Avoiding Complications in the Diabetic Patient

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Educational Objectives

By completing this educational activity, the participant should be better able to:

1. Describe the incidence and prevalence of various diabetic complications that result from poor control.
2. Identify glycemic goals that are likely to minimize acute and long-term diabetes-related complications.
3. Discuss diabetic complications that can impact patient compliance.
4. Incorporate screening modalities for diabetic patients to avoid complications, including hypoglycemia, foot and eye issues, cardiovascular issues, and nerve and kidney damage, and recognize the importance of achieving control to avoid these complications.

Speaker Disclosure

Dr. Cryar has disclosed that neither he nor members of his immediate family have a relevant financial relationship with an ineligible company.

Avoiding Complications in Patients with Diabetes

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Disclaimers

No conflicts of interest

Opinions presented are personal and not necessarily those of BSWH or its Controlled Affiliates

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Types of Diabetic Complications

Microvascular Disease

- Retinopathy
- Nephropathy
- Neuropathy

Macrovascular Disease

- Coronary artery disease
- Cerebrovascular disease
- Peripheral vascular disease

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Glucose Control

Remains the single most important factor in the development of complication

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Glucose Control

Polyuria and Polydipsia

- Acute symptoms due to hyperglycemia
- Most eventually developed complications

Although intuitive to assume, there was no actual proof that improving glucose levels would prevent or delay the complications

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Does Improved Glucose Control Improve Complications?

Type 2 Diabetes – UK Prospective Diabetes Study (**UKPDS**)

- Randomized, multicenter trial of glycemic therapies in 5,102 patients with newly diagnosed type 2 diabetes from 1977 to 1997

Type 1 Diabetes – Diabetes Control and Complications Trial (**DCCT**)

- Randomized, multicenter trial of intensive insulin therapy in 1,441 patients from 1989 to 1993
- Halted one year early by the oversight committee due to the improved outcomes in the experimental arm

Conclusively proved that better glucose control resulted in decreased incidence or slower progression of diabetic complications

- The only available medications were metformin, sulfonylureas, regular insulin and NPH insulin (along with a few other insulins no longer in use)

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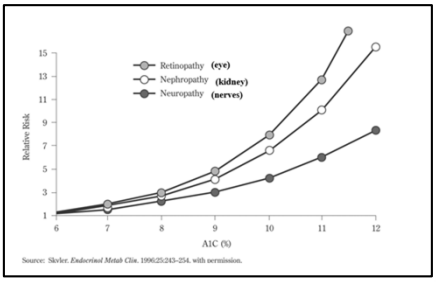
Relationship Between HgbA1c and Complications



Source: Skyler. *Endocrinol Metab Clin.* 1996;25:243–254. with permission.

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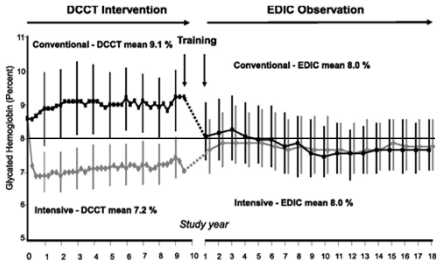
Median HbA1c concentrations during DCCT, the "training" period between DCCT and EDIC, and EDIC. P < 0.001 for INT vs.



David M. Nathan, and for the DCCT/EDIC Research Group Dia Care 2014;37:9-16

American Diabetes Association.

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What about Hypoglycemia?

Hypoglycemia was a limiting factor in the DCCT

- Hyperglycemia symptoms are mostly absent or mild
- Hypoglycemia symptoms are unpleasant, frightening, and, potentially, result in morbidity and mortality

Our toolbox has improved significantly since the 1990s

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Glycemic Goals

A1C goal <7% without significant hypoglycemia is appropriate. A

CGM to assess glycemia, a Time in Range (TIR) of 70% with time below range <4%. B

Less stringent A1C goals (such as <8%) may be appropriate for patients with limited life expectancy, or where the harms of treatment are greater than the benefits. B

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Recommended Blood Sugar Goals for Adults

