

Multiple Small Feedings of the Mind: Diabetes

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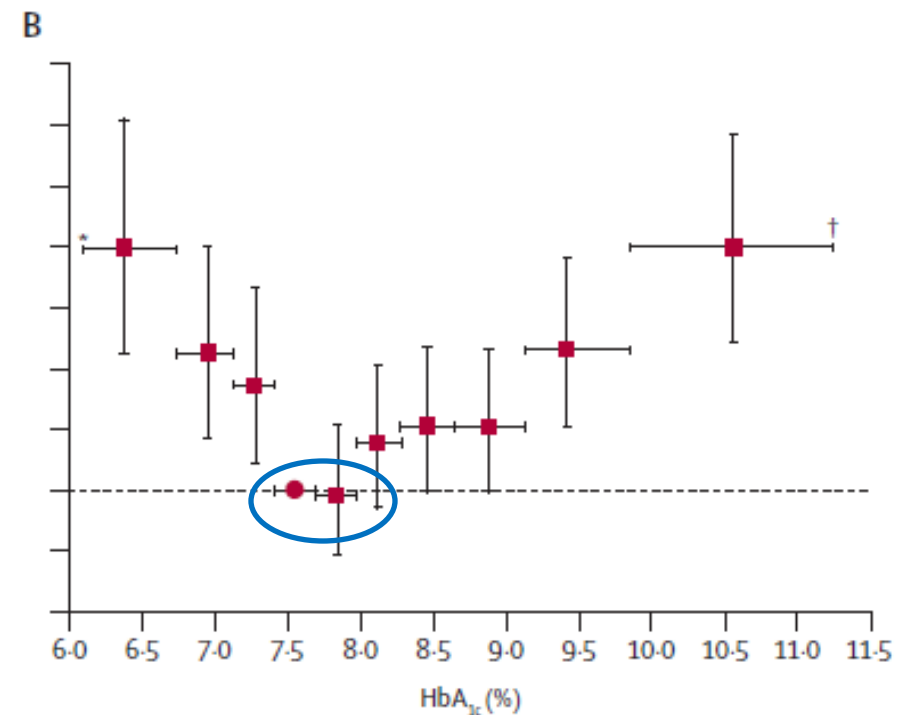
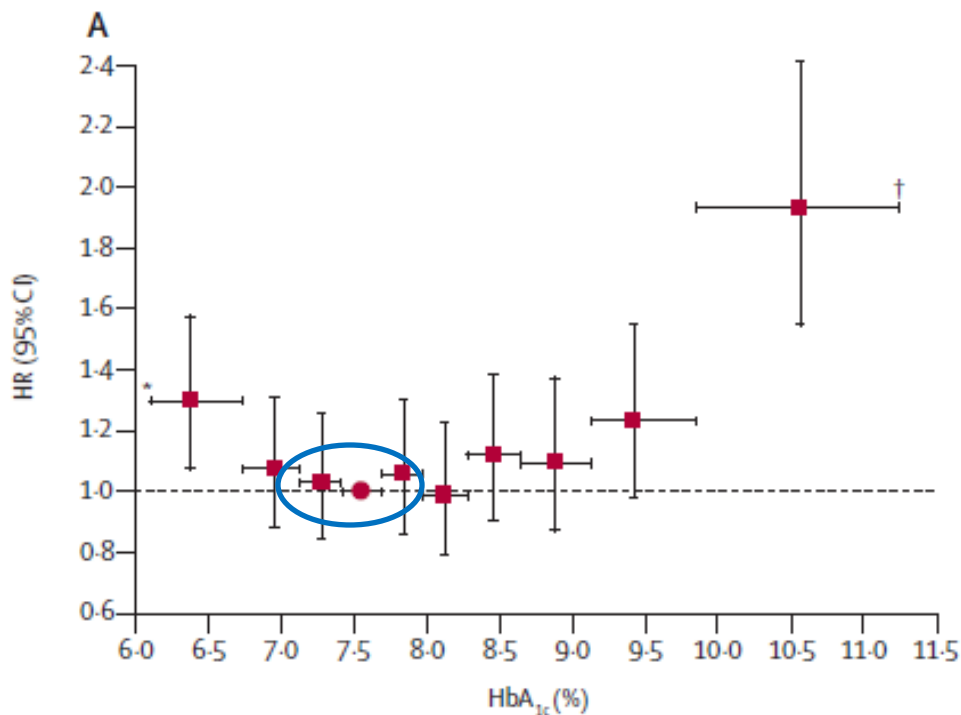
Question 1: Setting A1c Goals

- Describe the evidence based approach to determining the target HgbA1c in different populations.
- What does the evidence reveal regarding mortality and morbidity in relation to HgbA1c?

