Initiating Treatment for Type 2 Diabetes: One Drug at a Time

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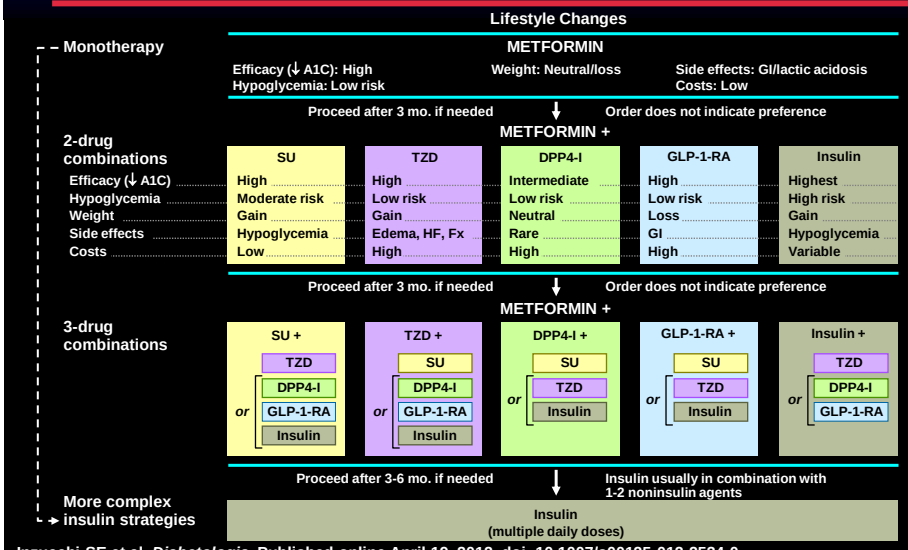
Disclosures

- Research Support: Lexicon, Lilly, Merck, Novo Nordisk, sanofi, Takeda
- Consultant: Astra-Zeneca, Boehringer, GSK, Lilly, Merck, Novo Nordisk, sanofi, Takeda,

➡ All honoraria directed toward a non-profit which supports education and research

ADA/EASD Position Statement: Managing Hyperglycemia in Type 2 Diabetes



Inzucchi SE et al. *Diabetologia*. Published online April 19, 2012. doi: 10.1007/s00125-012-2534-0.

ADA/EASD Position Statement: Managing Hyperglycemia in Type 2 Diabetes

"Metformin remains the optimal drug for monotherapy. Its low cost, proven safety record, weight neutrality and possible benefits on cardiovascular outcomes have secured its place as the favored initial drug choice.

"Initial combination therapy with metformin plus a second agent may allow patients to achieve HbA1c targets more quickly than sequential therapy.

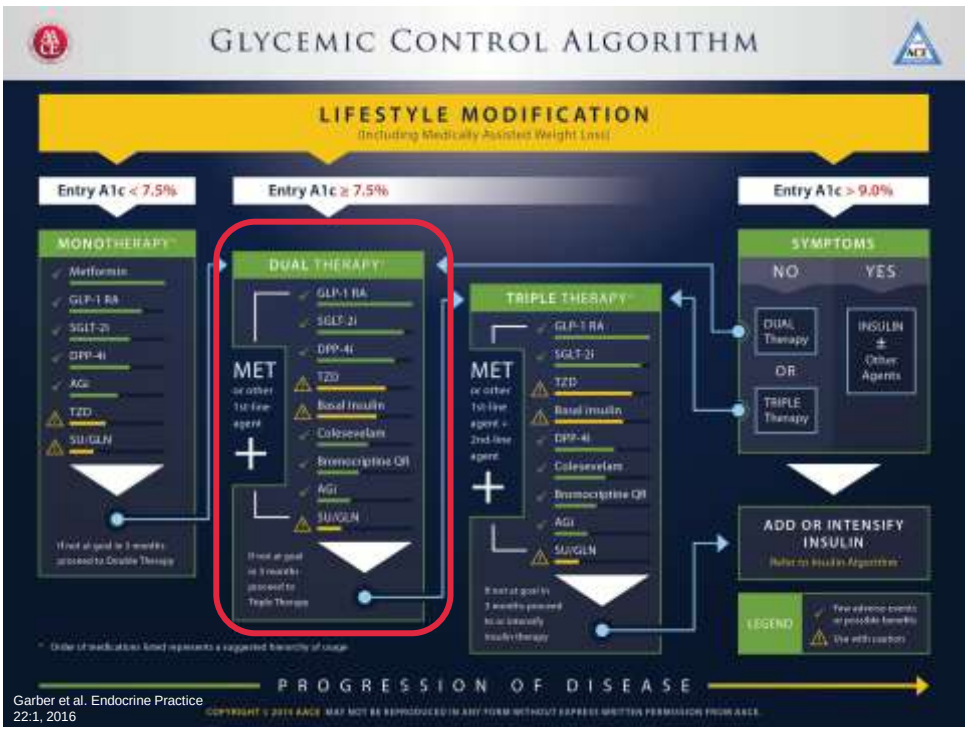
"A reasonable threshold HbA1c for this consideration is ≥ 9%.

