



Glycemic Management of Type 2 Diabetes

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Disclosures

- None

Learning Objectives

- Understand the importance of lifestyle therapy in diabetes management
- Know the classes of antihyperglycemic agents, mechanism of action, benefits and side effects of these agents
- Recognize the importance of individualized treatment goals for diabetic patients

AACE Comprehensive Care Plan

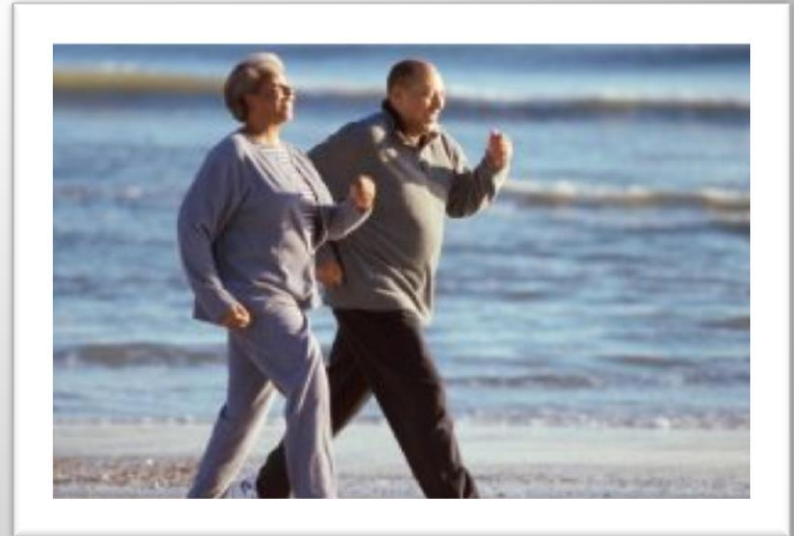
Disease management from
a multidisciplinary team

Antihyperglycemic
pharmacotherapy

Comprehensive
Care Plan

Comprehensive diabetes
self-education for the
patient

Therapeutic lifestyle
change



Glycemic Management of Type 2 Diabetes

THERAPEUTIC LIFESTYLE CHANGE

Components of Therapeutic Lifestyle Change

- Healthful eating
- Sufficient physical activity
- Sufficient sleep
- Avoidance of tobacco products
- Limited alcohol consumption
- Stress reduction



Glycemic Management of Type 2 Diabetes

ANTIHYPERGLYCEMIC THERAPY

Cardiovascular Outcomes Trials: A Brief History

- 2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs
 - Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo
 - Some study designs tested for superiority if noninferiority criteria were met
 - Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke
 - Some primary endpoints included additional components

MACE = major adverse cardiovascular events; RCTs, randomized controlled trials.

FDA. Guidance for industry: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes.
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf>.

Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
α -Glucosidase inhibitors	<ul style="list-style-type: none"> Delay carbohydrate absorption from intestine 	Acarbose Miglitol	Precose or generic Glyset
Amylin analogue	<ul style="list-style-type: none"> Decrease glucagon secretion Slow gastric emptying Increase satiety 	Pramlintide	Symlin
Biguanide	<ul style="list-style-type: none"> Decrease HGP Increase glucose uptake in muscle 	Metformin	Glucophage or generic
Bile acid sequestrant	<ul style="list-style-type: none"> Decrease HGP? Increase incretin levels? 	Colesevelam	WelChol
DPP4 inhibitors	<ul style="list-style-type: none"> Increase glucose-dependent insulin secretion Decrease glucagon secretion 	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
Dopamine-2 agonist	<ul style="list-style-type: none"> Activates dopaminergic receptors 	Bromocriptine	Cycloset
Glinides	<ul style="list-style-type: none"> Increase insulin secretion 	Nateglinide Repaglinide	Starlix or generic Prandin

Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
GLP1 receptor agonists	<ul style="list-style-type: none"> • Increase glucose-dependent insulin secretion • Decrease glucagon secretion • Slow gastric emptying • Increase satiety 	Albiglutide Dulaglutide Exenatide Exenatide XR Liraglutide	Tanzeum Trulicity Byetta Bydureon Victoza
SGLT2 inhibitors	<ul style="list-style-type: none"> • Increase urinary excretion of glucose 	Canagliflozin Dapagliflozin Empagliflozin	Invokana Farxiga Jardiance
Sulfonylureas	<ul style="list-style-type: none"> • Increase insulin secretion 	Glimepiride Glipizide Glyburide	Amaryl or generic Glucotrol or generic DiaBeta, Glynase, Micronase, or generic
Thiazolidinediones	<ul style="list-style-type: none"> • Increase glucose uptake in muscle and fat • Decrease HGP 	Pioglitazone Rosiglitazone	Actos Avandia

GLP1, glucagon-like peptide; HGP, hepatic glucose production; SGLT2, sodium glucose cotransporter 2.

Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

ADA. *Diabetes Care.* 2017;40:S64-S74.

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Current Insulin Options

Type	Basal Insulins	Prandial Insulins	Premixed Insulins
Human	U-100 NPH	U-100 regular human insulin U-500 regular human insulin Technosphere inhaled insulin	U-100 70/30 RHI
Analog	U-100 glargine U-100 glargine equivalent* U-100 detemir U-100 degludec U-200 degludec U-300 glargine	U-100 lispro U-100 aspart U-100 glulisine U-200 lispro	U-100 50/50 lispro U-100 70/30 aspart U-100 75/25 lispro U-100 70/30 degludec/aspart

- Analogue insulins are associated with less hypoglycemia than human insulins, although these differences are not always statistically significant

*In the US, U-100 glargine equivalent is not approved as a biosimilar product.

Singh SR, et al. *CMAJ*. 2009;180:385-397. Drugs@FDA. <http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA>. FDA.
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm477734.htm>.