Survival vs A1c in Type 2 Diabetes

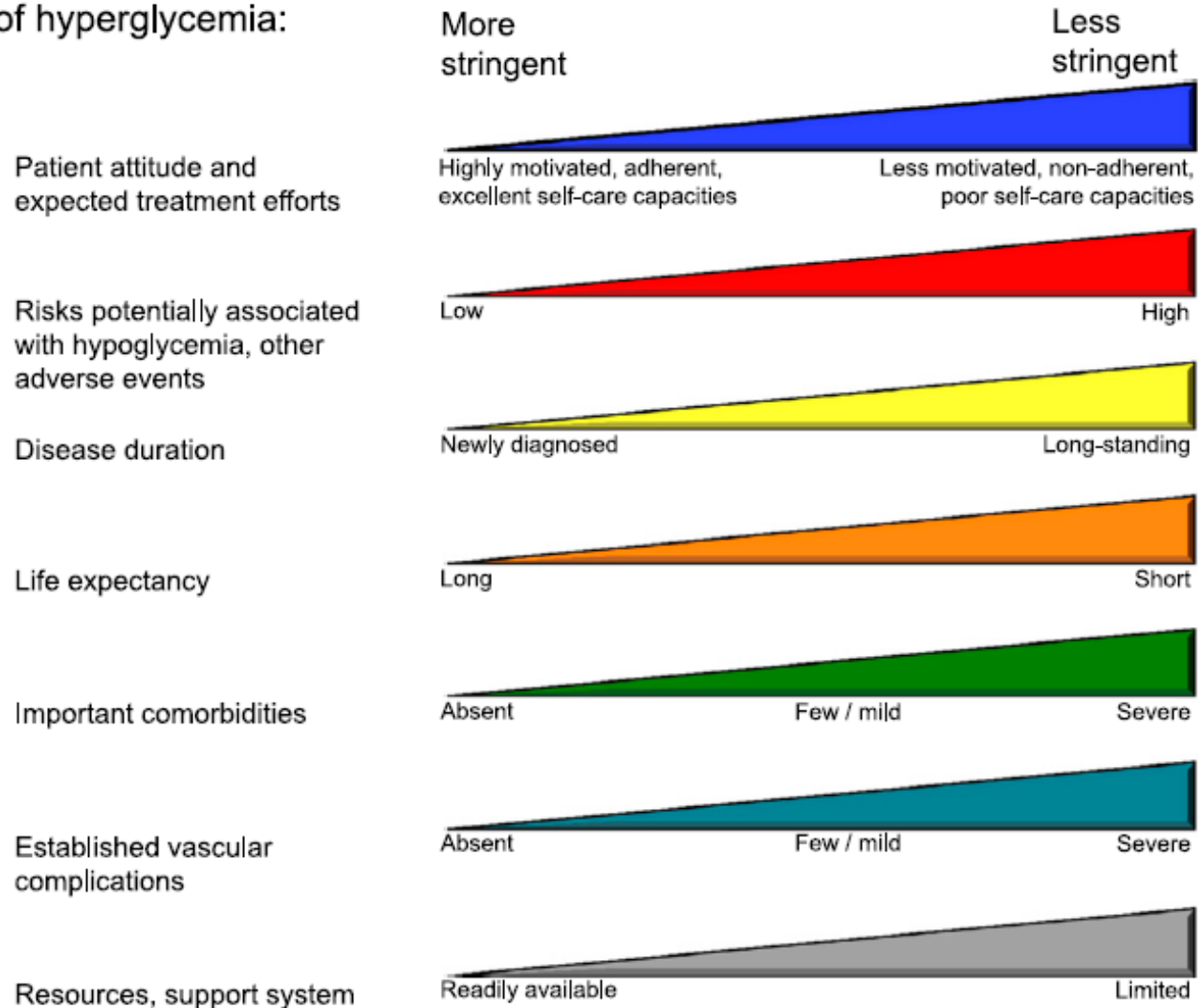
Cohort #1: patients using oral medications