Inzucchi SE et al. *Diabetologia*. Published online April 19, 2012. doi: 10.1007/s00125-012-2534-0.

ADA/EASD Position Statement: Managing Hyperglycemia in Type 2 Diabetes

"Of course, there is no proven overall advantage to achieving a glycemic target more quickly by a matter of weeks or even months. Accordingly, as long as close patient follow-up can be ensured, prompt sequential therapy is a reasonable alternative.

Inzucchi SE et al. *Diabetologia*. Published online April 19, 2012. doi: 10.1007/s00125-012-2534-0.



Garber et al. Endocrine Practice 22:1, 2016

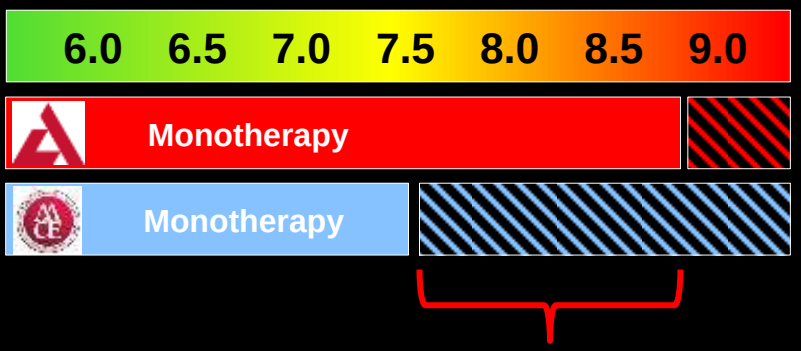
AACE Consensus Statement

"Combination therapy is usually required and should involve agents with complementary mechanisms of action

"Patients who present with an A1c of > 7.5% should be started on metformin plus another agent in addition to lifestyle therapy

Garber et al. Endocrine Practice 22:1, 2016

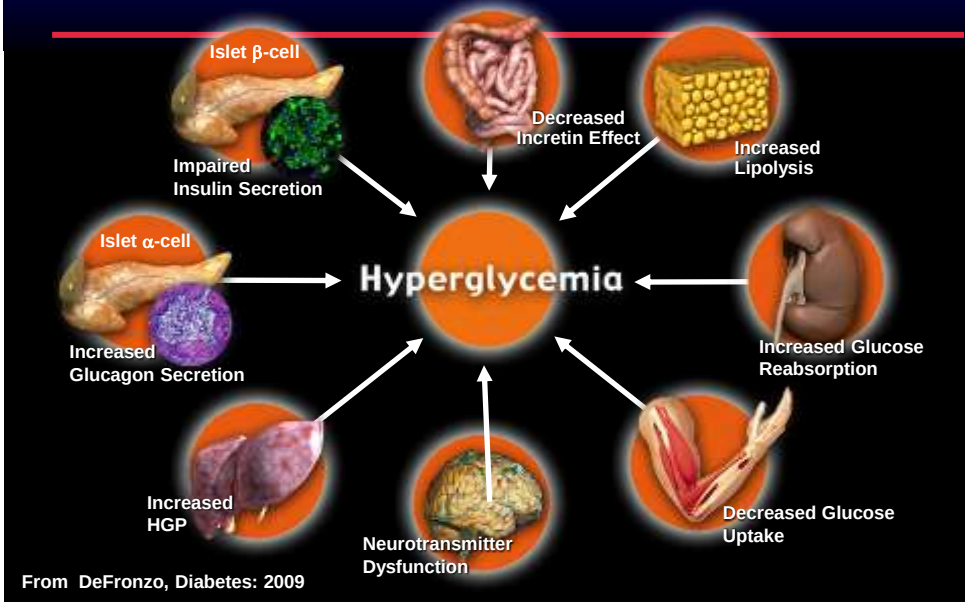
So, Where's the Controversy?