Fixed-Dose Oral Combination Agents for Type 2 Diabetes

Class	Added Agent	Available as
DPP4 inhibitor + SGLT-2 inhibitor	Linagliptin + empagliflozin	Glyxambi
	Saxagliptin + dapagliflozin	Qtern
Metformin + DPP4 inhibitor	Alogliptin	Kazano
	Linagliptin	Jentadueto
	Sitagliptin	Janumet
Metformin + glinide	Repaglinide	Prandimet
Metformin + SGLT2 inhibitor	Canagliflozin	Invokamet
	Dapagliflozin	Xigduo XR
Metformin + sulfonylurea	Glipizide	Metaglip and generic
	Glyburide	Glucovance and generic
Metformin + thiazolidinedione	Pioglitazone	ACTOplus Met
	Rosiglitazone*	Avandamet
Thiazolidinedione + DPP4 inhibitor	Pioglitazone + alogliptin	Oseni
Thiazolidinedione + sulfonylurea	Pioglitazone	Duetact
	Rosiglitazone	Avandaryl

Fixed-Ratio Injectable Combination Agents Available for Type 2 Diabetes

GLP1 receptor agonist +	Basal insulin	Available as
Liraglutide +	Degludec	Xultophy
Lixisenatide +	Glargine	Soliqua

Antihyperglycemic Agent Considerations

SE

- Hypoglycemia, Weight, Renal/GU, GI Sx, Cardiac, Bone, Ketoacidosis

A1c

- Reduction

Individualize

- Elderly
- Serious Illness

Cost

- Insurance formulary
- Medicare
- Uninsured

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contrain- dicated if eGFR < 30 mL/ min/1.73 m ²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/ 1.73 m ² Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Possible Benefit of Liraglutide	Possible Benefit of Empagliflozin	Possible Risk for Saxagliptin and Alogliptin	Neutral	Moderate	More CHF Risk	Neutral	Neutral	More CHF Risk	Neutral
CARDIAC*		Possible CV Benefit	Possible CV Benefit	Neutral		May Reduce Stroke Risk	?	Benefit	Safe	Neutral	
ASCVD											
BONE	Neutral	Neutral	Canagliflozin Warning	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Occurring in T2D in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral



Few adverse events or possible benefits



Use with caution



Likelihood of adverse effects



Uncertain effect

* FDA indication to prevent CVD death in diabetes plus prior CVD events

Metformin

Neutral

- Hypoglycemia
- Cardiac
- Bone
- Ketoacidosis

Possible Benefits

- Weight loss

Adverse Effects

- Gastrointestinal

Contraindications

- eGFR <30 ml/min/1.73m²

Glucagon-like Peptide 1 Receptor Agonists (GLP1 Ras)

Neutral

- Hypoglycemia
- Bone
- Ketoacidosis

Possible Benefits

- Weight loss
- Renal/Genitourinary (liraglutide)
- CHF (liraglutide)
- ASCVD

Adverse Effects

- Gastrointestinal

Contraindications

- eGFR <30 ml/min/1.73m² (exenatide)

Sodium Glucose Cotransporter 2 Inhibitors (SGLT2is)

Neutral

- Hypoglycemia
- Gastrointestinal

Possible Benefits

- Weight loss
- Renal (empagliflozin)
- CHF
- ASCVD (empagliflozin)

Adverse Effects

- Bone (canagliflozin)
- DKA
- Genital mycotic infections

Contraindications

- eGFR <45 ml/min/1.73m²

Dipeptidyl Peptidase 4 Inhibitors (DPP4is)

Neutral

- Hypoglycemia
- Weight loss
- ASCVD
- Bone
- Ketoacidosis
- Gastrointestinal

Possible Benefits

- Reducing albuminuria

Adverse Effects

- Renal dose adjustment (except linagliptin)
- CHF (possible saxagliptin and alogliptin)
- Possible pancreatitis

Contraindications

Secretagogues (SU, GLN)

Neutral

- Gastrointestinal
- Bone
- Ketoacidosis

Possible Benefits

- Reduced microvascular and macrovascular complications*
- Inexpensive

Adverse Effects

- Hypoglycemia
- Weight gain
- CHF

Contraindications

Thiazolidinediones (TZDs)

Neutral

- Hypoglycemia
- Renal
- Gastrointestinal
- Ketoacidosis

Possible Benefits

- May reduce stroke risk

Adverse Effects

- Moderate fracture risk
- Weight gain
- CHF

Contraindications

Alpha Glucosidase Inhibitors (AGIs)

