American Diabetes Association
28th Annual Clinical Conference on Diabetes
Orlando, Florida
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New ADA-EASD Guidelines: The Patient Centered Approach to Therapy in Type 2 Diabetes

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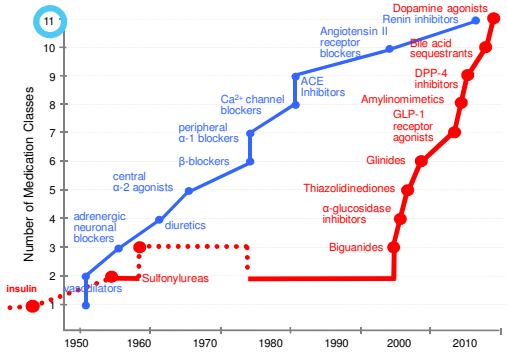
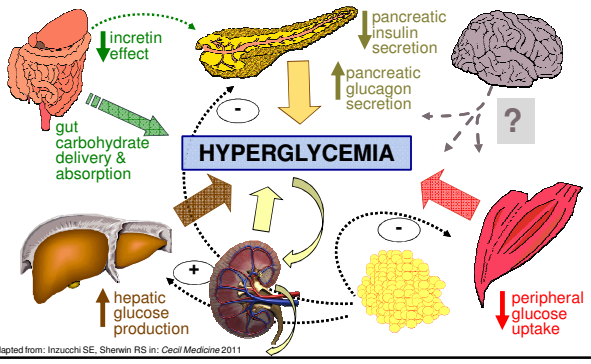
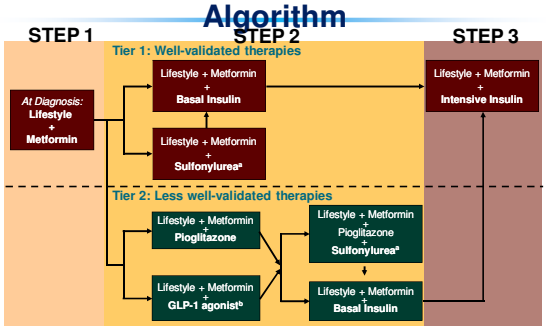
Hypertension & Diabetes: Drug Classes* in the U.S. over the Past Half-Century



The Complex Pathogenesis of T2DM



2008 ADA / EASD Consensus Algorithm



Reinforce lifestyle changes at every visit and check A1C every 3 months until < 7.0%, then at least every 6 months thereafter. Change interventions whenever A1C ≥ 7.0%.

[a]Sulfonylureas other than glibenclamide (glyburide) or chlorpropamide.
[b]Insufficient clinical use to be confident regarding safety.

Nathan DM, et al. *Diabetes Care*. 2008;31:1

Reasons for a New Guideline

1. Increasing number & variety of anti-hyperglycemic agents.
2. New data re: benefits vs. risks of tight glycemic control.
3. Increasing concerns about drug safety.
4. Increasing discourse about personalized medicine and 'patient-centered' care.
5. Prior guidelines were *consensus documents* – not official 'position statements.' ADA & EASD requested that a more formal process be followed - leading to review / endorsement by their respective Professional Practice & Executive Committees.

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

American Diabetes Association. EASD

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

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

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med.* 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329:977.
Nathan DM et al. *N Engl J Med.* 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

Initial Trial
Long Term Follow-up
* in T1DM

Survival as a Function of HbA1c in T2DM after Treatment Intensification: Insights from UK's GPRD

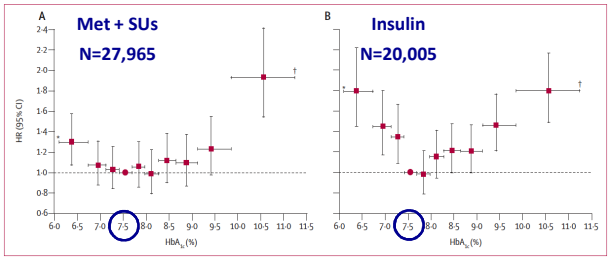


Figure 1: Adjusted hazard ratios for all-cause mortality by HbA_{1c} deciles in people given oral combination and insulin-based therapies
Cox proportional hazards models were used, with the HbA_{1c} base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA_{1c} range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).

- Age>50
- During 1986-2008

Currie CJ *et al. Lancet* 2010;375:481

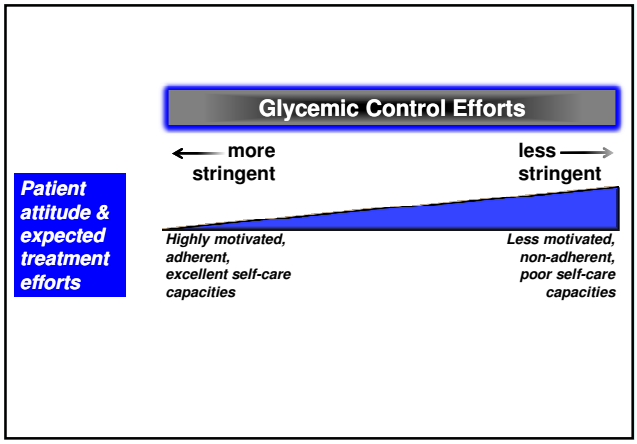
ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