Arguments for Combination Therapy

- Multiple metabolic abnormalities contribute to hyperglycemia in T2DM
- The efficacy of any single agent is limited – combination therapy is necessary to get patients to goal
- Combinations of drugs with complementary mechanisms of action will be significantly better
- Getting to goal faster will improve outcomes

Multiple Metabolic Defects Contribute to Hyperglycemia in T2DM



From DeFronzo, Diabetes: 2009

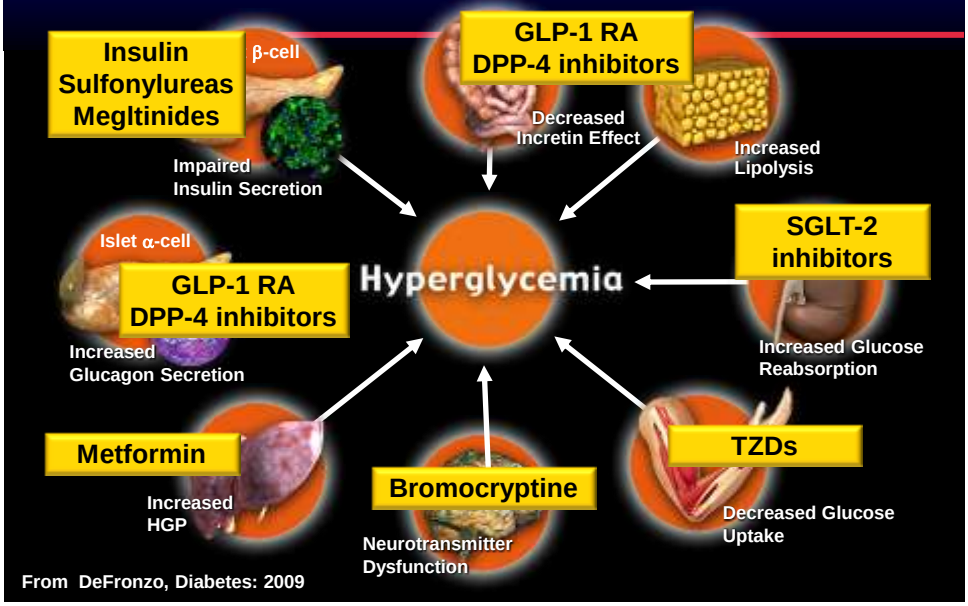
12 Classes of Antihyperglycemic Agents for T2DM

Class	A_{1c} Reduction	Hypo-glycemia	Weight Change	Dosing (times/day)	Other Safety Issues
Metformin	1.5	No	Neutral	2	GI, lactic acidosis, B12 deficiency
Basal insulin analog	1.5–2.5	Yes	Gain	1, injected	Hypoglycemia
Rapid-acting insulin	1.5–2.5	Yes	Gain	1-4,injected	
Sulfonylureas	1.5	Yes	Gain	1	Allergies, secondary failure
Thiazolidinediones	0.5–1.4	No	Gain	1	Edema, CHF, bone fractures
Short-acting GLP-1 RAs	0.5–1.0	No	Loss	2, injected	GI, ? pancreatitis, ARF
Long-acting GLP-1 RAs	~1.5	No	Loss	1, injected	GI, ? pancreatitis, ?MTC, ?ARF
Repaglinide	1–1.5	Yes	Gain	3	
Nateglinide	0.5–0.8	Rare	Gain	3	
Alpha-glucosidase inhibitors	0.5–0.8	No	Neutral	3	GI
Amylin mimetics	0.5–1.0	No	Loss	3, injected	GI
DPP-4 inhibitors	0.6–0.8	No	Neutral	1	Pancreatitis
Bile acid sequestrant	0.5	No	Neutral	1 or 2	GI
Bromocriptine quick release	0.7	No	Neutral	1	GI
SGLT2s	0.8-1.0	No	Loss	1	Genital mycotic infections

GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; RA = receptor agonist; CHF = congestive heart failure; ARF = acute renal failure; MTC = medullary thyroid carcinoma; DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium-dependent glucose cotransporter -2.