	People without diabetes	People with Diabetes Suggested ADA* goal
Fasting and before meals	Less than 100 mg/dl	80 - 130 mg/dl
1 to 2 hours after meals	Less than 140 mg/dl	Less than 180 mg/dl
Bedtime	Less than 120 mg/dl	100 - 180 mg/dl
A1C (average blood sugar over past 2 to 3 months)	Less than 5.7	Less than 7

* ADA = American Diabetes Association

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Improvements in Short-acting Insulins

Regular insulin:

- Compared to insulin patterns seen post-prandially in normal individuals
  - Later, lower peak level – missed the meal absorption peak
  - Longer duration – about 6 hours (long enough or overlap with next meal)

Short-acting analogue insulins closely mimic the normal insulin curve

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Improvements in Basal Insulins

NPH Insulin

- Does not last 24 hours, so 2 injections are usually needed
- Has a peak level
  - Sufficient to cover the Noon meal when given at breakfast (NPH/Reg 70/30)
  - When administered at supper or bedtime often cause nocturnal hypoglycemia

Current Basal Insulins

- Provide near constant insulin levels over 24 hours
- Glargine and detemir can have a low peak or not maintain levels a full 24 hours, but this is often subclinical
- Degludec lasts more than 24 hours, has no peak, and maintains a nearly flat insulin level

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Insulin Pump Improvements

Variety and ease of use

- Several types are available and are increasingly user-friendly

Better basal delivery

- Some can be linked with continuous glucose monitoring to adjust the basal rates as insulin needs change during the day due to activity or while the patient is asleep

Prandial insulin dosing

- Insulin pumps are better at determining the precise insulin needed for a meal
- There is now an electronic pen that can determine insulin dosing with same accuracy as an insulin pump (but requires the patient to inject the insulin)

Development of an external, artificial pancreas

- Clinical trials have been conducted with short-term success

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Other Improvements

Medications for Type 2 diabetes are now available that:

- Don't cause hypoglycemia or weight gain
- Although developed for diabetes, have renal and CV benefits and are being prescribed to patients without diabetes for these benefits
- I will cover these as we consider specific complications

Continuous glucose monitoring (CGM) is advancing and becoming mainstream

- The most cost-effective have a daily cost equal to 4-5 fingerstick glucose readings a day
  - Some can continuously upload to the cloud
    - Others can follow the results and contact the patient if the patient is distracted and not noticing an impending problem
  - There is a developing consensus on how to best interpret the information they provide

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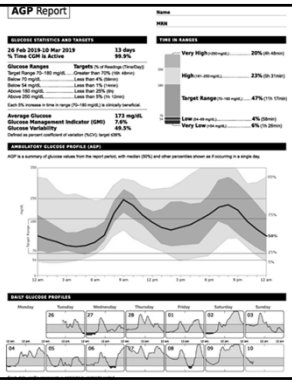

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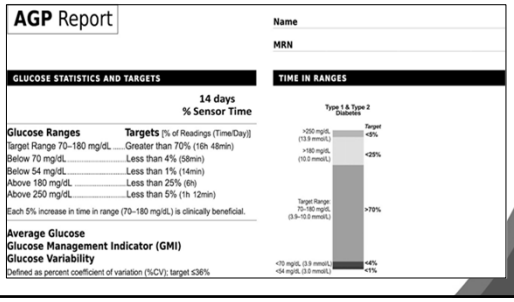
CGM Report



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Retinopathy

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Primary Risk Factors for Diabetic Retinopathy

- Level of glycemic control
- Duration of diabetes

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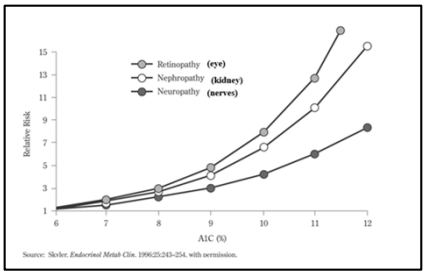
HgbA1c and Risk for Retinopathy



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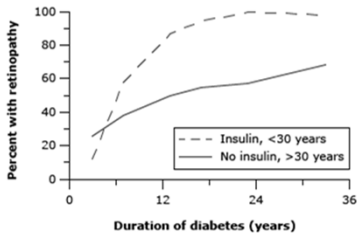
Incidence of Retinopathy Increases Over Time

<30 and >30 Indicate Age at Diagnosis



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Additional Risk Factors for Diabetic Retinopathy

- Hypertension
- The presence of other microvascular complications
  - Nephropathy
  - Neuropathy
- Dyslipidemia
- Pregnancy
  - Transiently increases risk and progression

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When and How Often to Perform Retinal Exams?