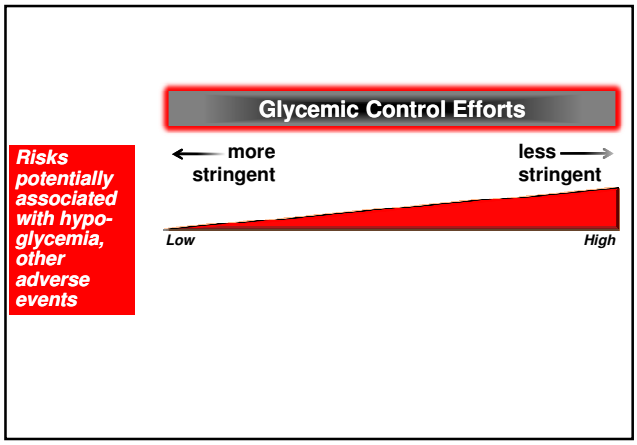
ANTI-HYPERGLYCEMIC THERAPY

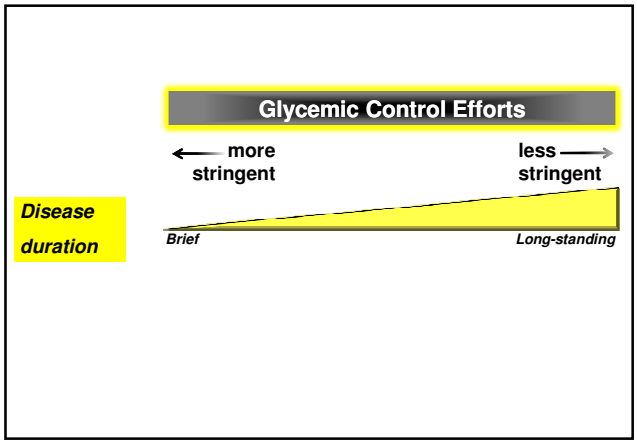
- **Glycemic targets**
  - **HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)
  - **Individualization** is key:
    - Tighter targets (6.0 - 6.5%) - younger, healthier
    - Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

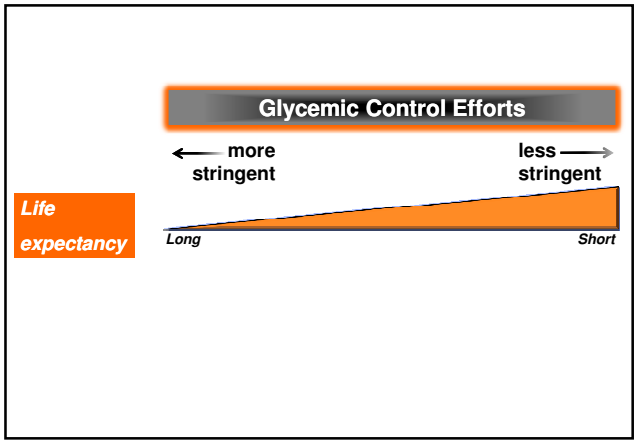
PG = plasma glucose

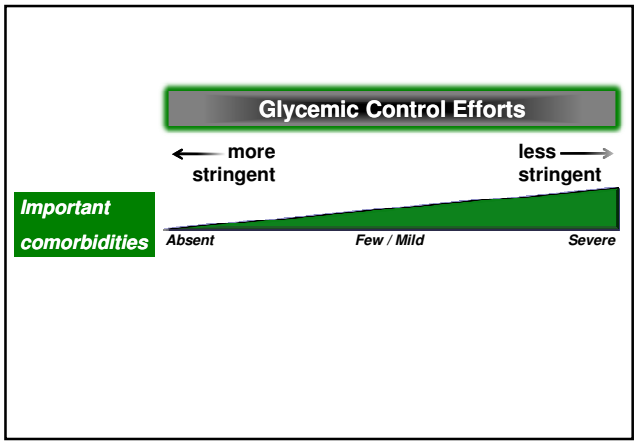
Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

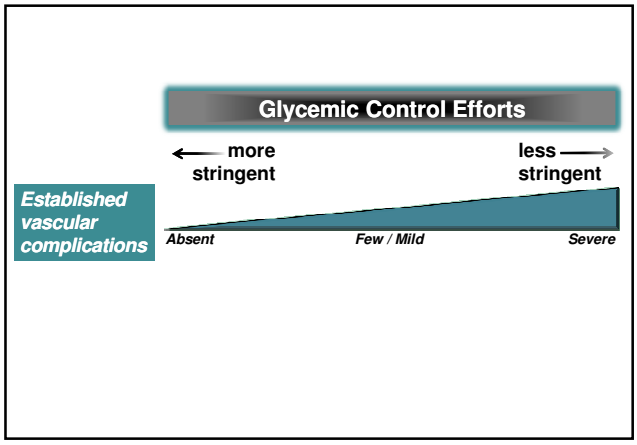

Glycemic Control Efforts
more stringent
less stringent
Patient attitude & expected treatment efforts
Highly motivated, adherent, excellent self-care capacities
Less motivated, non-adherent, poor self-care capacities