Adapted from: Nathan DM, et al. *Diabetes Care.* 2007;30(3):753-759. Nathan DM, et al. *Diabetes Care.* 2006;29(8):1963-1972. Nathan DM, et al. *Diabetes Care.* 2009;32(1):193-203. ADA. *Diabetes Care.* 2008;31:S12-S54. Buse J, et al. *Lancet.* 2009;374(9683):39-47.

Complementary Mechanisms of Action of Current Diabetes Medications



From DeFronzo, Diabetes: 2009

Potential 2-Drug Noninsulin Combinations in the US

SU/GLN[a] (5 Agents)	10	
TZD[b] (2 Agents)	4	10

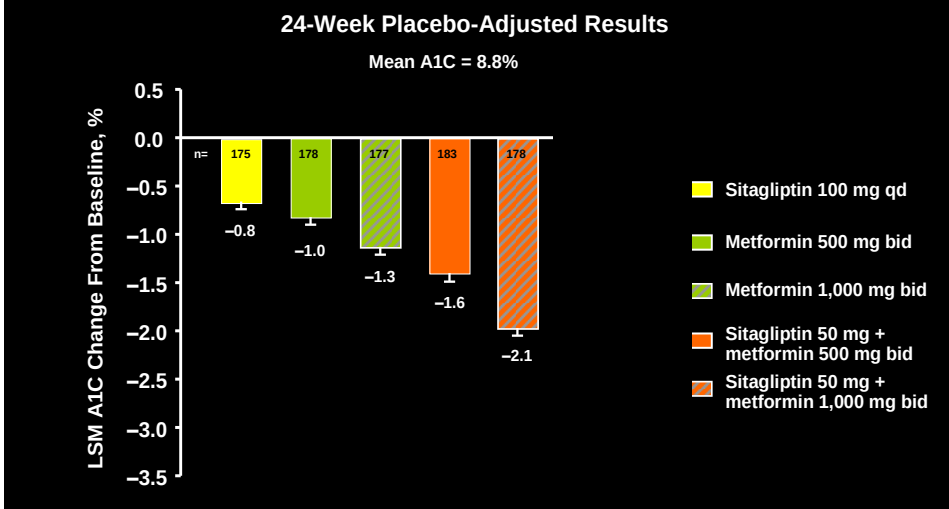
159 Possible Noninsulin Combinations in 2-Drug Regimens

Which is best?

(What about bromocriptine and colesevelam?)

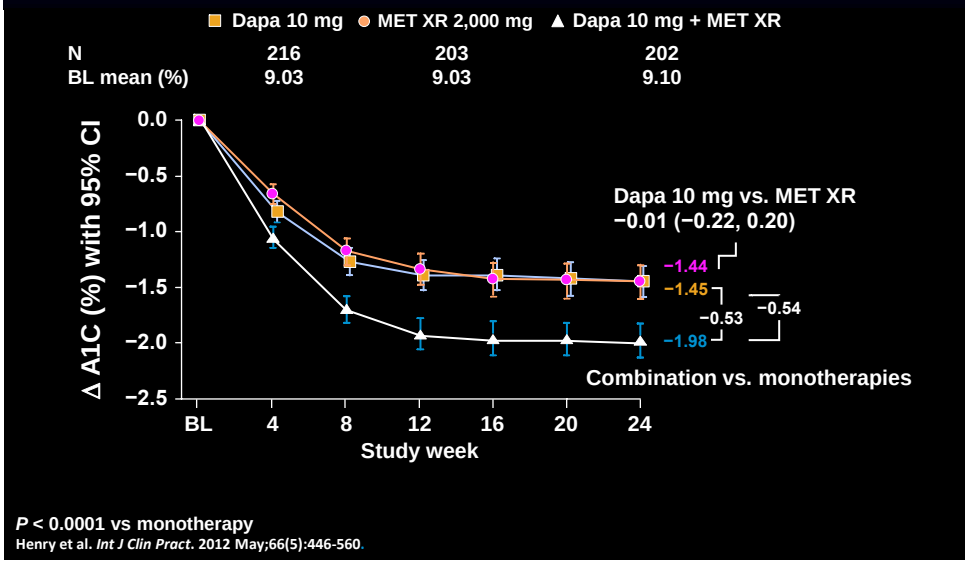
[a]Possible SUs and GLNs include glimepiride, glipizide, glyburide, nateglinide, and repaglinide; [b]Possible TZDs include pioglitazone and rosiglitazone; [c]Possible DPP-4 inhibitors include alogliptin, sitagliptin, linagliptin, and saxagliptin; [d]Possible SGLT-2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin; [e]Possible GLP-1 RAs include exenatide twice daily, exenatide once weekly, liraglutide, dulaglutide, and albiglutide; [f]Possible metformin drugs include standard and extended release formulations.