Neutral

- Hypoglycemia
- Cardiac
- Bone
- Ketoacidosis
- Weight loss
- Renal

Possible Benefits

Adverse Effects

- Gastrointestinal

Contraindications

Colesevelam and Bromocriptine Mesylate

Neutral

- Hypoglycemia
- Weight
- Bone
- Ketoacidosis
- CHF

Possible Benefits

- ASCVD

Adverse Effects

- Gastrointestinal

Contraindications

Insulin

Neutral

- GI
- ASCVD
- Bone
- Ketoacidosis

Possible Benefits

Adverse Effects

- Hypoglycemia
- Weight gain
- CHF risk

Contraindications

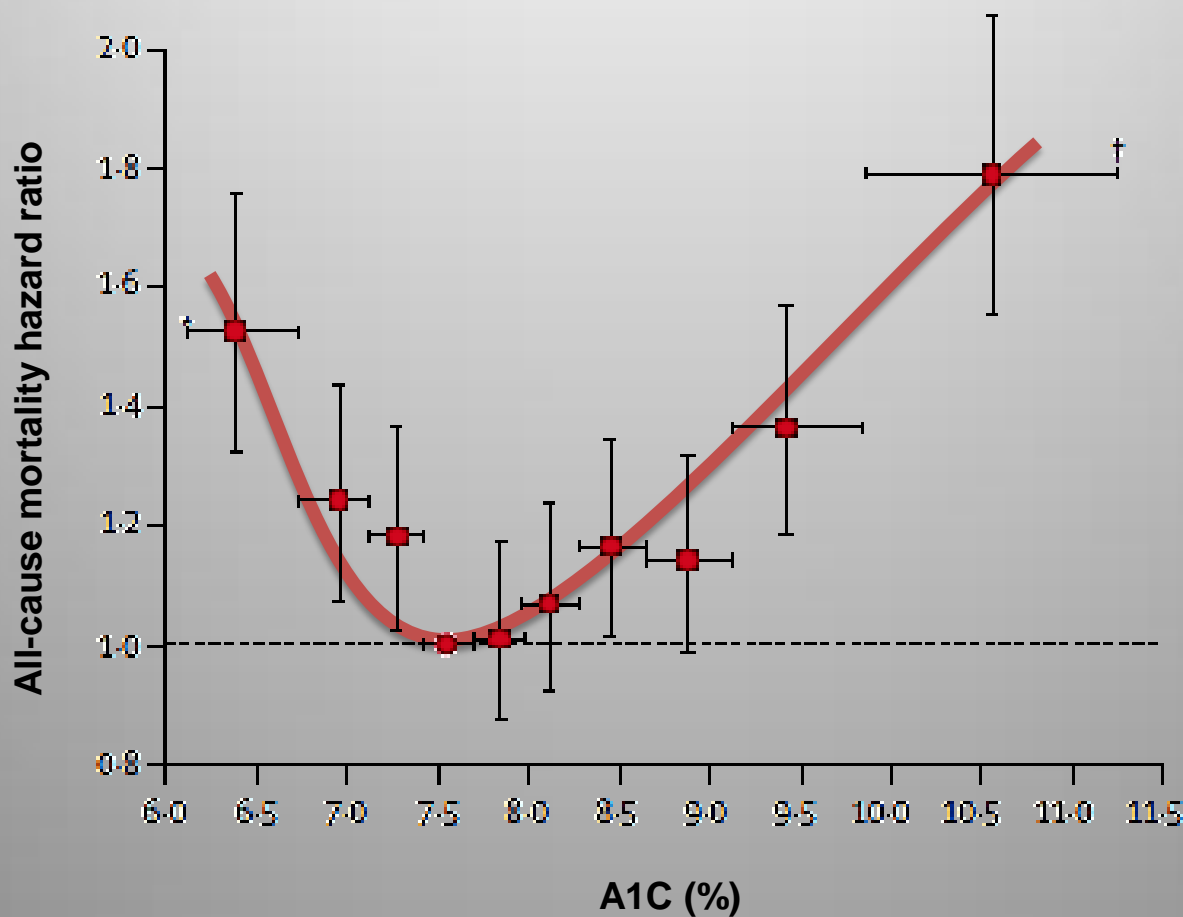


Glycemic Management of Type 2 Diabetes

REDUCING COMPLICATIONS

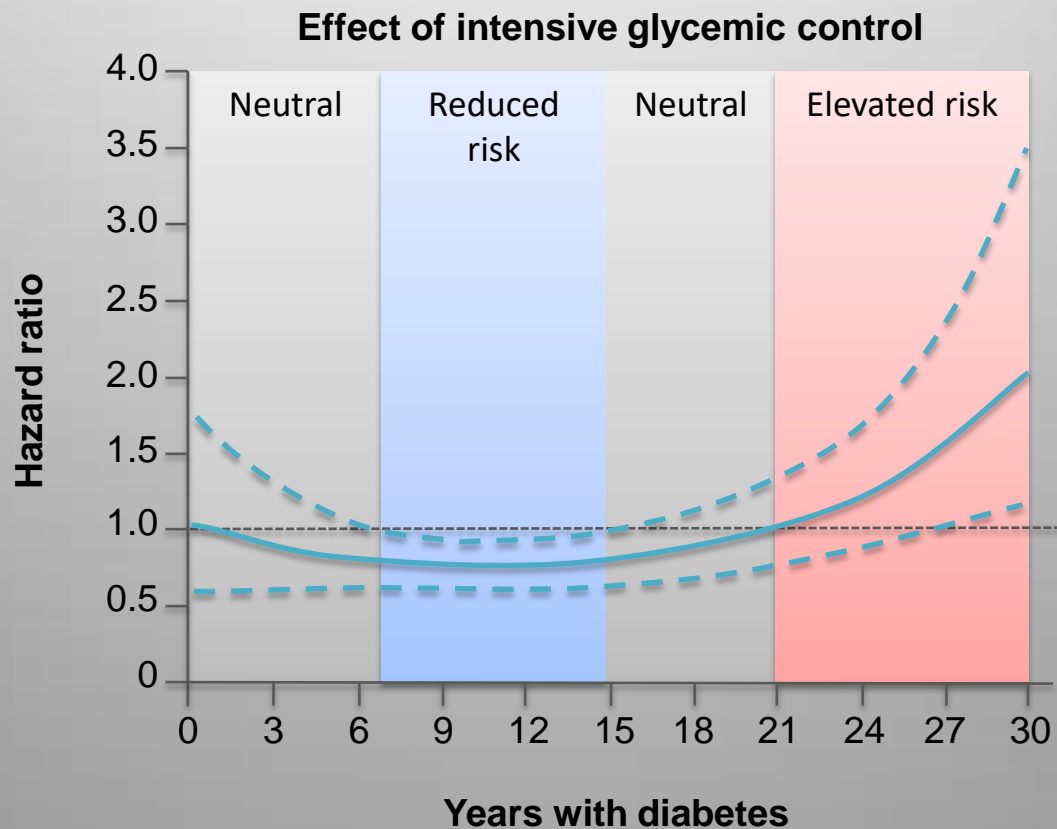
A1C and Mortality in Clinical Practice

Retrospective Cohort Study
(N=27,965)