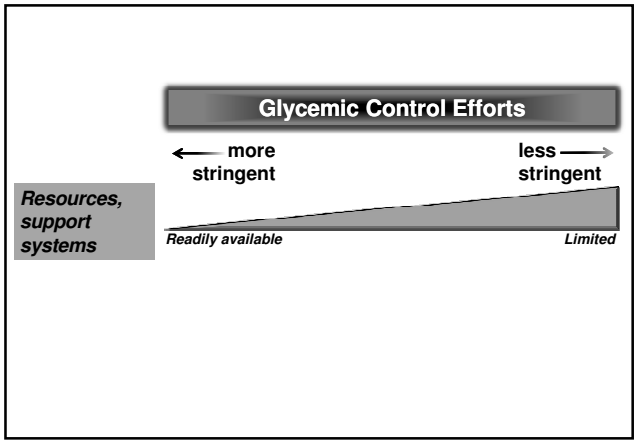

Glycemic Control Efforts
more stringent
less stringent
Risks potentially associated with hypo-glycemia, other adverse events
Low
High

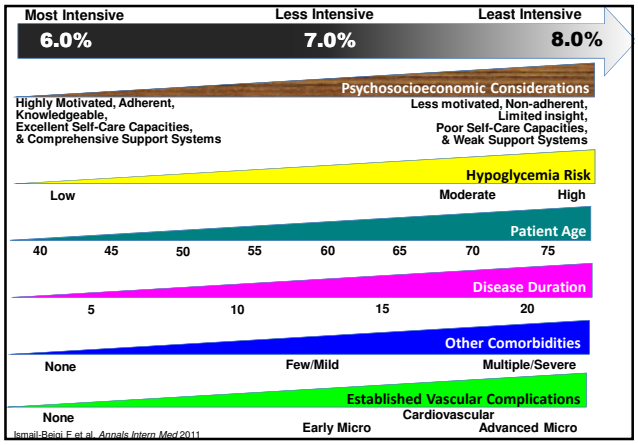

Glycemic Control Efforts
more stringent
less stringent
Disease duration
Brief
Long-standing

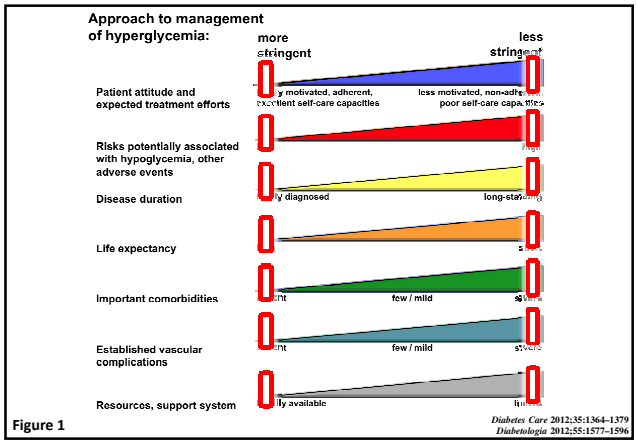

Glycemic Control Efforts
more stringent
less stringent
Life expectancy
Long
Short


Glycemic Control Efforts
more stringent
less stringent
Important comorbidities
Absent
Few / Mild
Severe


Glycemic Control Efforts
more stringent
less stringent
Established vascular complications
Absent
Few / Mild
Severe


Glycemic Control Efforts
more stringent
less stringent
Resources, support systems
Readily available
Limited


Most Intensive
Less Intensive
Least Intensive
6.0%
7.0%
8.0%
Psychosocioeconomic Considerations
Highly Motivated, Adherent, Knowledgeable, Excellent Self-Care Capacities, & Comprehensive Support Systems
Less motivated, Non-adherent, Limited insight, Poor Self-Care Capacities, & Weak Support Systems
Hypoglycemia Risk
Low
Moderate
High
Patient Age
40 45 50 55 60 65 70 75
Disease Duration
5 10 15 20
Other Comorbidities
None
Few/Mild
Multiple/Severe
Established Vascular Complications
None
Cardiovascular
Early Micro
Advanced Micro
Ismail-Beigi F et al. Annals Intern Med 2011


Approach to management of hyperglycemia:
more stringent
less stringent
Patient attitude and expected treatment efforts
Risks potentially associated with hypoglycemia, other adverse events
Disease duration
Life expectancy
Important comorbidities
Established vascular complications
Resources, support system
few / mild
Figure 1
Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