Glycemic Efficacy of Initial Combination Therapy With Sitagliptin + Metformin



[a]LSM change from baseline without adjustment for placebo.
qd=once a day; bid=twice a day.

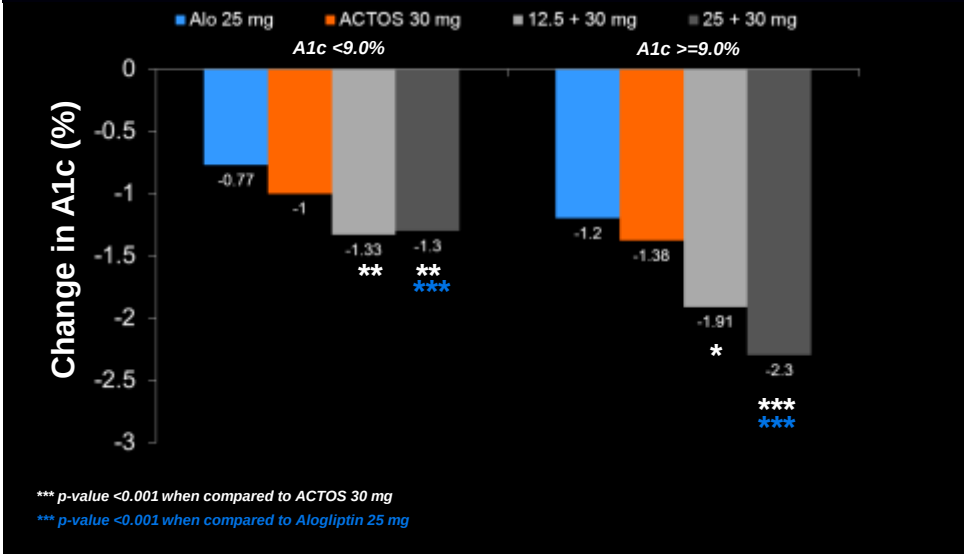
Dapagliflozin 10 mg vs. Metformin XR vs. Combination Therapy: A1C at Week 24



P < 0.0001 vs monotherapy

Henry et al. *Int J Clin Pract*. 2012 May;66(5):446-560.

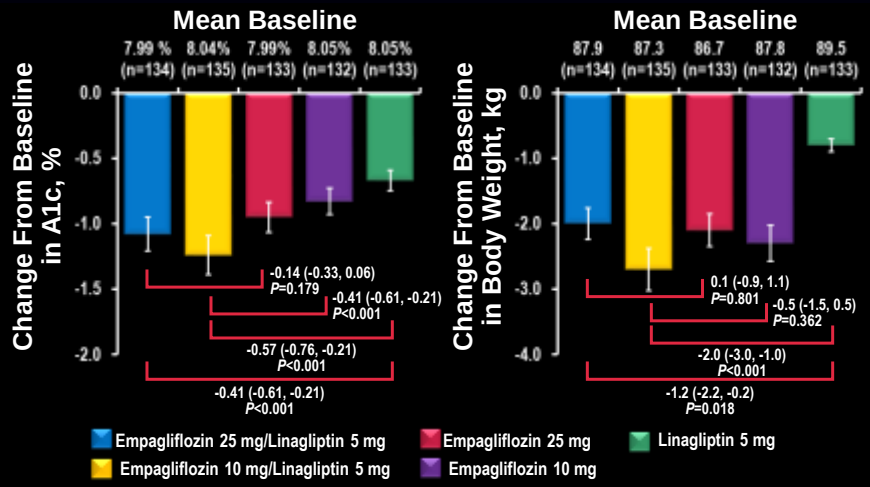
Initial Combination Therapy: Alogliptin + Pioglitazone



