2008;358:2560-2572; Duckworth W, et al. *N Engl J Med.* 2009;360:129-139 (erratum: Moritz T. *N Engl J Med.* 2009;361:1024-1025).

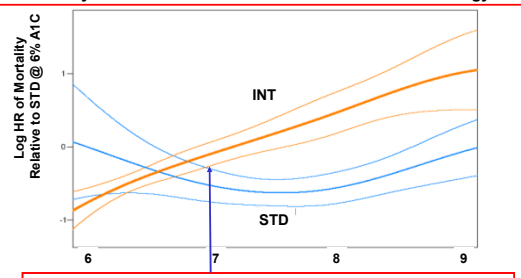
ACCORD: Exploring Lower Targets

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: Risk of Death vs A1C

Steady increase of risk 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.

What Are We to Do?

Current approaches for diabetes risk management

1) Screen for diabetes and its co-morbidities
2) Manage lipids, blood pressure, glucose, and tobacco in everyone
3) Aspirin therapy for selected individuals

Screening For Diabetes

Testing at least every 3 yrs 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..

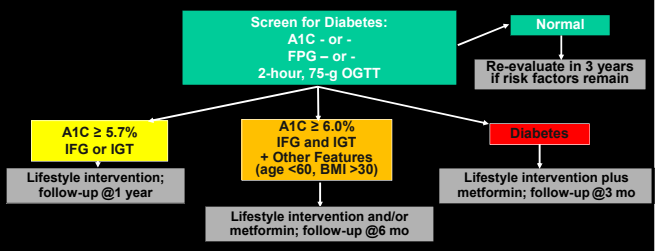
Younger/More Frequent Testing

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



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

METFORMIN IS NOT FDA APPROVED FOR PREVENTION

Glycemic Targets

- A1C target flexibility, individualization
  - General A1C goal … for many nonpregnant adults is 7%.
  - Providers might reasonably suggest more stringent A1C goals for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients might include those with short duration of diabetes, long life expectancy, and no significant CVD.
  - Conversely, less stringent A1C goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain . . . .

ADA. *Diabetes Care* 36:s11, 2013

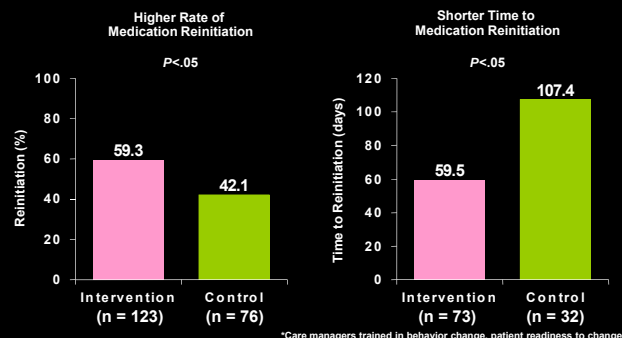
"Everything else": the mainstay of medical care

"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

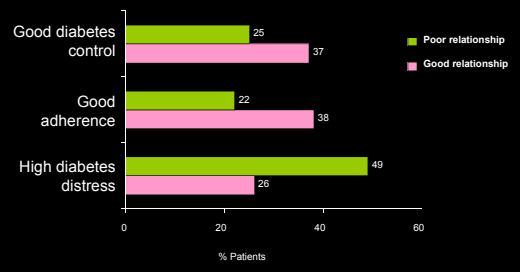
Intervention Focused on Patient Communication* Improves Medication Use



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

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

Relationship With Provider Predicts Diabetes Outcomes (US)



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

Factors Affecting Patient Adherence to Diabetes Medications

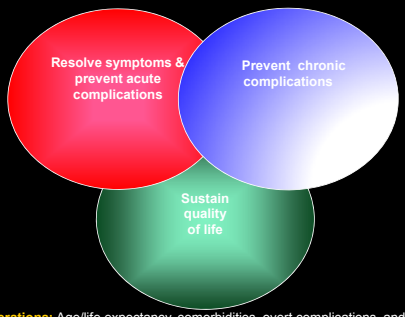
Patient Belief/Concern	Odds Ratio for Poor Adherence	Confidence Interval
Feeling medicines are hard to take	14.0	4.4–44.6
Belief that they have diabetes only when sugar is high	7.4	2–27.2
No need to take medicine when glucose level was normal	3.5	0.9–13.7
Worry about side effects	3.3	1.3–8.7
Lack of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

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

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

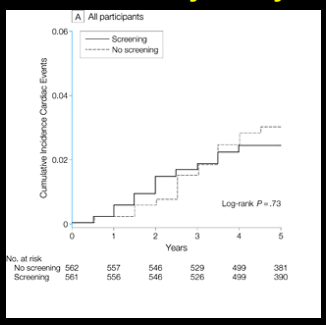
Patient-Centered Goals of Diabetes Care



Clinical considerations: Age/life expectancy, comorbidities, overt complications, and various psychosocial and cultural factors, such as patient motivation and adherence, depression, health literacy, physical mobility/activity, food choices, and other behaviors.