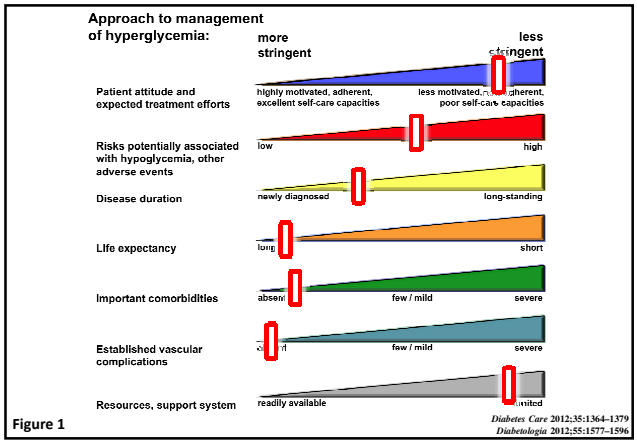


Figure 1

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

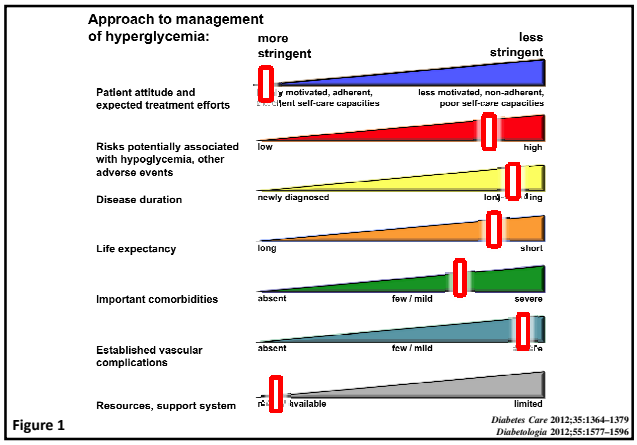


Figure 1

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

ANTI-HYPERGLYCEMIC THERAPY

- **Therapeutic options:**

Oral agents & non-insulin injectables

- **Metformin**	- Meglitinides
- **Sulfonylureas**	- α-glucosidase inhibitors
- **Thiazolidinediones**	- Bile acid sequestrants
- **DPP-4 inhibitors**	- Dopamine-2 agonists
- **GLP-1 receptor agonists**	- Amylin mimetics

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides (Metformin)	• Activates AMP-kinase • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD events	• Gastrointestinal • Lactic acidosis • B-12 deficiency • Contraindications	Low
SUs / Meglitinides	• Closes KATP channels • ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk	• Hypoglycemia • Weight gain • Low durability • ? ↓ Ischemic preconditioning	Low
TZDs	• Activates PPAR-γ • ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↓ TGs, ↑ HDL-C • ? ↓ CVD events (pio)	• Weight gain • Edema / heart failure • Bone fractures • ? ↑ MI (rosi) • ? Bladder ca (pio)	Low

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

Class	Mechanism	Advantages	Disadvantages	Cost
DPP-4 inhibitors	• Inhibits DPP-4 • Increases GLP-1, GIP	• No hypoglycemia • Well tolerated	• Modest ↓ A1c • ? Pancreatitis • Urticaria	High
GLP-1 receptor agonists	• Activates GLP-1 receptor • ↑ Insulin, ↓ glucagon • ↓ gastric emptying • ↑ satiety	• Weight loss • No hypoglycemia • ? ↑ Beta cell mass • ? CV protection	• GI • ? Pancreatitis • Medullary ca • Injectable	High
Insulin	• Activates insulin receptor • ↑ Glucose disposal • ↓ Hepatic glucose production	• Universally effective • Unlimited efficacy • ↓ Microvascular risk	• Hypoglycemia • Weight gain • ? Mitogenicity • Injectable • Training requirements • "Stigma"	variable

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

ANTI-HYPERGLYCEMIC THERAPY

- **Therapeutic options: Insulin**
  - Human Neutral protamine Hagedorn (NPH)
  - Human Regular
  - Basal analogues (glargine, detemir)
  - Rapid analogues (lispro, aspart, glulisine)
  - Pre-mixed varieties

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

AHRQ: Comparative Effectiveness & Safety of T2DM Medications: *EFFICACY*

Comparison (Drug 1 vs. Drug 2)	Studies (N)	Median Change From Baseline HbA_{1c} with Drug 2, %	Mean Difference in HbA_{1c} (95% CI), %	Strength of Evidence
Rosi vs. Pio	3 (886)	-0.7	0.08 (-0.17 to 0.33)	Moderate
Met vs. SU	17 (6936)	-1.2	0.07 (-0.12 to 0.26)	High
SU vs. Meg	7 (1543)	-0.2	0.07 (-0.15 to 0.29)	High
Met vs. TZD	14 (5592)	-1	-0.07 (-0.18 to 0.04)	Moderate
TZD vs. SU	13 (5578)	-0.9	-0.10 (-0.22 to 0.01)	Moderate
Met vs. DPP-4	3 (1908)	-0.7	-0.37 (-0.54 to -0.20)	Moderate
Met vs. Met + SU	14 (3619)	-1.6	1.00 (0.75 to 1.25)	High
Met vs. Met + DPP-4	6 (4236)	-0.9	0.69 (0.56 to 0.82)	Moderate
Met vs. Met + TZD	11 (3495)	-0.8	0.66 (0.45 to 0.86)	High
Met + basal vs. Met + premixed	3 (530)	-1.1	0.30 (-0.26 to 0.86)	Low
Met + TZD vs. Met + SU	6 (2729)	-0.9	-0.06 (-0.17 to 0.06)	Moderate
Met + SU vs. TZD + SU	6 (1844)	-1.1	-0.09 (-0.19 to 0.01)	Moderate

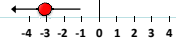
Favors Drug 1 Favors Drug 2
Pooled Between-Group Difference in H

140 head-to-head trials + 26 observational studies

Bennett WL, et al. *Ann Intern Med.* 2011;154:602.