*** p-value <0.001 when compared to ACTOS 30 mg

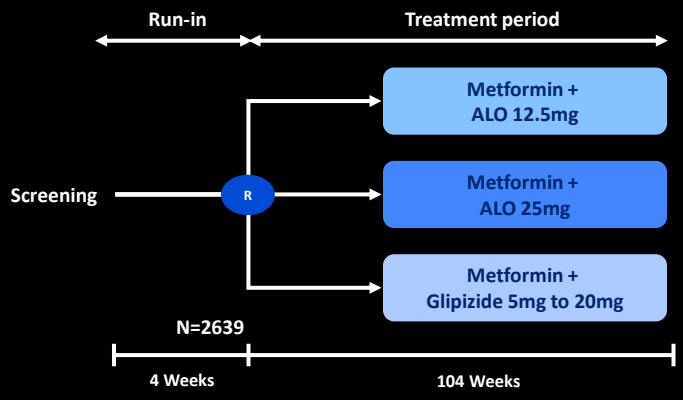
*** p-value <0.001 when compared to Alogliptin 25 mg

Initial Combination Therapy with Empagliflozin and Linagliptin



N=674 individuals with T2DM who had not received diabetes therapy for ≥12 weeks (week 24 data).
Lewin A, et al. *Diabetes Care*. 2015;38(3):394-402.

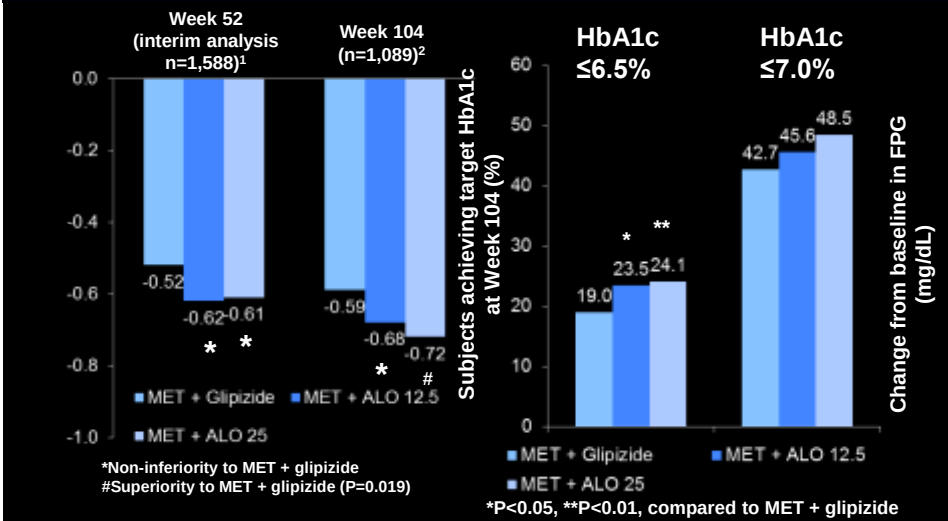
ENDURE Study design



Mean glipizide dose at end of study: 5.2mg

Del Prato S, et al. Poster presented at ADA 2013 [66-LB]. ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT00856284. [Last accessed July 2013]

ENDURE: Change in A1c after 104 Weeks with Alo/Met vs Glip/Met



1. Del Prato S, et al. Poster 1061-P presented at ADA 2013. 2Del Prato S, et al. Poster 66-LB presented at ADA 2013

Arguments for Combination Therapy

- Multiple metabolic abnormalities contribute to hyperglycemia in T2DM
  - True
- The efficacy of any single agent is limited – combination therapy is necessary to get patients to goal
  - One drug is often enough
- Combinations of drugs with complementary mechanisms of action will be significantly better
  - Meh….
- Getting to goal faster will improve outcomes
  - Where's the evidence?