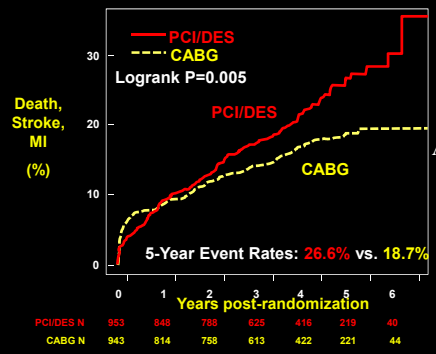
What Are We NOT to Do?

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: PRIMARY OUTCOME



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.

Overview

- Overview
  - Hyperglycemia management matters
  - Adherence
  - Shared decision-making
  - Patient-centered goals
- ADA/EASD "algorithm"
  - Could we do better?
- Drug safety/tolerability is a critical issue

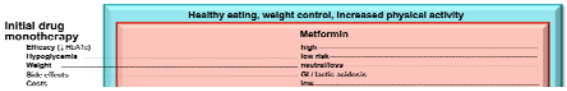
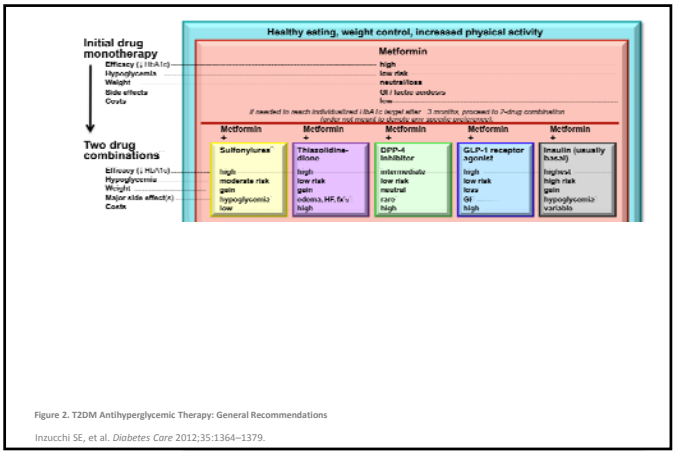


Figure 2. T2DM Antihyperglycemic Therapy: General Recommendations

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



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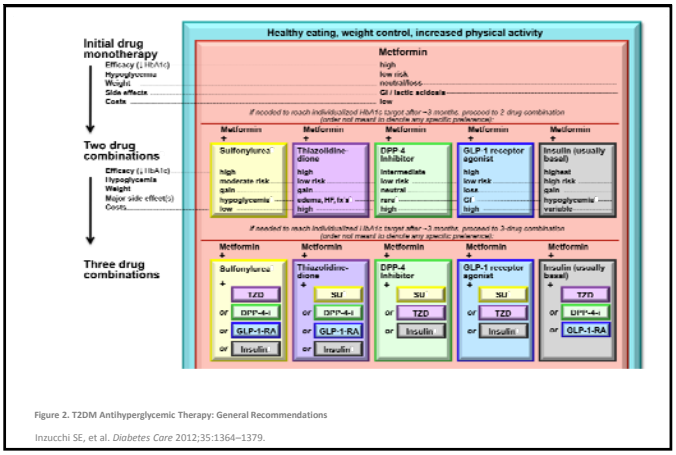

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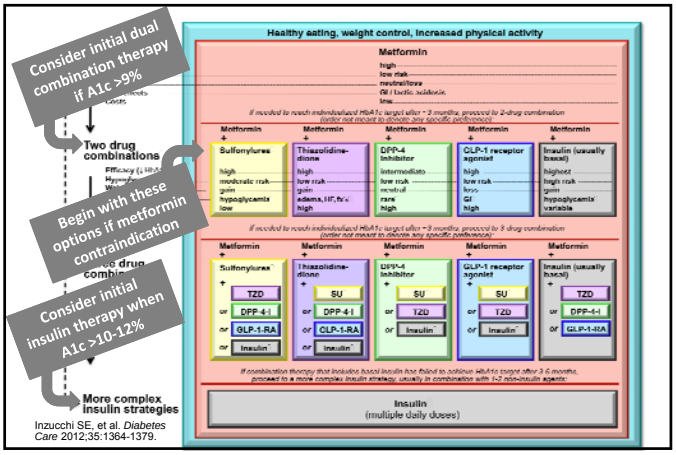


Inzucchi SE, et al. *Diabetes Care* 2012;35:1364-1379.