AHRQ: Comparative Effectiveness & Safety of T2DM Medications: *WEIGHT*

Comparison (Drug 1 vs. Drug 2)	Studies (N)	Median Change from Baseline Wt. w/ Drug 2, kg	Mean Difference in Weight (95% CI), kg	Strength of Evidence
SU vs. GLP-1	3 (1310)	-0.7	2.5 (1.2 to 3.8)	Moderate
TZD vs. SU	5 (6226)	1.9	1.2 (0.6 to 1.9)	Low
SU vs. Meg	6 (1329)	-0.1	0.0 (-1.0 to 1.0)	High
Rosi vs. Pio	3 (886)	2	-0.4 (-0.8 to 0.0)	Low
Met vs. DPP-4	3 (1908)	-0.6	-1.4 (-1.8 to -1.00	Moderate
Met vs. TZD	8 (5239)	-0.5	-2.6 (-4.1 to -1.2)	High
Met vs. SU	12 (5067)	1.6	-2.7 (-3.5 to -1.9)	High
Met vs. Met + DPP-4	3 (4263)	-0.4	-0.2 (-0.7 to 0.2)	Moderate
Met vs. Met + TZD	5 (2647)	1.5	-2.2 (-2.6 to -1.9)	High
Met vs. Met + SU	10 (2510)	0.7	-2.3 (-3.3 to -1.2)	High
Met + TZD vs. Met + SU	5 (2407)	1.5	0.9 (0.4 to 1.3)	Moderate
Met + basal vs. Met + premixed	3 (530)	2.2	-1.8 (-7.8 to 4.2)	Low
Met + SU vs. TZD + SU	4 (2341)	2.2	-3.2 (-5.2 to -1.1)	Moderate



Favors Drug 1 Favors Drug 2
Pooled Between-Group Difference in Weight, *kg*

Bennett WL, et al. *Ann Intern Med.* 2011;154:602.

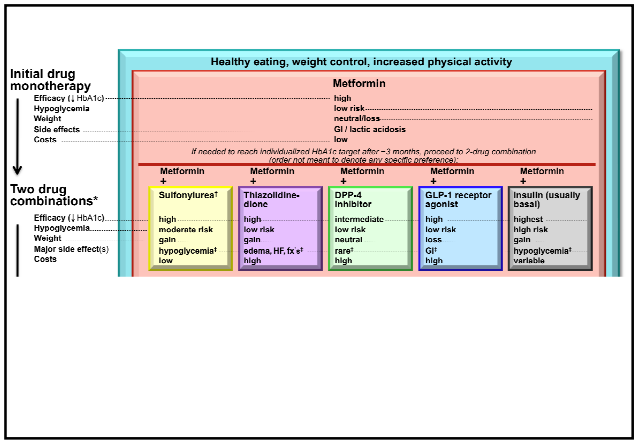
AHRQ: Comparative Effectiveness & Safety of T2DM Medications: HYPOGLYCEMIA

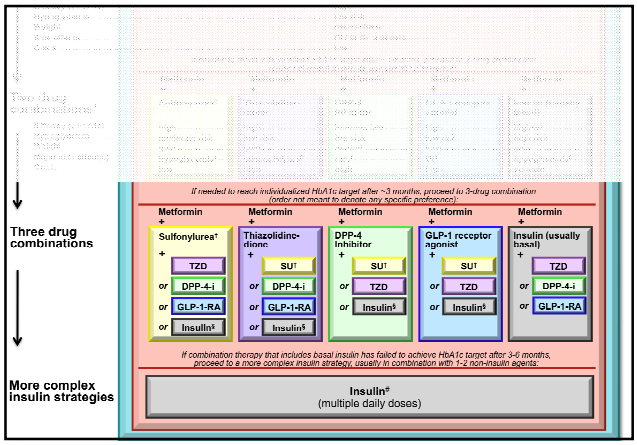
	Drug 1	Drug 2	
Comparis (Drug 1 vs			Strength of vidence
Met vs. SU			w
Met vs. Me			oderate
TZD vs. SU			igh
Met vs. SU			igh
Met vs. Me			oderate
Met vs. Me			oderate
Met vs. Mo			w
Met + TZD			igh

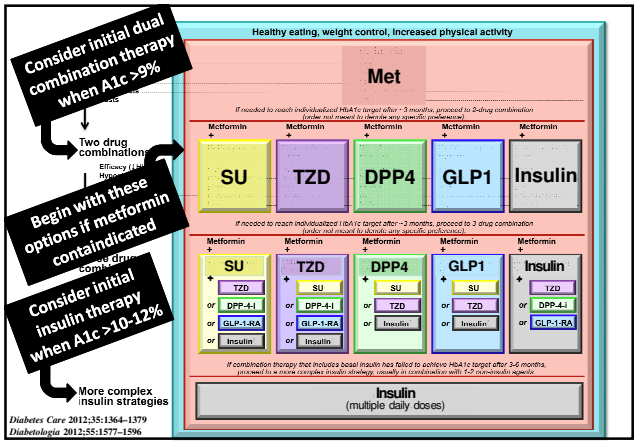
- "Most medications decreased A1c level by ≈1%"
- "Evidence supports metformin as a first-line agent...."
- Most 2-drug combinations similarly reduce A1c levels, but some increased risk for hypoglycemia and other adverse events."
- "Evidence on long-term clinical outcomes *(e.g., mortality, CV disease, nephropathy, and neuropathy)* was…insufficient."