Cohort #2: patients using insulin



ADA (2012)

Approach to management of hyperglycemia:



American Geriatrics Society (2012)

Patient Health Status	Rationale	Reasonable A1c Goal
Healthy	Longer remaining life expectancy	<7.5%
Complex/ Intermediate	<ul style="list-style-type: none">•Intermediate remaining life expectancy•high treatment burden•hypoglycemia vulnerability•fall risk	<8.0%
Very complex/ poor health	Limited remaining life expectancy makes benefit uncertain	<8.5%

Predictors of CVD Events: VADT

Parameter	Hazard Ratio	P Value
Age	1.041	<0.0001
Prior CVD Event	3.565	<0.0001
HDL	0.442	<0.0001
Recent Severe Hypoglycemia*	2.232	0.0086

*within 3 months

Predictors of Mortality: ACCORD

<u>Parameter</u>	<u>Hazard Ratio (CI interval)</u>
Severe Hypoglycemia*	
Intensive Arm	1.41 (1.03 to 1.93)
Standard Arm	2.30 (1.73 to 4.76)
Self-reported neuropathy	1.95 (1.41 to 2.69)

*Needing help of another person

30-second message

Tight Control (<7% or lower)

- Young
- Short duration of diabetes
- Low risk of hypoglycemia

Less Intensive Control (7-8% or even higher)

- Older
- Longer duration of diabetes
- History of severe hypoglycemia or unawareness
- Significant co-morbidities, such as vascular disease
- Significant microvascular disease, particularly neuropathy
- Shorter life expectancy

Question 1: Setting A1c Goals

- What does the evidence reveal regarding mortality and morbidity in relation to HgbA1c?

U-shaped

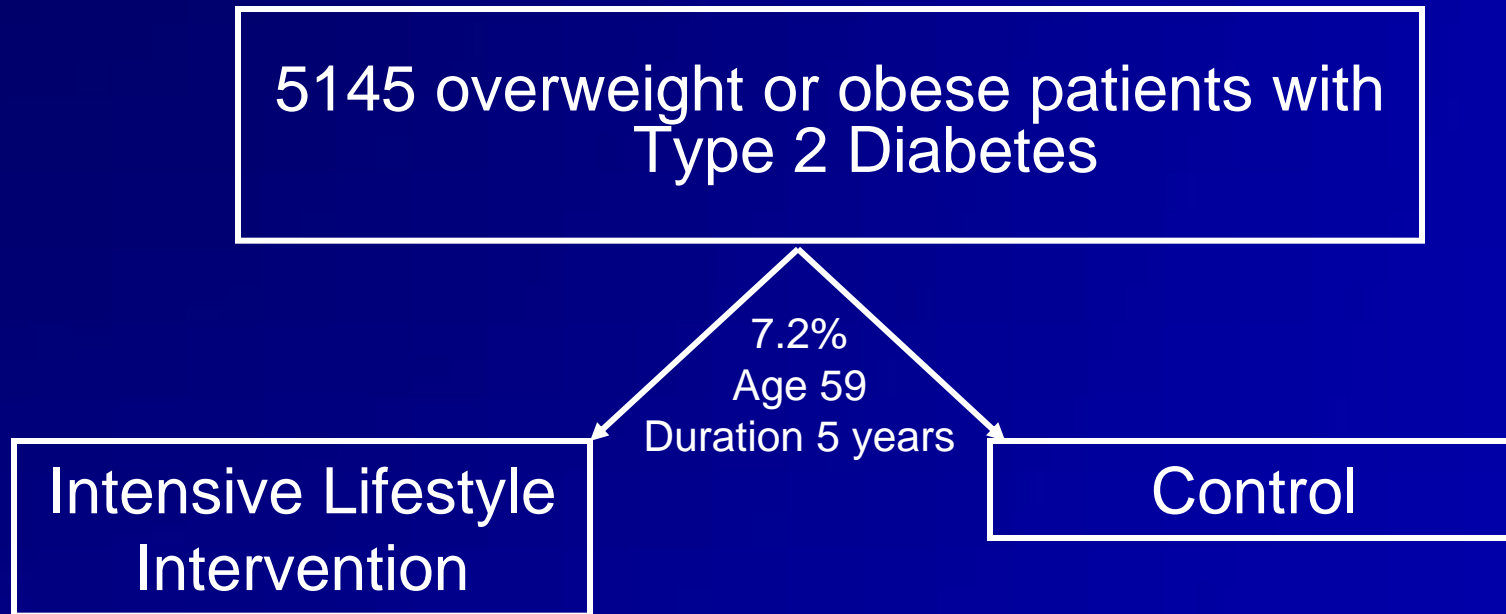
- Describe the evidence based approach to determining the target HgbA1c in different populations.