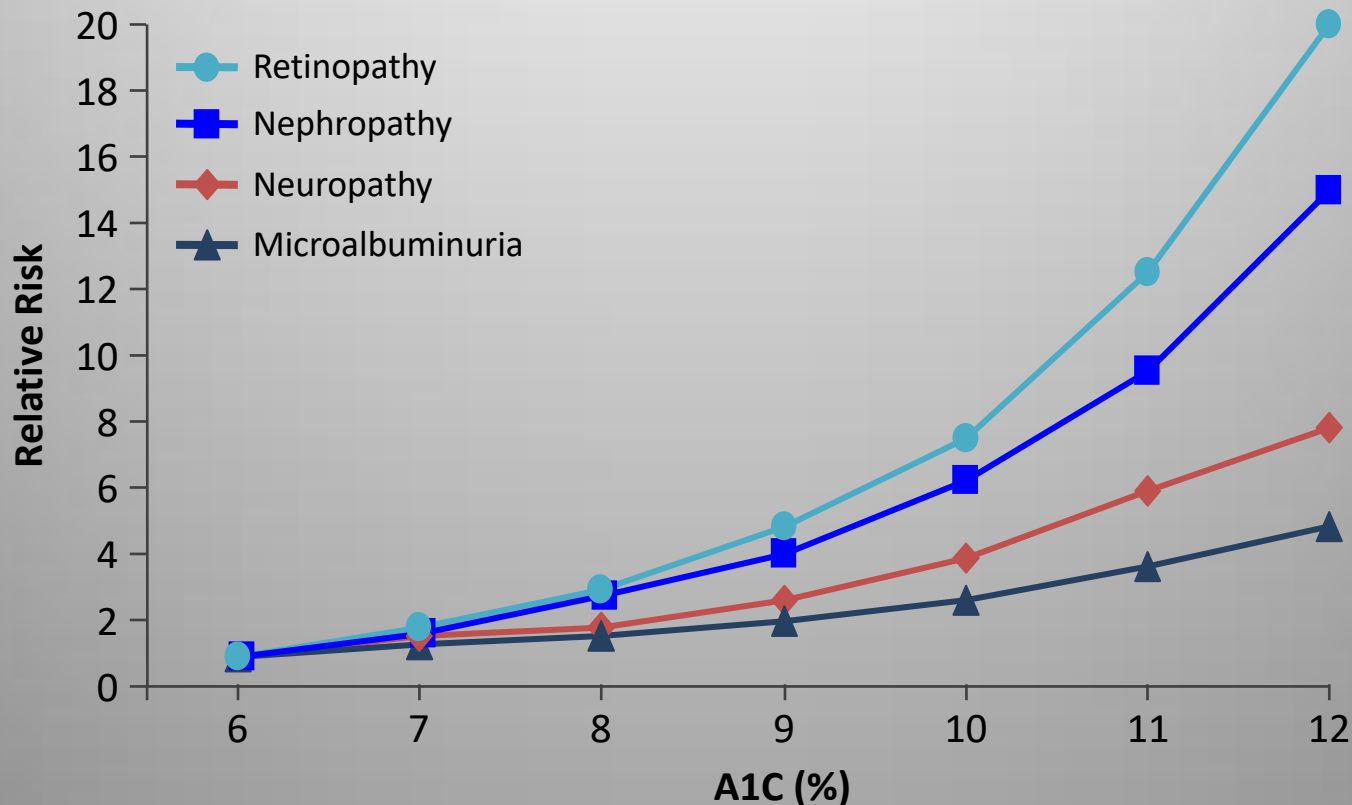
Macrovascular Benefits of Glycemic Control Depend on Duration of Diabetes

Veterans Affairs Diabetes Trial



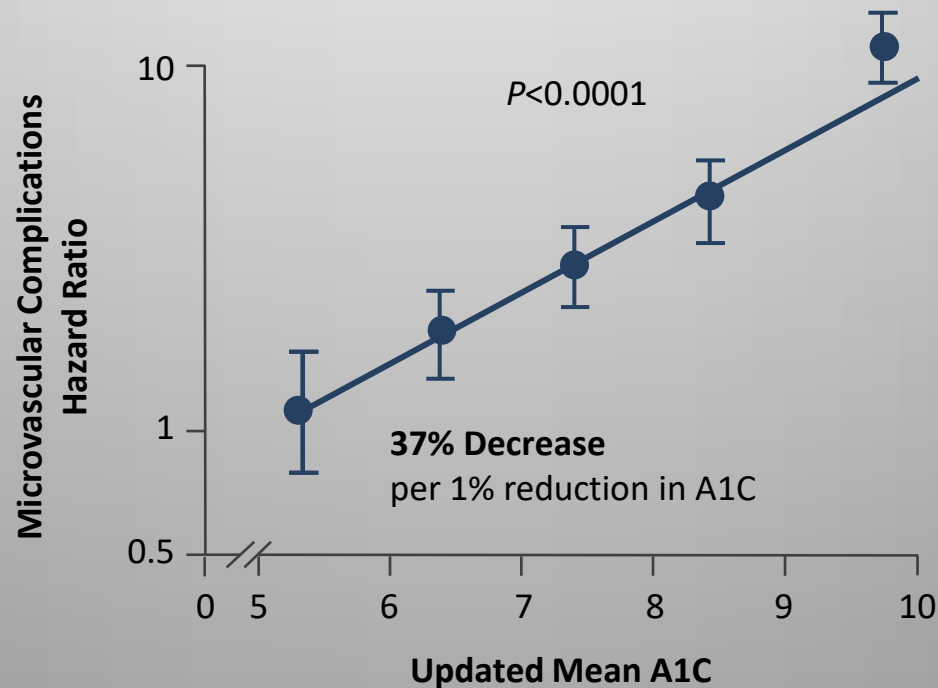
Microvascular Complications Increase With Increasing A1C

Diabetes Control and Complications Trial



Reducing A1C Reduces Microvascular Risk

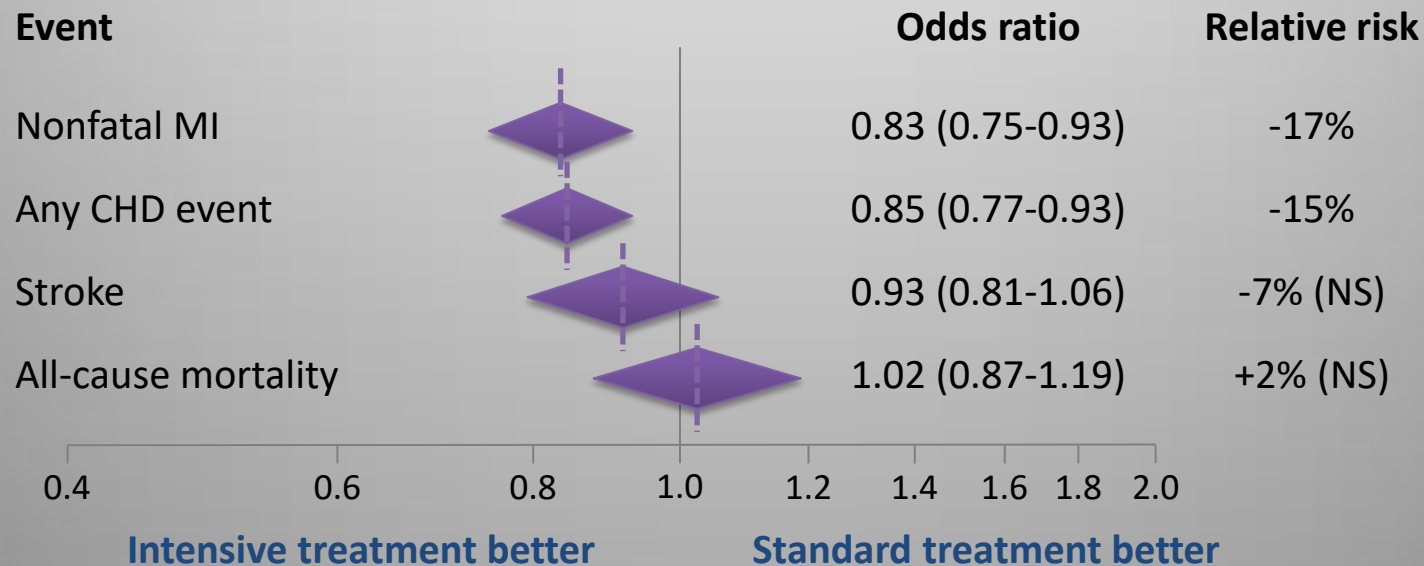
United Kingdom Prospective Diabetes Study