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 once weekly	Brand	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
Canagliflozin	Brand	0.6 – 1.2	1	Oral	No	Loss	LDL, ARF, Genital infections, K

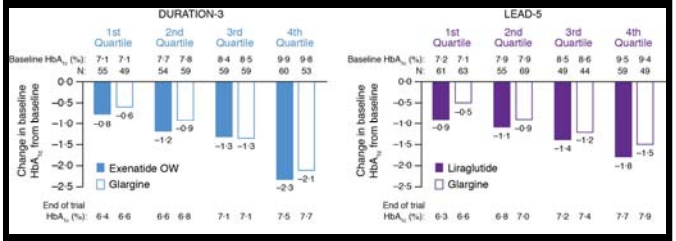
Adapted from: Nathan DM, et al. *Diabetes Care*. 2009; 32:193-203. ADA. *Diabetes Care*. 2010;33:S11-S61. WelChol PI. 1/2008. Cycloset PI. 10/2010. Victoza PI. 4/2012. Bydureon PI, 1/2012. Invokana PI, 4/2013. Buse J, et al. In: *Williams Textbook of Endocrinology*, 12th ed . 2012

Clinical Effects of SGLT2 Inhibitors

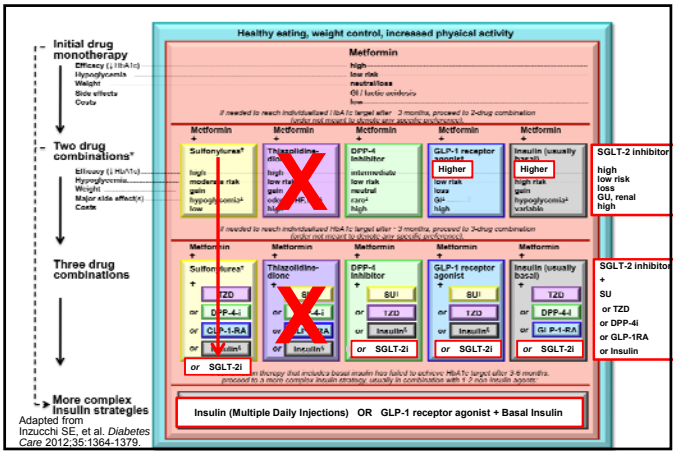
- Efficacy similar to other oral antihyperglycemic agents in A1C reduction
- Low risk for hypoglycemia
- Modest weight loss (2-3 kg at 26 weeks vs placebo)
- Modest blood pressure reduction (2-7 mm Hg vs placebo)
- AE's largely genitourinary, though minimal increase in LDL and uncommon issues with dehydration have also been observed.

Selected available data:
Misra M. *J Pharm Pharmacol.* 2013;65(3):317-327.
Ferrannini E, et al. *Diabetes Obes Metab.* 2013 Feb 8. [Epub ahead of print]
Fonseca VA, et al. *J Diabetes Complications.* 2012 Dec 28. [Epub ahead of print]
Mudaliar S, et al. *Diabetes Care.* 2012;35(11):2198-2200.
Zambrowicz B, et al. *Clin Pharmacol Ther.* 2012;92(2):158-169.
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm334549.htm
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm262993.htm

Is insulin the most effective injectable antihyperglycemic therapy?



Manuscript in preparation. Buse, Peters, Russell-Jones, Furber, Donsmark, Han, MacConnell, Maggs, Diamant.



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

Opportunities to Tailor Therapies to Meet Mutually Agreeable Goals

- **Low co-pay:**
  - 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.

Antihyperglycemic Drug Classes Under Development

Class	Mechanism	Advantages	Disadvantages	Cost
GPR-40 agonists	• Activates GLP-40 receptors in beta-cells • ↑ Insulin secretion	• No hypoglycemia	• ?	High (likely)
11β-HSD inhibitors	• Inhibits 11-beta-HSD in liver, adipose tissue • ↓ Insulin resistance	• No hypoglycemia	• ↑ Androgens (women) • ? ↓ Cortisol	High (likely)
GK Activators	• Activates glucokinase in liver and beta-cells • ↑ insulin secretion • ↓ hepatic glucose production	• 'Combination therapy' in one compound	• ? Hypoglycemia • ? Steatosis	High (likely)

Majumdar S, Inzucchi SE. *Endocrine.* 2013 Jan 25. Epub ahead of print.