Individualize

Question 2: Lifestyle Modification

- What is the evidence regarding the long term effects of dietary modifications and exercise in patients with type 2 diabetes?
- What happens if my patient already has complications such as neuropathy, retinopathy, CVD – can they still be referred for exercise and if so what is the evidence that their outcomes will be improved?

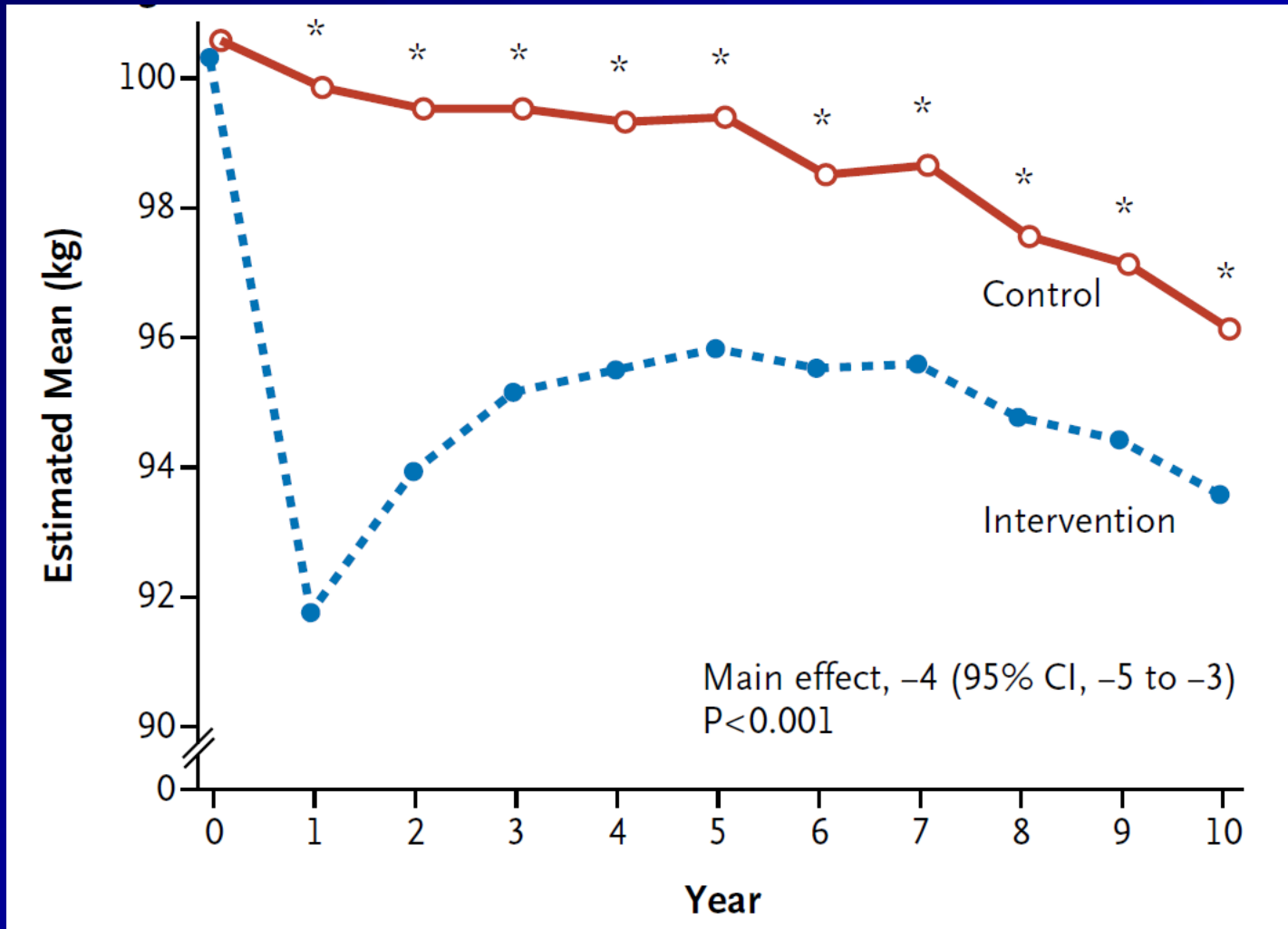
Look AHEAD



Median f/u 9.6 years

Composite of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization for angina

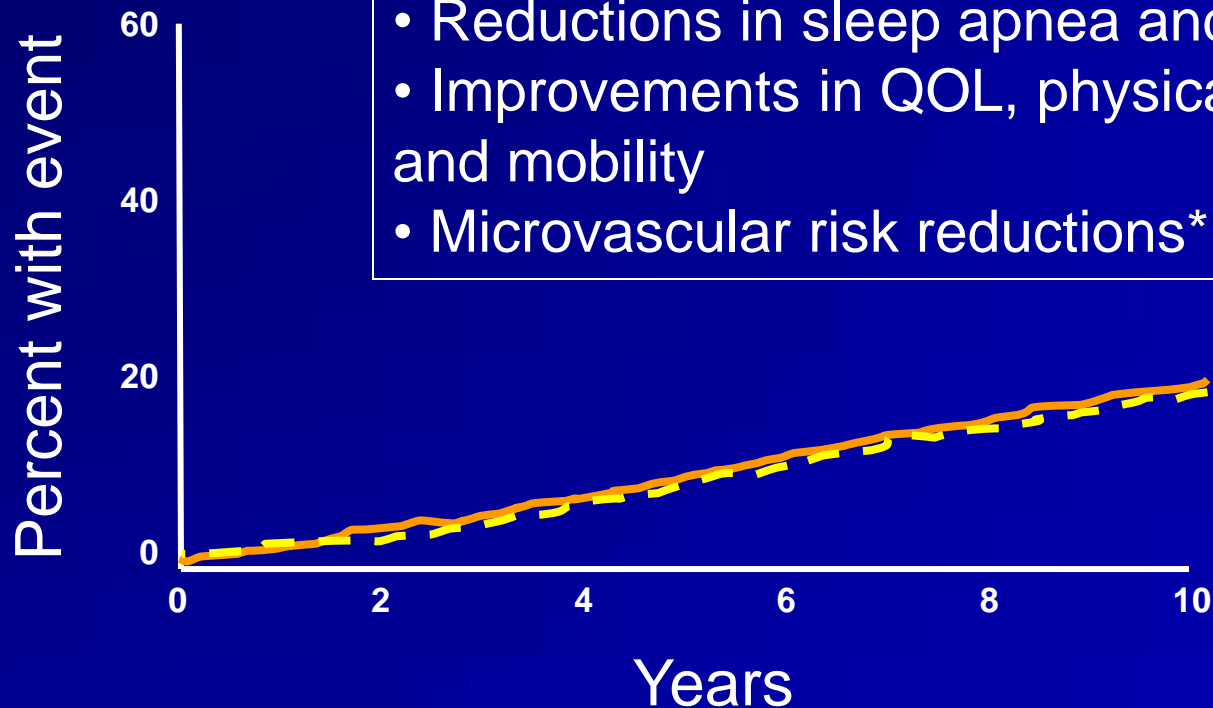
Weight



Primary CVD Outcome

No CVD Risk Reduction, BUT...