Patient group	Recommended first examination	Minimum routine follow-up
Type 1 diabetes	Within 5 years after diagnosis of diabetes once patient is age 10 years or older*.	Yearly, if retinopathy present¶ Every 2 years if there is no evidence of retinopathy
Type 2 diabetes	At time of diagnosis of diabetes.	Yearly, if retinopathy present¶ Every 2 years if there is no evidence of retinopathy
Pregnancy in preexisting diabetes	Prior to conception and during first trimester. Counsel on the risk of development and/or progression of retinopathy.	Close follow-up throughout pregnancy and for 1 year postpartum

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Vision Threatening Complications

Macular Edema

- The macula is responsible for central vision
- Macular edema is intraretinal fluid (edema) and thickening involving the macula
- It is a vision-threatening complication of diabetes and can occur at any stage or severity of diabetic retinopathy.

Proliferative Retinopathy

- Abnormal vessel growth that can physically impair vision or result in intra-ocular bleeds that obscure vision

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Therapies

Photo Coagulation

- Prevents blindness
- Destructive to retina and results in peripheral vision loss

Vitrectomy

- Clears hemorrhages and resolves traction

Anti-Vascular Endothelial Growth factor (Anti-VEGF) agents

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What Will the Ophthalmologist do?

Specific choices or combinations depend on several factors

- Poor or unlikely follow-up favors surgery over anti-VEGF agents
- Change based on failure or suboptimal response of the initial therapy
- Combination of surgery and anti-VEGF when the condition is severe

Results are improved for both surgery or medical therapy if glucose control is better

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Nephropathy

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Background – 1990s

Diabetic Kidney Disease was recognized as a leading cause of End Stage Renal Disease (ESRD)

- ACE inhibitors (and later ARBs) were discovered to delay progression of renal disease in patients with diabetes

Elevations of the serum creatinine or standard urinalysis dipstick protein assays do not occur until late in disease progression

- Earlier detection was needed to optimize outcomes
- Random urine microalbumin/creatinine (MA/Cr) index
- eGFR

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Medical Attention for Diabetic Nephropathy
The standard since the 1990s

A yearly assessment of a random urine microalbumin/creatinine (MA/Cr) index

- It is a screening study to detect early diabetic kidney disease and encourage ACE/ARB use

Because it is screening study

- There are multiple exclusions including
  - Prior documentation of microalbuminuria
  - Current use of ACE/ARB
  - Established CKD

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Medicine Advances

The American Diabetes Association recommends:

- Yearly screening for the onset of diabetic kidney disease
- Yearly monitoring for progression

Kidney Health Evaluation for Patients with Diabetes (KED)

- Several payors have adopted this recommendation as a quality measure
- It is a HEDIS quality measure for health plans
- I anticipate adoption of this standard will soon be universal

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KED (Kidney Health Evaluation for Patient with Diabetes)

Yearly urine MA/Cr and serum creatinine (to calculate eGFR)

Few exclusions

- The following are no longer exclusions
  - Use of ACE/ARB, established CKD, or prior documentation of microalbuminuria
- Less complicated to follow

Expands from ages 18-75 to 18-85

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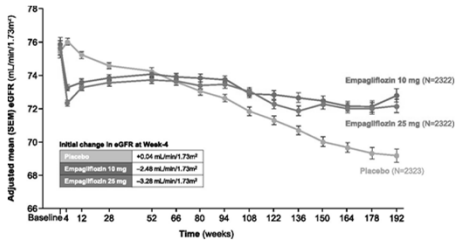
eGFR and SGLT2



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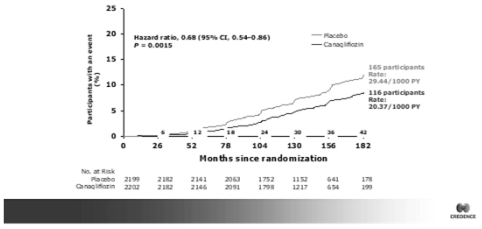
End-stage Kidney Disease (ESKD)