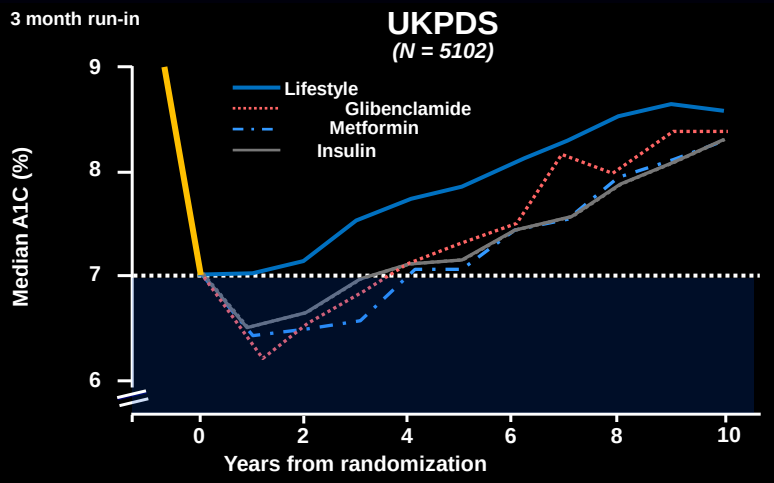
Arguments Against Initial Combination Therapy

- One drug is often sufficient for those with an A1c 7.5-9
- There is a lack of evidence that early control improves outcomes or durability of response
- There is virtually no comparative efficacy data on initial combination therapies
- Decreased flexibility of dosing with initial combination – diminished opportunity to personalize therapy
- Attribution of side effects may be confounded

Arguments Against Initial Combination Therapy

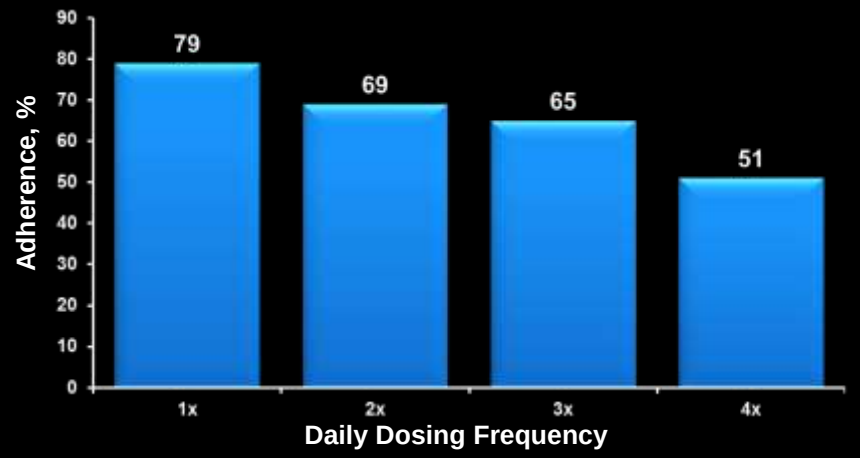
- Pill burden may decrease adherence
- Costs are higher
- Insurance companies only cover stepped-care
- Polypharmacy may contribute to adverse events

UKPDS: Diet Run-in in New Onset T2DM



UKPDS 34. *Lancet*. 1998;352:854-865.

Adherence Decreases With Increasing Frequency of Dosing



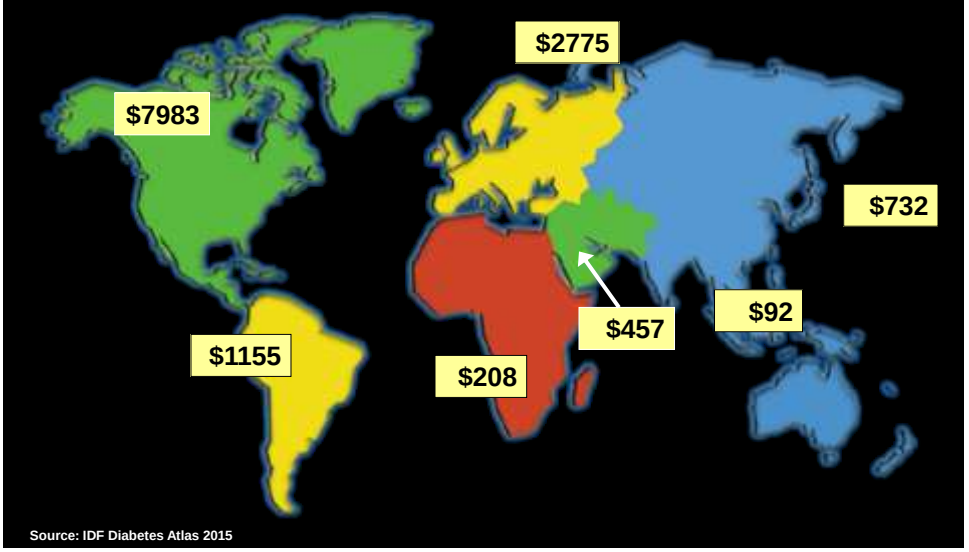
Claxton AJ, et al. *Clin Ther*. 2001;23:1296-1310; Laufs U, et al. *Eur Heart J*. 2011;32:264-268.