- Fewer medications
- Reductions in sleep apnea and depression
- Improvements in QOL, physical functioning and mobility
- Microvascular risk reductions* (renal/eye)



Look AHEAD Baseline Disease

- 14% participants with CVD at baseline
- CVD risk in intervention vs control
 - Nonsignificantly lower in those without baseline CVD
 - Nonsignificantly higher in those with baseline CVD
 - No interaction between the groups ($p=0.06$)
- No reporting of microvascular disease at baseline

Pre-existing Microvascular complications: ADA recommendations

Retinopathy

- PDR or severe NPDR – vigorous aerobic or resistance exercise may be contraindicated

Peripheral Neuropathy

- Moderate intensity walking ok
- Wear proper footwear and examine feet daily
- Foot injury or open sore: restrict to non-weight bearing activities

Autonomic Neuropathy

- Undergo cardiac investigation

Albuminuria/Nephropathy

- No restrictions

Question 2: Lifestyle Modification

- What is the evidence regarding the long term effects of dietary modifications and exercise in patients with type 2 diabetes?

May not live longer, but live better.

- What happens if my patient already has complications such as neuropathy, retinopathy, CVD – can they still be referred for exercise and if so what is the evidence that their outcomes will be improved?

Yes. Paucity of evidence.

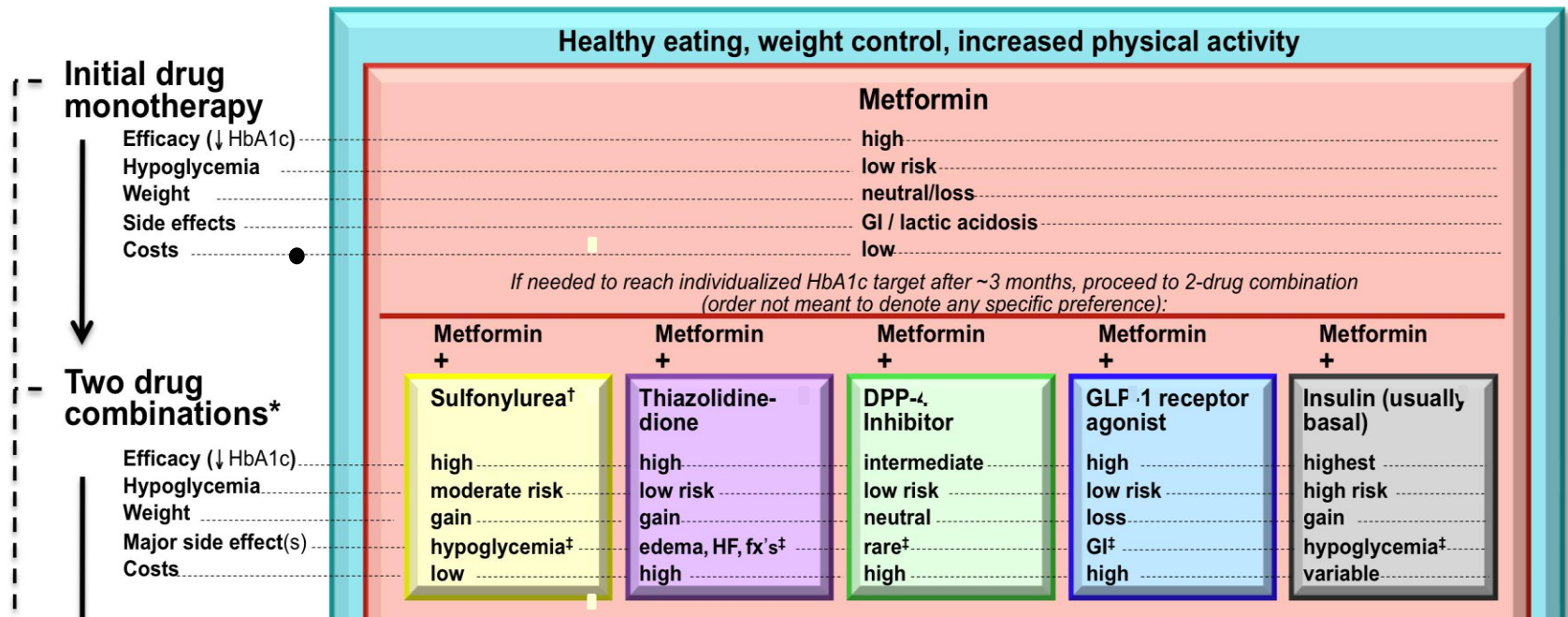
Question 3: Oral Agents

- What “oral” agents are reasonable to use when metformin is not enough? Which have the best efficacy and which the best safety profiles?
- What is the role of the glitazones?