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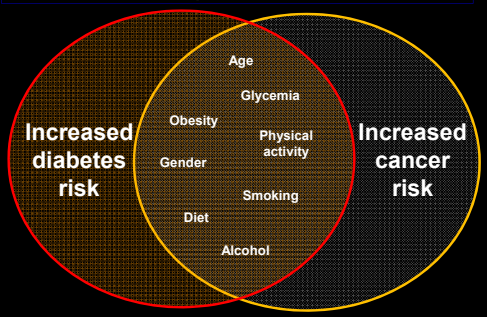
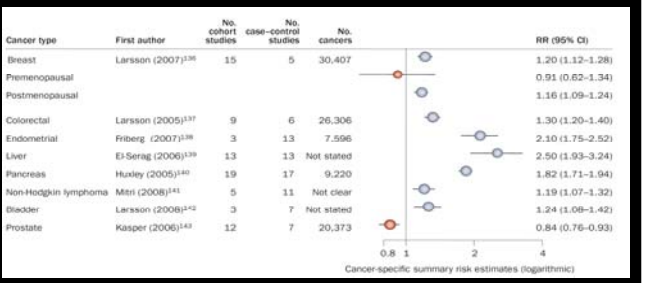
Common Risk Factors for Diabetes and Cancer

ADA Consensus Report on Diabetes and Cancer



Giovannucci E et al. *Diabetes Care* 2010;33:1674-85.

Diabetes and Cancer Risk

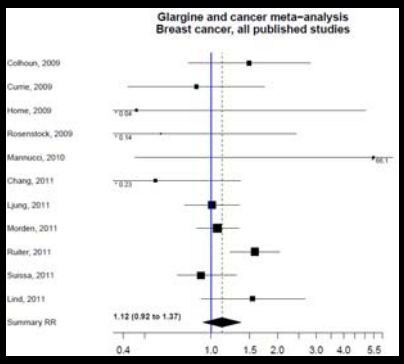


Cancer type	First author	No. cohort studies	No. case–control studies	No. cancers	RR (95% CI)
Breast	Larsson (2007)[136]	15	5	30,407	1.20 (1.12–1.28)
Premenopausal					0.91 (0.62–1.34)
Postmenopausal					1.16 (1.09–1.24)
Colorectal	Larsson (2005)[137]	9	6	26,306	1.30 (1.20–1.40)
Endometrial	Friberg (2007)[138]	3	13	7,596	2.10 (1.75–2.52)
Liver	El-Serag (2006)[139]	13	13	Not stated	2.50 (1.93–3.24)
Pancreas	Huxley (2005)[140]	19	17	9,220	1.82 (1.71–1.94)
Non-Hodgkin lymphoma	Mitri (2008)[141]	5	11	Not clear	1.19 (1.07–1.32)
Bladder	Larsson (2006)[142]	3	7	Not stated	1.24 (1.08–1.42)
Prostate	Kasper (2006)[143]	12	7	20,373	0.84 (0.76–0.93)

Diabetes increased the risk of cancer of the breast, colorectum, endometrium, liver and pancreas (reverse causality?).
Diabetes appears to protect against prostate cancer.

Clayton PE, *et al. Nat Rev Endocrinol* 2011;7:11–24.

Meta-analysis and Forest Plot of risk of breast cancer in glargine users in all published studies



P Boyle, IDF, Dubai 2/2012

Number of patients 464,585 and person-years 1,059,478

Pioglitazone HCl (ACTOS)

Clinical Study No. 01-03-TL-OPI-524

Cohort Study of Pioglitazone and Bladder Cancer in Patients with Diabetes

Fourth Interim Analysis (8-Year) Report with Data from January 1, 1997 to December 31, 2010

In summary, in our cohort analysis, there is no overall statistically significant increased risk of bladder cancer among patients ever treated with pioglitazone. The analyses addressing increasing exposure to pioglitazone suggest a possible small increased risk with longer-term therapy. However, the tentative signal from the 5 year study has not gotten any stronger, which one would have expected as more time has accumulated. In absolute terms, the incidence of bladder cancer among patients who received 4 or more years of pioglitazone was 115 per 100,000 person-years. Furthermore, it remains reassuring that only seven of 137 bladder cancers diagnosed in patients treated with pioglitazone were advanced stage.