Effects of Intensive Glucose Control on Macrovascular Risk in T2D

Meta-analysis of 5 Prospective RCTs Assessing Effect of Intensive Glucose Lowering on CV Outcomes

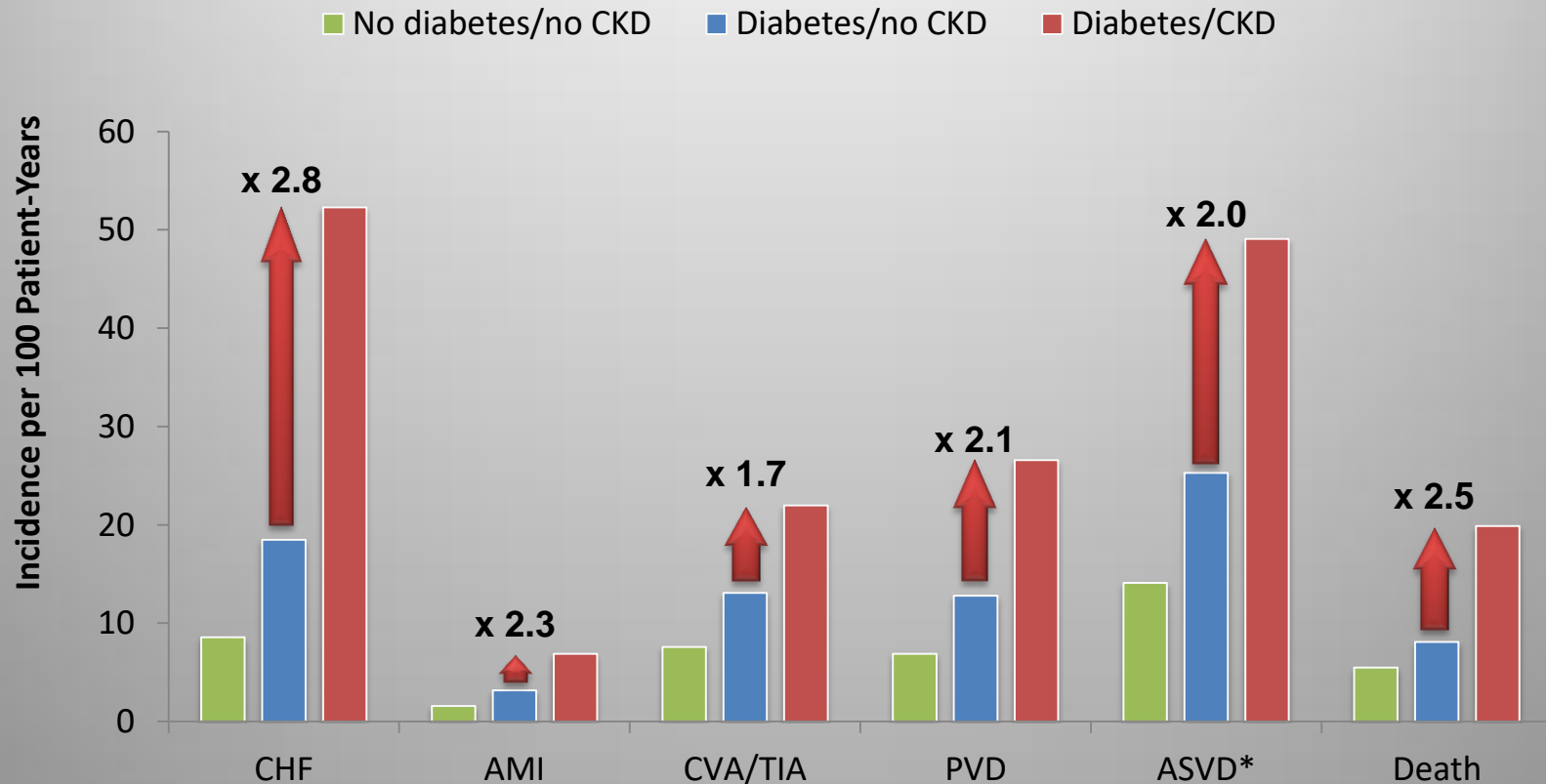
(ACCORD, ADVANCE, PROactive, UKPDS, VADT)



ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation; NS, not significant; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Ray KK, et al. *Lancet*. 2009;373:1765-1772.

CV Risk Increases With Comorbid Diabetes and CKD



AMI, acute myocardial infarction; ASVD, atherosclerotic vascular disease; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PVD, peripheral vascular disease.

*ASVD was defined as the first occurrence of AMI, CVA/TIA, or PVD.

Foley RN, et al. *J Am Soc Nephrol.* 2005;16:489-495.

Macrovascular Risk Reduction in Type 2 Diabetes

- Individualized glucose control
- Hypertension control
- Dyslipidemia control
- Smoking cessation
- Aspirin therapy
- Diagnosis and management of:
 - Autonomic cardiac neuropathy
 - Kidney disease

Vaccinations for Patients with Diabetes

Vaccine, frequency of administration	Patient age
Routine childhood immunizations, according to standard schedule (eg, measles, mumps, rubella, varicella, polio, tetanus-diphtheria)	6 months to 18 years
Influenza, annually	≥6 months
Pneumococcal polysaccharide vaccine	≥2 years
PVC13, 1-2 injections	2-18 years
PPSV23, 1 injection	19-64 years
PVC13 plus PPSV23, 1 injection each, in series	≥65 years
Hepatitis B, 1 injection	20-59 years*
Tetanus-diphtheria booster, every 10 years in adults	≥19 years
Individuals not already immunized for childhood diseases and those requiring vaccines for endemic diseases should be immunized as required by individual patient needs	Any age
*Consider for patients ≥60 based on assessment of risk and likelihood of adequate immune response.	