FDA-Approved “Oral” Hypoglycemic Agents

- Acarbose
- Alogliptin (Nesina)
- Bromocriptine (Cycloset)
- Canagliflozin (Invokana)
- Chlorpropamide
- Colesevelam (Welchol)
- Dapagliflozin (Farxiga)
- Exenatide (Byetta)
- Exenatide ER (Bydureon)
- Glimepiride
- Glipizide
- Glyburide
- Linagliptin (Trajenta)
- Liraglutide (Victoza)
- Metformin
- Miglitol (Glyset)
- Nateglinide (Starlix)
- Pioglitazone
- Repaglinide (Prandin)
- Rosiglitazone
- Saxagliptin (Onglyza)
- Sitagliptin (Januvia)
- Tolazamide
- Tolbutamide

American Diabetes Association 2012



Equally weighs sulfonylureas, TZDs, DPP-4 inhibitors, GLP-1 receptor agonists and insulin as second line agents

Factors to Consider

- Cost
- Hypoglycemia risk
- Effect on weight
- Medication side effects
- Patient characteristics
 - Age
 - Renal disease
 - Hepatic disease
 - Heart failure
 - Etc

Comparison of Non-Insulin, 2nd-line Agents

Class	Medications	Cost	Hypoglycemia Risk	Weight	↓ A1c (%)
Sulfonylureas	Glipizide Glyburide Glimeperide	\$	Moderate	Increase	1-2
Meglitinides	Repaglinide Nateglinide	\$\$\$\$	moderate	Increase	0.5-1.5
Alpha-Glucosidase Inhibitors	Acarbose Miglitol	\$\$	low	Neutral	0.5-0.8
Thiazoladinediones	Pioglitazone Rosiglitazone	\$\$	low	Increase	0.5-1.4
DPP-4 inhibitors	Sitagliptin Saxagliptin Alogliptin Linagliptin	\$\$\$\$	low	Neutral	0.5-0.8
GLP-1 agonists	Exenatide Exenatide ER Liraglutide	\$\$\$\$	low	Decrease	0.5 – 1 1.5 – 2
SGLT-2 Inhibitors	Canagliflozin Dapagliflozin	\$\$\$\$	low	Decrease	0.7-1

Class	Medications	Side Effects and Patient Considerations	
Sulfonylureas	Glipizide Glyburide Glimeperide	--?Blunts ischemic pre-conditioning (glyburide!) -Lower durability -Reduce dose in renal insufficiency (avoid glyburide!) -Caution if hepatic impairment	
Meglitinides	Repaglinide Nateglinide	--?Blunts pre-ischemic conditioning -Caution if renal insufficiency/hepatic impairment -Consider: boa constrictor diet, travelling salesman, hypoglycemia on SU	
Alpha-Glucosidase Inhibitors	Acarbose Miglitol	-Flatulence, diarrhea -Less A1c lowering -Avoid use if Cr >2 or cirrhosis -Glucose tablets for hypoglycemia!	
TZDs	Pioglitazone Rosiglitazone	-Weight gain -Edema/heart failure (caution with insulin!) -Fractures -?Bladder cancer	
DPP-4 inhibitors	Sitagliptin Saxagliptin Alogliptin Linagliptin	-Less A1c lowering -?Pancreatitis -↑infections (URI/UTI) -renal dose (except linagliptin)	
GLP-1 agonists	Exenatide Exenatide ER Liraglutide	-GI side effects (caution if gastroparesis) -?Pancreatitis -?thyroid cancer (do not use if MEN2 or personal/FHx of medullary thyroid CA) -Caution with renal insufficiency	
SGLT-2 Inhibitors	Canagliflozin Dapagliflozin	-Mycotic genital infections -Osmotic diuresis/volume depletion -Raises LDL	-dose reduce mild renal impairment -contraindicated CrCl <30 -caution in the elderly

Question 3: Oral Agents

- What oral agents are reasonable to use when metformin is not enough? Which have the best efficacy and which the best safety profiles?

Individualize

- What is the role of the glitazones?

Limited