Favors Drug 2 Favors Drug 1
Pooled Odds Ratio (95% CI) for Mild-Moderate Hypoglycemia

Bennett WL, et al. *Ann Intern Med.* 2011;154:602.


Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):
Two drug combinations*
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Major side effect(s)
Costs
Metformin + Sulfonylurea†
high
moderate risk
gain
hypoglycemia†
low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fx ±
high
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare‡
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI‡
high
Metformin + Insulin (usually basal)
highest
high risk
gain
hypoglycemia‡
variable


If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):
Three drug combinations
Metformin + Sulfonylurea† + TZD or DPP-4-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU† or DPP-4-i or GLP-1-RA or Insulin§
Metformin + DPP-4 Inhibitor + SU† or TZD or Insulin§
Metformin + GLP-1 receptor agonist + SU† or TZD or Insulin§
Metformin + Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:
More complex insulin strategies
Insulin‡ (multiple daily doses)


Consider initial dual combination therapy when A1c >9%
Two drug combinations
Begin with these options if metformin contraindicated
Consider initial insulin therapy when A1c >10-12%
More complex insulin strategies
Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596
Healthy eating, weight control, increased physical activity
Met
If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):
Metformin + SU
Metformin + TZD
Metformin + DPP4
Metformin + GLP1
Metformin + Insulin
If needed to reach individualized HbA1c target after ~3 months, proceed to 3 drug combination (order not meant to denote any specific preference):
Metformin + SU + TZD or DPP-4-i or GLP-1-RA or Insulin
Metformin + TZD + SU or DPP-4-i or GLP-1-RA or Insulin
Metformin + DPP4 + SU or TZD or Insulin
Metformin + GLP1 + SU or TZD or Insulin
Metformin + Insulin + TZD or DPP-4-i or GLP-1-RA
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:
Insulin (multiple daily doses)

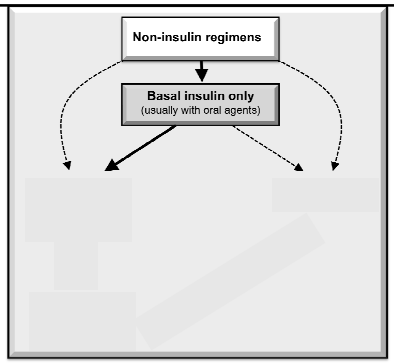


Fig. 3. Sequential Insulin Strategies in T2DM

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- **Age: Older adults**
  - Reduced life expectancy
  - Higher CVD burden
  - Reduced GFR
  - At risk for adverse events from polypharmacy
  - More likely to be compromised from hypoglycemia

✓ **Less ambitious targets**
✓ **HbA1c <7.5–8.0% if tighter targets not easily achieved**
✓ **Focus on drug safety**

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- **Weight**
  - Majority of T2DM patients overweight / obese
  - Intensive lifestyle program
  - Metformin
  - GLP-1 receptor agonists
  - ? Bariatric surgery
  - Consider LADA in lean patients

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- **Sex/ethnic/racial/genetic differences**
  - Little is known!
  - MODY & other monogenic forms of diabetes
  - Latinos: more insulin resistance
  - East Asians: more beta cell dysfunction
  - Gender may drive concerns about adverse effects (e.g., bone loss from TZDs)

Diabetes Care 2012;35:1364–1379
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ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- **Comorbidities**
  - **Coronary Disease** ----->
  - **Heart Failure**
  - **Renal disease**
  - **Liver dysfunction**
  - **Hypoglycemia**

- Metformin: CVD benefit (UKPDS)
- Avoid hypoglycemia
- ? SUs & ischemic preconditioning
- ? Pioglitazone & ↓ CVD events
- ? Effects of incretin therapies

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ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- **Comorbidities**
  - **Coronary Disease**
  - **Heart Failure** ---------->
  - **Renal disease**
  - **Liver dysfunction**
  - **Hypoglycemia**

- Metformin: May use unless condition is unstable or severe
- Avoid TZDs
- ? Effects of incretin therapies

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- **Comorbidities**
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

- Increased risk of hypoglycemia
- Metformin & lactic acidosis
  - US: stop @SCr ≥ 1.5 (1.4 women)
  - UK: half-dose @GFR < 45 & stop @GFR < 30
- Caution with SUs (esp. glyburide)
- DPP4-i's – dose adjust for most
- Avoid exenatide if GFR < 30

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ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- **Comorbidities**
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

- Most drugs not tested in advanced liver disease
- Pioglitazone may help steatosis
- Insulin best option if disease severe

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ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- **Comorbidities**
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