Glycemic Management of Type 2 Diabetes

SPECIAL DISEASE MANAGEMENT CONSIDERATIONS

Management of Diabetic Nephropathy

- Optimal control of blood pressure, glucose, and lipids
- Smoking cessation
- RAAS blockade
 - ACE inhibitor, ARB, or renin inhibitor
 - Do not combine RAAS blocking agents
 - Monitor serum potassium
- Nephrologist referral
 - Atypical presentation
 - Rapid decline in eGFR or albuminuria progression
 - Stage 4 CKD

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAAS = renin angiotensin aldosterone system.

Handelsman YH, et al. *Endocr Pract.* 2015;21(suppl 1):1-87.

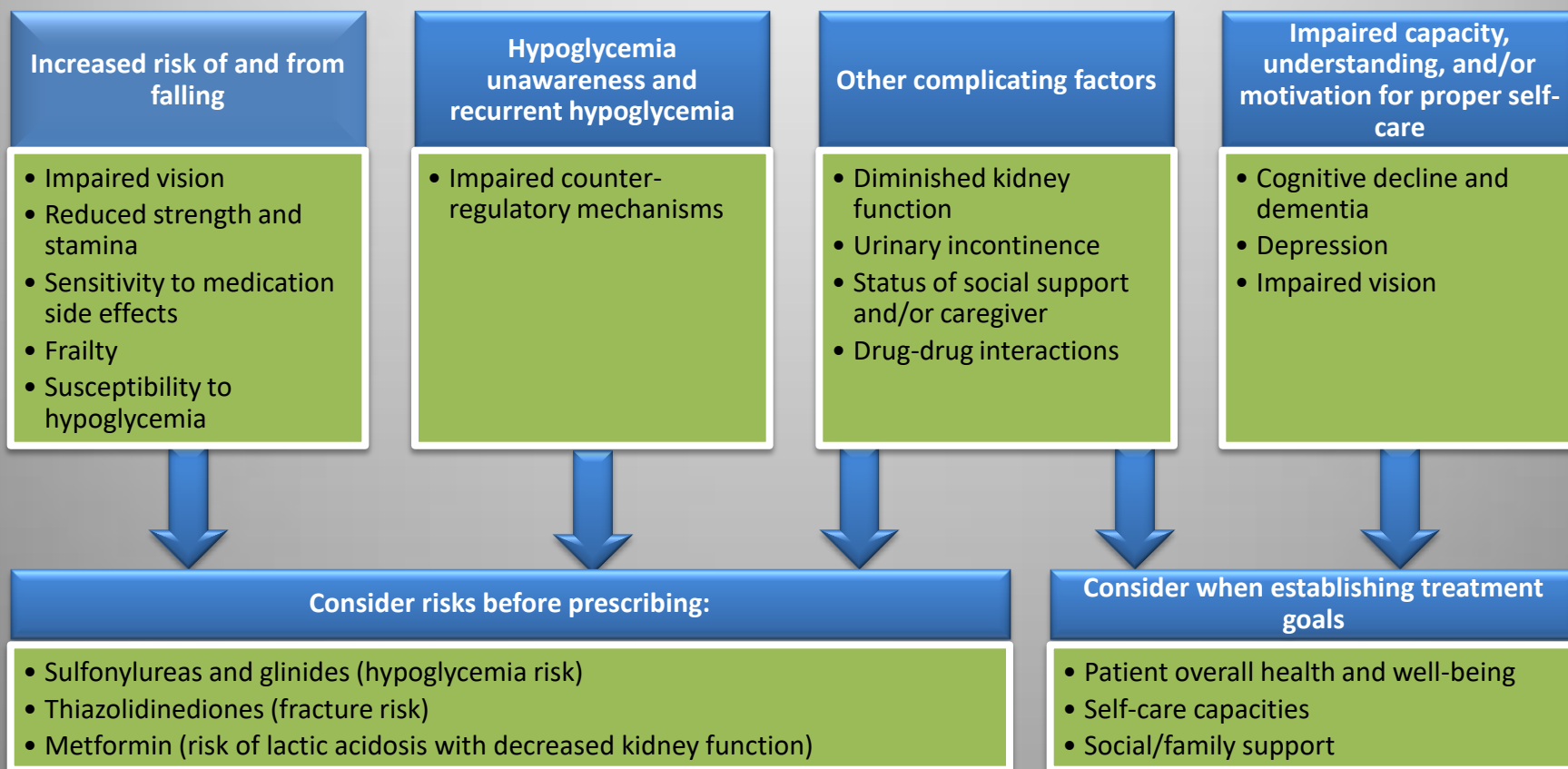
DKD Risk Factor Management

Risk Factor	Goal	Management Recommendation
Hyperglycemia	Individualized A1C goals ≤6.5% for most (AACE) ~7.0% (NKF)	Avoid metformin in moderate to severe CKD Consider need for dose reductions and/or risk of hypoglycemia and other renal-related AEs with other antidiabetic agents Do not target A1C <7% in patients at risk of hypoglycemia
Hypertension	BP ~130/80 mmHg	Use ACE inhibitor or ARB in combination with other antihypertensive agents as needed
Proteinuria		Use ACE inhibitor or ARB as directed
Dyslipidemia	LDL-C <100 mg/dL, <70 mg/dL an option for high risk	Statin +/- ezetimibe therapy recommended for all patients except those on dialysis (NKF) Fibrate dose reduction may be required

Use of Antihyperglycemic Agents in Kidney Disease

Class: Agent(s)	Kidney Disease Recommendation
Amylin analog: pramlintide	Not recommended for CKD stage ≥ 4
Biguanide: metformin	Contraindicated if SCr >1.5 (men) or 1.4 (women) mg/dL
Bile acid sequestrant: colestevlam	No dosage adjustment
Dopamine-2 agonist: bromocriptine	Use with caution
DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin	Reduce dosage for alogliptin, saxagliptin and sitagliptin if CrCl <50 mg/dL
Glinides: nateglinide, repaglinide	Start at lowest effective dose if GFR <30 mL/min/ 1.73 m ²
GLP-1 receptor agonists: albiglutide, dulaglutide, exenatide, exenatide XR, liraglutide	Exenatide and liraglutide not recommended with GFR <30 mL/min/ 1.73 m ²
α -Glucosidase inhibitors: acarbose, miglitol	Avoid if GFR <25 (miglitol) or <30 (acarbose) mL/min/ 1.73 m ²
Insulin: aspart, detemir, glargine, glulisine, inhaled, lispro, NPH, regular	Adjust dose based on patient response
SGLT inhibitors: canagliflozin, dapagliflozin, empagliflozin	Ineffective if GFR <30 mL/min/ 1.73 m ²
Sulfonylureas: glimepiride, glipizide, glyburide	No dose adjustment for glipizide; start glimepiride conservatively; avoid glyburide and all other SUs
Thiazolidinediones: pioglitazone, rosiglitazone	No dosage adjustment