FDA & EMA Statement in NEJM
February 27, 2014

Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment

Amy G. Egan, M.D., M.P.H., Eberhard Blind, M.D., Ph.D., Kristina Dunder, M.D., Pieter A. de Graeff, M.D., B. Timothy Hummer, Ph.D., Todd Bourcier, Ph.D., and Curtis Rosebraugh, M.D., M.P.H.

". . . the FDA and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data.

Egan AG, Blind E, Dunder K, de Graeff PA, Hummer BT, Bourcier T, Rosebraugh C. Pancreatic Safety of Incretin-based Drugs – FDA and EMA Assessment. N Engl J Med 2014;370:794-7. DOI: 10.1056/NEJMp1314078

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

Summary 2:

- 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 the setting of multivessel coronary disease, coronary artery bypass surgery is preferable to percutaneous intervention.

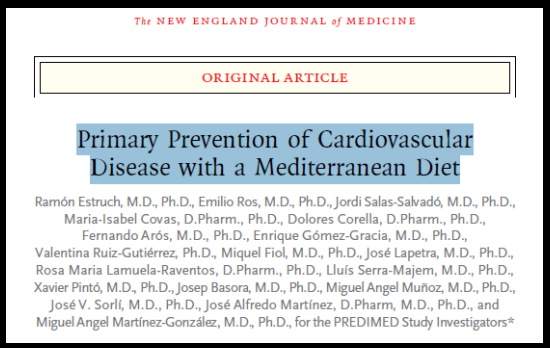
Summary 3:

- **CVD outcome trials exploring more intensive management strategies suggest:**
  - **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]**
  - **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.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

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

- Parallel group multi-center randomized controlled trial
- Inclusion/exclusion criteria
  - Men: 55 to 80 years of age Women: 60 to 80 years of age
  - No CVD, but at high risk for CVD
    - Type 2 diabetes OR (~50%)
    - At least 3 of the following major risk factors: smoking, hypertension, elevated LDL, low HDL, overweight, family history of CHD
- From 10/2003 – 6/2009, 7441 participants randomized in 1:1:1 ratio to
  - Med diet plus extra virgin olive oil
  - Med diet plus nuts
  - Control diet (lower fat diet)

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

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

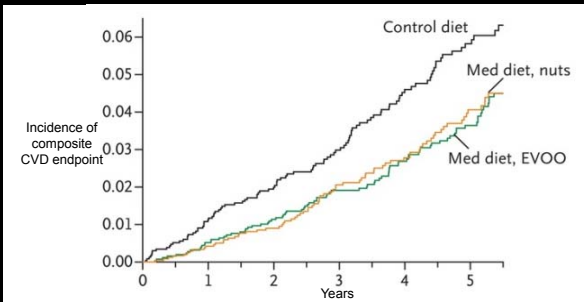
Estruch R, et al. *N Engl J Med.* 2013; 368:1279-90.

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.

Primary Endpoint



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

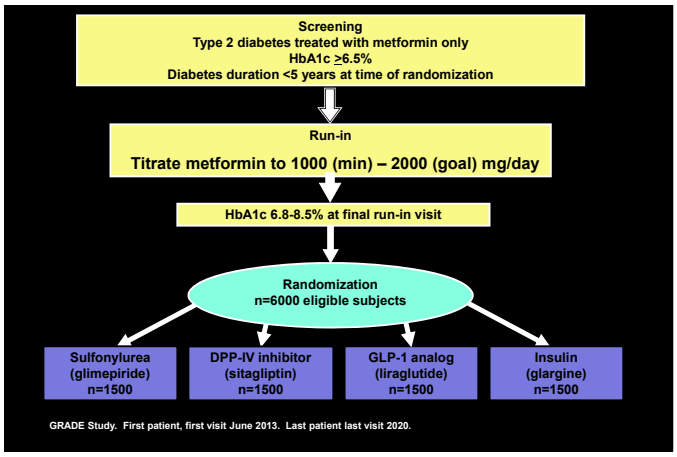
Summary 3:

- CVD outcome trials exploring lifestyle interventions suggest:
  - Intensive lifestyle efforts targeting weight loss has 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
Type 2 diabetes treated with metformin only
HbA1c ≥6.5%
Diabetes duration <5 years at time of randomization
Run-in
Titrate metformin to 1000 (min) – 2000 (goal) mg/day
HbA1c 6.8-8.5% at final run-in visit
Randomization
n=6000 eligible subjects
Sulfonylurea
(glimepiride)
n=1500
DPP-IV inhibitor
(sitagliptin)
n=1500
GLP-1 analog
(liraglutide)
n=1500
Insulin
(glargine)
n=1500
GRADE Study. First patient, first visit June 2013. Last patient last visit 2020.