- Emerging concerns regarding association with increased morbidity / mortality
- Proper drug selection is key in the hypoglycemia prone

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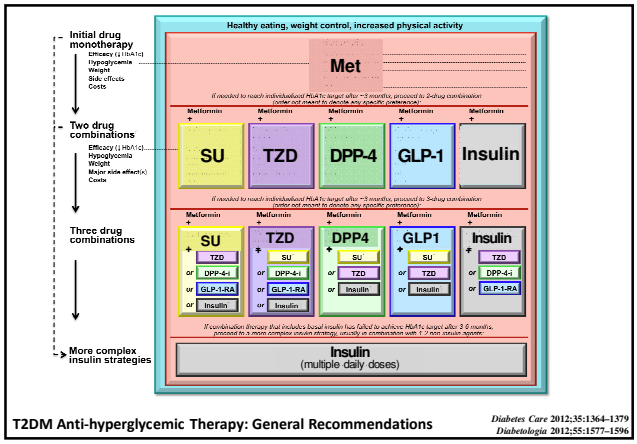

T2DM Anti-hyperglycemic Therapy: General Recommendations

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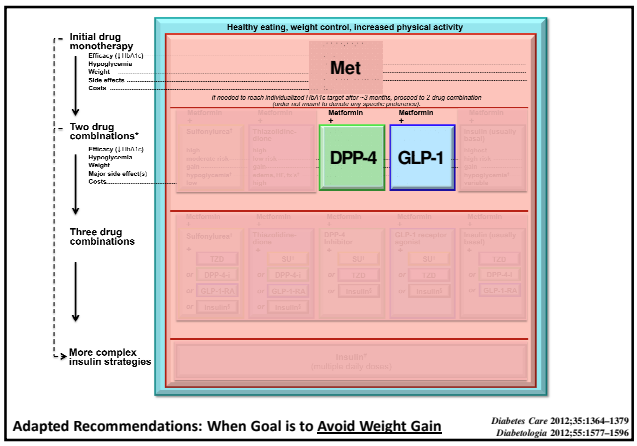

Adapted Recommendations: When Goal is to Avoid Weight Gain

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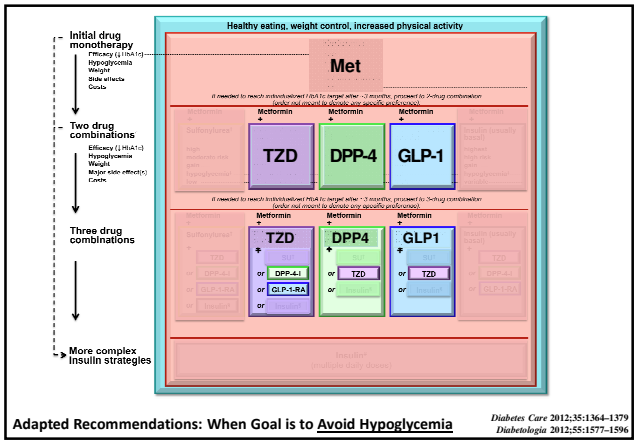

Adapted Recommendations: When Goal is to Avoid Hypoglycemia

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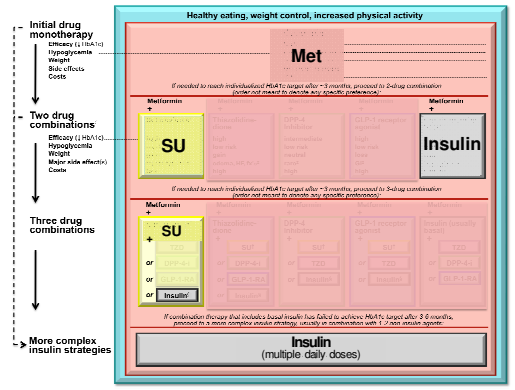

Adapted Recommendations: When Goal is to Minimize Costs

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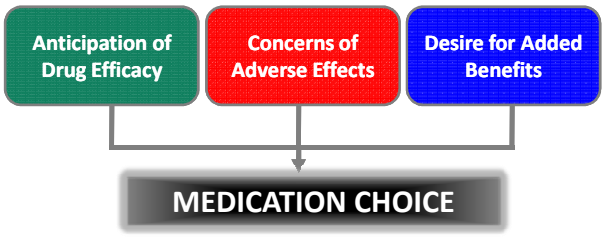
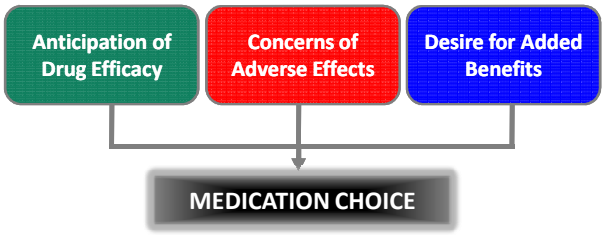
Since We Can't Yet use Patient *Genotype*, We Often Use Patient *Phenotype* to Personalize Therapy



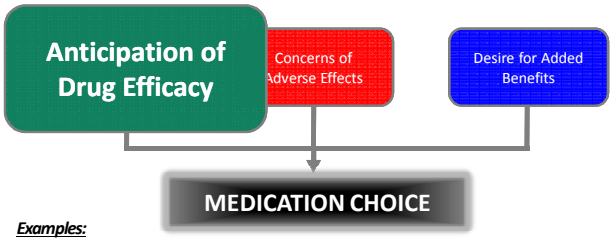
What Phenotypic Features Might Guide Optimal Drug Selection?