Management Considerations for Elderly Patients with Diabetes





Glycemic Management of Type 2 Diabetes

OTHER DIABETES TREATMENT MODALITIES

Inhaled Insulin

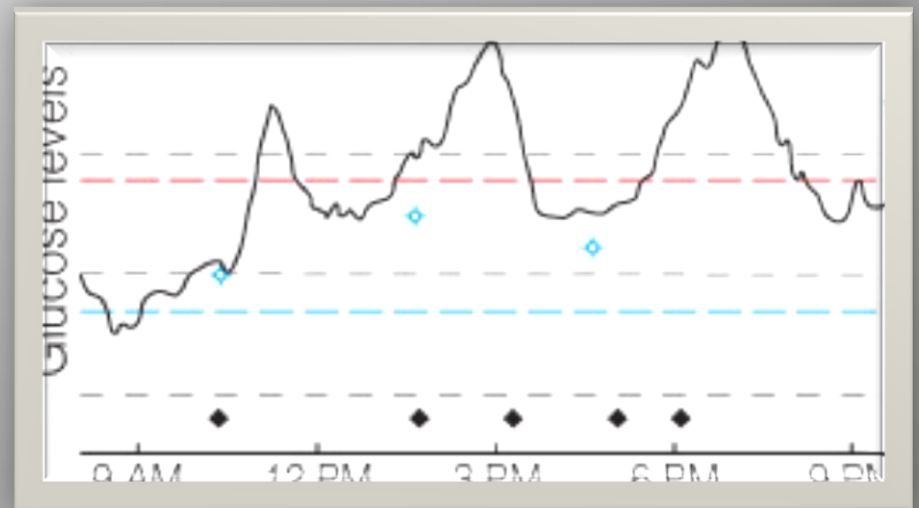
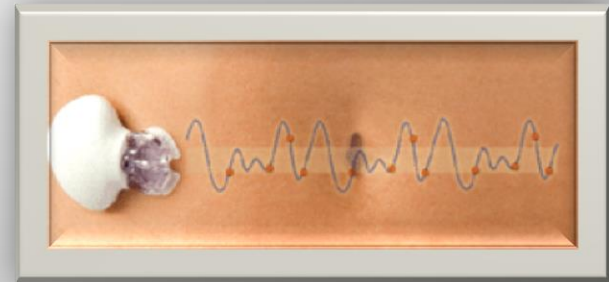
- Inhaled administration
- Rapid-acting insulin
 - Peak levels achieved in ~15 minutes



Safety Considerations with Inhaled Insulin

Lung disease	<ul style="list-style-type: none">• Contraindicated in asthma, COPD, and other chronic lung diseases• Perform spirometry to assess lung function before initiating inhaled insulin, after 6 months of therapy, and annually thereafter, even in the absence of pulmonary symptoms• Do not use in patients with active lung cancer and use with caution in patients with a history of lung cancer or those at risk for lung cancer
Heart failure	<ul style="list-style-type: none">• Observe for signs and symptoms of fluid retention or heart failure, especially when used with TZDs
Hypoglycemia	<ul style="list-style-type: none">• Increase frequency of glucose monitoring

Insulin Pumps and Continuous Glucose Sensors



CSII in Type 2 Diabetes: Patient Candidates

- Absolutely insulin-deficient
- Take 4 or more insulin injections a day
- Assess blood glucose levels 4 or more times daily
- Motivated to achieve tighter glucose control
- Mastery of carbohydrate counting, insulin correction, and adjustment formulas
- Ability to troubleshoot problems related to pump operation and plasma glucose levels
- Stable life situation
- Frequent contact with members of their healthcare team, in particular their pump-supervising physician



Glycemic Management of Type 2 Diabetes

TREATMENT APPROACH

Approach to management of hyperglycemia:

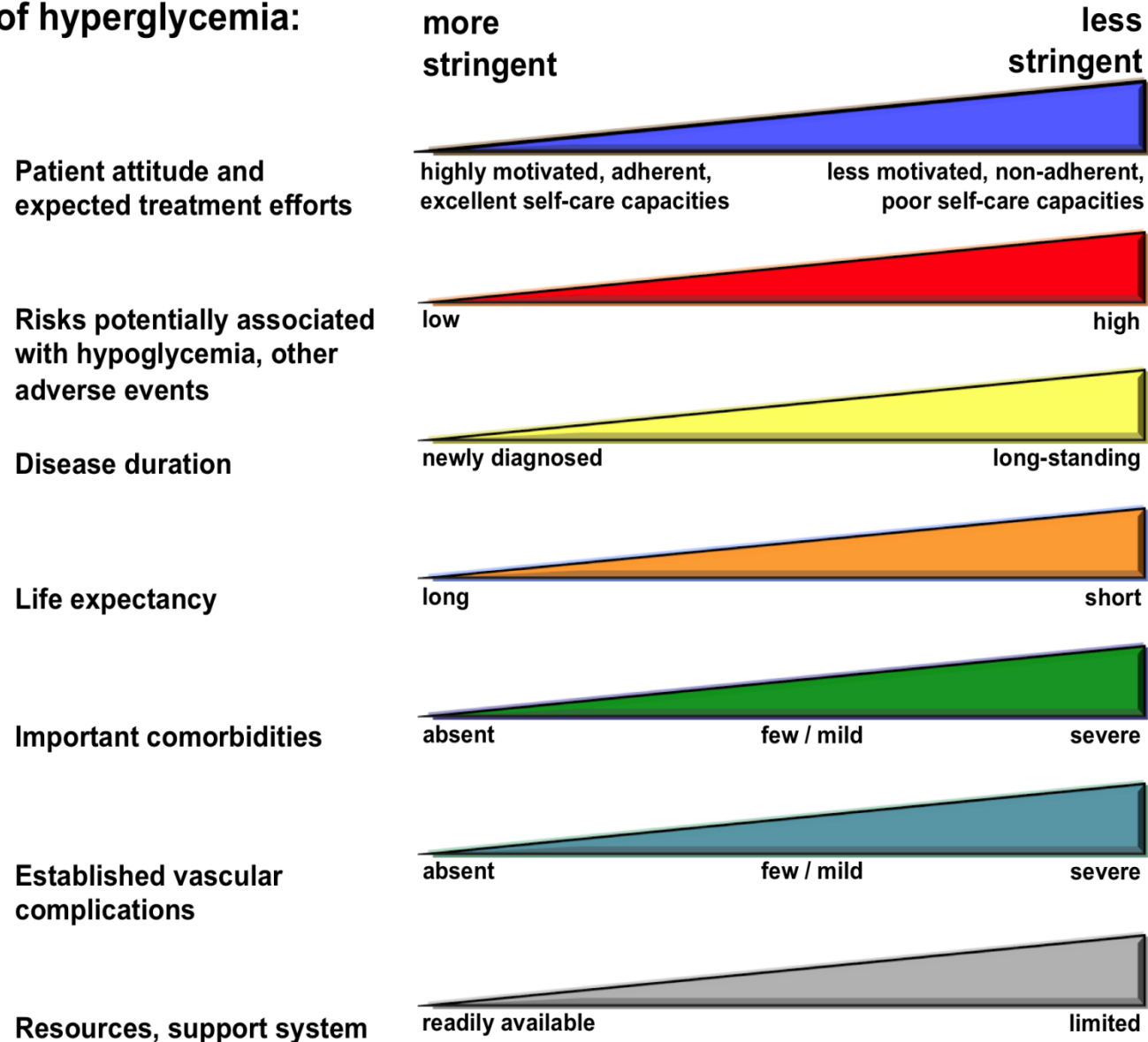


Figure 1

Guidelines for Glycemic, BP, & Lipid Control

	American Diabetes Association Standard of Care 2017 Goals
A1C	<7.0% (Individualization)
Pre-prandial glucose	70-130 mg/dl
Postprandial glucose	<180 mg/dl
Blood pressure	<140/90 mmHg
Lipids	LDL: <100 mg/dl <70 (overt CVD) HDL: >40 mg/dl (males) HDL: >50 mg/dl (females) TG: <150 mg/dl

A1c Reduction

Drug	A1C Reduction
Biguanide	1-1.5%
Sulfonylurea	1-1.5%
GLP-1 Receptor Agonists	1-1.5%
Thiazolidinediones	1-1.5%
DPP-4 Inhibitors	0.5-1%
SGLT2 Inhibitors	0.5-1%
Alpha-glucosidase Inhibitors	0.5-1%
Pramlintide	0.5%
Colesevelam	0.5%
Bromocriptine	0.5%

Entry A1C

Life Style



A1c <
7.5%

Metformin

Recheck 3
months

A1c \geq
7.5%

Metformin
+ OA

Recheck 3
months

A1c >
9%

Metformin
+ 2 agents

Recheck 3
months

A1c not
at goal

Start
Insulin

Entry A1C

Life Style



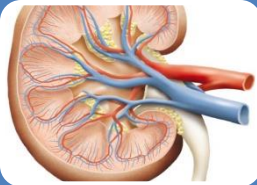
A1C > 9% (Symptomatic)



Start Insulin

- 0.3-0.5 units/kg/day
- 50% basal and 50% bolus
- ↑ basal by 10% if fasting BG > 110 mg% every 3 days
- ↑ prandial by 10% if pre meal BG > 140 mg% every 3 days

Adverse Effects



Renal

- Metformin $< 30 \text{ ml/min/1.73 m}^2$
- Exenatide $< 30 \text{ ml/min/1.73 m}^2$
- Insulin and sulfonylurea - \uparrow hypoglycemic risk



Bone

- Canagliflozin
- Thiazolidinediones



Diabetic Ketoacidosis

- SGLT2 Inhibitors

Adverse Effects



Cardiac

- CHF risk
- Saxagliptin, Alogliptin, TZD, Insulin, SU



Weight Gain

- TZD
- Insulin & SU



GI

- Metformin, GLP-1 RA, AGI
- Bromocriptine, Pramlin

Benefits



Renal

- Liraglutide
- Empagliflozin



Cardiac

- Liraglutide – CHF and ASCVD
- Empagliflozin – CHF
- TZD – may reduce stroke risk
- Colesevelam
- Bromocriptine



Weight loss

- GLP-1 RA
- Pramlintide
- SGLT2i
- Metformin

Non-Insulin Costs

Medication	\$ Cost (30 day supply)
Sulfonylurea	2.30-8.70
Thiazolidinediones	9.00
Metformin	9.10-35.00
Alpha-Glucosidase Inhibitors	48.00-170.00
DPP-4 Inhibitors	195.00-363.00
Bromocriptine	200.00
GLP-1 Receptor Agonists	249.00-626.00
SGLT2 Inhibitors	392.00
Combinations	41.00-576.00
Pramlintide	885.00

MORE



Insulin Costs

Medication	\$ Cost (per unit)
Long Acting (10 ml vial, 3ml pen)	63.00-248.00
Pre-Mix (10 ml vial, 3ml pen)	98.00-265.00
Long Acting + GLP1 (3ml pen)	127.00 -191.00
NPH (10 ml vial, 3ml pen)	138.00
Regular insulin (10 ml vial)	138.00
Rapid Acting (10 ml vial, 3ml pen)	255.00
Inhaled Insulin	279.00



Other Costs

Device	\$ Cost
Glucose meter	20-80
Insulin pen needles	250/yr.
Glucose lancets	270/yr.
Insulin syringes	360/yr.
Glucose strips	1,500/year
Insulin pump	5,500
Insulin pump supplies	1,200/yr.
CGM monitor	1000-1400
CGM sensors	4,800/yr.



Average Diabetes Medical Costs



\$13,700/Year

Summary

1. Lifestyle optimization
2. A1c target individualized
3. Choice of anti-hyperglycemic agents individualized
 - a. Efficacy
 - b. Mechanism of action
 - c. Hypoglycemia risk
 - d. Weight gain
 - e. Adverse effects
 - f. Tolerability
 - g. Likely adherence
 - h. Cost
 - i. Heart, kidney safety
4. Comprehensive management of lipid and blood pressure
5. Therapy evaluated every 3 months, titrate as needed until stable

References

- AACE 2017 Consensus Statement Type 2 Diabetes Management – Endocrine Practice Vol 23 No. 2 February 2017
- Drugs for Type 2 Diabetes – Medical Letter Vol 59 January 16, 2107
- Standard of Medical Care in Diabetes 2017 – Vol 40 Supplement 1