Polypharmacy Increases Risks of Adverse Drug Reactions in T2DM

- Polypharmacy increases the number of adverse drug events for those with T2DM including[1]:
  - Severe hypoglycemia[2]
  - Drug-drug interactions[3]
  - Interactions with coexisting comorbidities[4]
- The higher the number of medications, the less likely the patient will remain adherent with the treatment regimen[5]

1. Lipska KJ, et al. *JAMA*, 2016;1034-1045; 2. Shorr RI, et al. *Arch Intern Med*. 1997;157:1681-1686;3. Doan J, et al. *Ann Pharmacother*. 2013;47:324-332; 4. Fitzgerald SP et al. *J Am Med Dir Assoc*. 2010;11(7):475- 484 5. Benner JS. et al. *Am J Health Syst Pharm*. 2009;66:1471-1477

Annual Total Expenditures for Diabetes Per Person 2014 (USD)



Source: IDF Diabetes Atlas 2015

Field Research

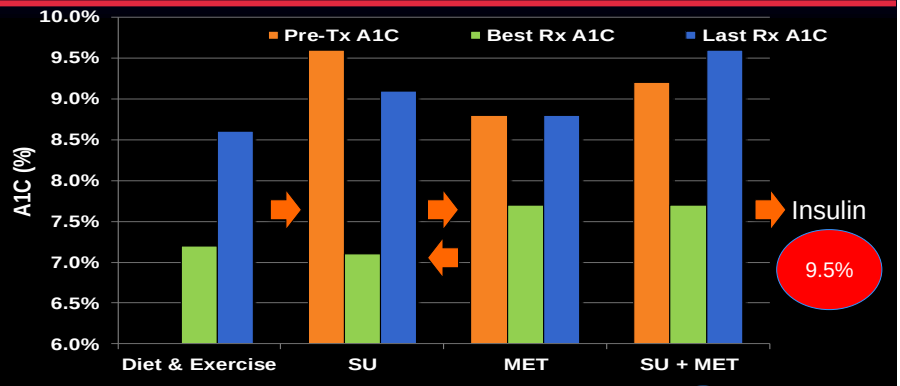
Metformin is cheaper than dirt

Lowest Available Retail Price of Diabetes Drugs in United States – 2015

Drug	Dose	Price for 1-mo Supply	Retailer
Metformin	1000 mg BID	$0	Publix
Glimepiride	4 mg QD	$8	Walmart
Pioglitazone	30 mg QD	$14.50	Walmart
Sitagliptin	100 mg QD	$343.37	Publix
Linagliptin	5 mg QD	$343.38	Publix
Canagliflozin	300 mg QD	$355.72	Publix
Dapagliflozin	5 mg QD	$334.59	Publix
Exenatide	10 mcg BID	$456.09	Walmart
Exenatide QW	2 mg QW	$489.92	Publix

Dsource: GoodRx- Downloaded 2015

Physicians Delay Intensifying Therapy for Months – This is the Real Problem!



A1C >8% (mon)	4	17	12	26
A1C >7% (mon)	16	37	26	51

Brown et al. *Diabetes Care.* 2004;27:1535-40.

Summary

- Sequential therapy is appropriate for patients with an A1c < 9%. It works!
- Sequential therapy allows for better personalization of therapy, minimizes side effects and contains costs
- Early control does not improve outcomes for patients
- There is a lack of clinical trial evidence to guide initial combination therapy
- Clinical inertia must be avoided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