Patient Features	*Disease Features*
✓ Age	Stage of disease
✓ Race / ethnicity / sex	Degree of hyperglycemia
✓ Body weight	Fasting *vs.* postprandial hyperglycemia ?
✓ Comorbidities	Insulin deficiency *vs.* insulin resistance ?
Anticipated propensity for or tolerance of side effects	Special circumstances: *MODY, LADA, pancreatic*
'Psycho-social-economic' context of the patient	

Patient Phenotype...Personalized Therapy?



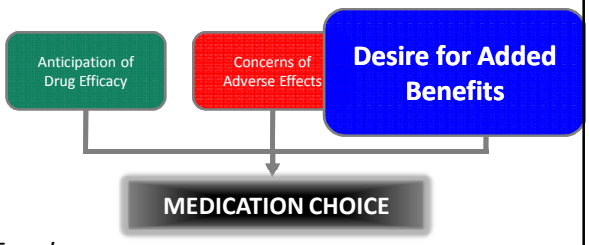
Patient Phenotype...Personalized Therapy?



Examples:

- "A 'glitazone will be highly effective in this patient because he appears to be very insulin resistant."
- "Exenatide is a good option here because of large PPG spikes."
- "Insulin is the only alternative due to her severe degree of hyperglycemia."
- "I just need to drop A1c by about 0.7% . . . a 'gliptin would be a perfect choice!"

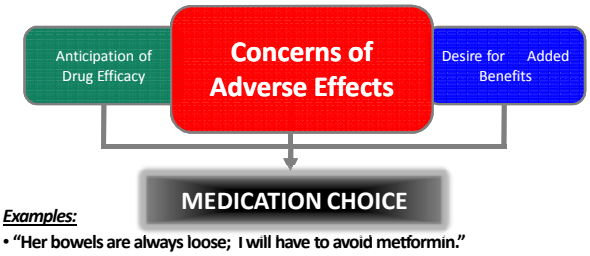
Patient Phenotype...Personalized Treatment?



Examples:

- "I will use a GLP-1 receptor agonist; she has so much weight to lose."
- "That LDL is stubborn! Colesevelam might be a great choice for him."
- "He has CAD (but good LV function); let's try some pio."
- "Chronic constipation? I have just the fix for you!"

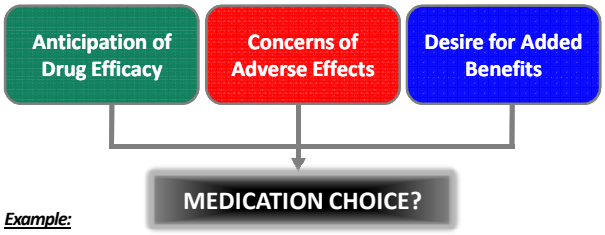
Patient Phenotype...Personalized Treatment?



Examples:

- "Her bowels are always loose; I will have to avoid metformin."
- "She had a hypoglycemic event a few years ago when her husband was alive. He's passed on and she now lives alone - let's avoid SUs."
- "A recent echo shows severe diastolic dysfunction; even though he is without symptoms, I don't feel comfortable using a TZD."
- "He already has gastroparesis; a GLP-1 agonist is a horrible choice for him!"

....But What to Do in the Complex Patient?



Example:

68 y/o WM w/ T2DM x14 yrs on metformin / glimepiride. CAD, OSA, prostate ca,? h/o pancreatitis 6 yrs ago. He smokes and his brother has carcinoma of the bladder. Exam: BMI 41.3, 2+ edema, but no heart failure. FBG 150–170mg/dl (8–10mmol/L), HbA1c 9.8%, eGFR 44; LDL 122, TG 358, HDL 31, on atorvastatin 40 mg.

What are his options at this stage of disease? Target? Strategies?

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

KEY POINTS

- Glycemic targets & BG-lowering therapies must be individualized.
- Diet, exercise, & education: foundation of any T2DM therapy program
- Unless contraindicated, metformin = optimal 1st-line drug.
- After metformin, data are limited. Combination therapy with 1-2 other oral / injectable agents is reasonable; minimize side effects.
- Ultimately, many patients will require insulin therapy alone / in combination with other agents to maintain BG control.
- All treatment decisions should be made in conjunction with the patient (focus on preferences, needs & values.)
- Comprehensive CV risk reduction - a major focus of therapy.

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ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

For Discussion....

- **How often should such guidelines be rewritten?**
- **What key data will be needed to inform future guidelines?**
- **What impact will the large incretin/CVD trials (if positive) have on future guidelines?**
- **Where will emerging drugs fit in (e.g. SGLT-2 inhibitors)?**
- **Where does bariatric surgery fit in?**
- **Where do anti-obesity drugs fit in?**

GRADE Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study