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Treatment of Type 2 Diabetes with CKD

First line therapy – metformin + SGLT2

- eGFR <45 decrease to metformin 500 bid
- eGFR <30 stop metformin and SGLT2

If eGFR <30 consider GLP1

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Decision Grid for Referral to Nephrology

Risk of progression by intensity of coloring + Guide to frequency of monitoring (number of times per year) + Referral decision making by GFR and albuminuria category				Persistent albuminuria categories, Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²), Description and range	G1	Normal or high	≥90	1 if CKD	1 Monitor	2 Refer
	G2	Mildly decreased	60-89	1 if CKD	1 Monitor	Refer
	G3a	Mildly to moderately decreased	45-59	1 Monitor	2 Monitor	3 Refer
	G3b	Moderately to severely decreased	30-44	2 Monitor	3 Monitor	3 Refer
	G4	Severely decreased	15-29	3 Refer	3 Refer	4+ Refer
	G5	Kidney failure	<15	4+ Refer	4+ Refer	4+ Refer

National Institute of Diabetes and Digestive and Kidney Diseases

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Simplified Referral to Nephrology

MA/Cr index >300

eGFR <30

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Neuropathy

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Diabetic Neuropathy

There are no specific preventative therapies other than glucose control

- Incidence and progression are related to glucose control
- Improved control sometimes improves the neuropathy, esp. early on

The most common is diabetic polyneuropathy

- When patients develop peripheral neuropathy, especially associated with PVD, the likelihood of ulceration leading to amputation is high

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Key components of the diabetic foot exam

Inspection
Dermatologic
Skin status – color, thickness, dryness, cracking
Sweating
Infection – check between toes for fungal infection
Ulceration
Calluses/blistering – hemorrhage into callus?
Musculoskeletal
Deformity (eg, claw toes, prominent metatarsal heads, Charcot joint)
Muscle wasting (guttering between metatarsals)
Neurologic assessment
10 g monofilament + 1 of the following 4
Vibration using 128 Hz tuning fork
Pinprick sensation
Ankle reflexes
VPT
Vascular assessment
Foot pulses
ABI, if indicated

VPT: vibration-perception threshold; ABI: ankle brachial index.

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Macrovascular Disease

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CV Disease

The most consequential diabetic complication

- Most likely to result in mortality
- Excess risk is not eliminated by glucose control

Essentially all patients with Type 2 and most with Type 1 should be additional therapy

- Statins
- SGLT2 (and GLP1)

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Statin Treatment—Primary Prevention

10.19 For patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy. A

10.20 For patients with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it maybe reasonable to initiate statin therapy in addition to lifestyle therapy. C

10.21 In patients with diabetes at higher risk, especially those with multiple atherosclerotic cardiovascular disease risk factors or aged 50–70 years, it is reasonable to use high-intensity statin therapy. B

10.22 In adults with diabetes and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL cholesterol levels by 50% or more. C

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Other Combination Therapy

10.32 Statin plus fibrate combination therapy has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. A

10.33 Statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. A

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Statin Intensity Table

Table 1. High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel)*

High intensity	*Moderate intensity*	*Low intensity*
Daily dosage lowers LDL-C by approximately ≥ 50% on average	Daily dosage lowers LDL-C by approximately 30% to 50% on average	Daily dosage lowers LDL-C by < 30% average
Atorvastatin (Lipitor), 40† to 80 mg	**Atorvastatin, 10** *(20)* **mg**	*Simvastatin, 10 mg*
Rosuvastatin (Crestor), 20 *(40)* **mg**	**Rosuvastatin,** *(5)* **10 mg**	**Pravastatin, 10 to 20 mg**
	Simvastatin (Zocor), 20 to 40 mg‡	**Lovastatin, 20 mg**
	Pravastatin (Pravachol), 40 *(80)* **mg**	*Fluvastatin, 20 to 40 mg*
	Lovastatin (Mevacor), 40 mg	*Pitavastatin, 1 mg*
	Fluvastatin XL (Lescol XL), 80 mg	
	Fluvastatin, 40 mg twice daily	
	Pitavastatin (Livalo), 2 to 4 mg	

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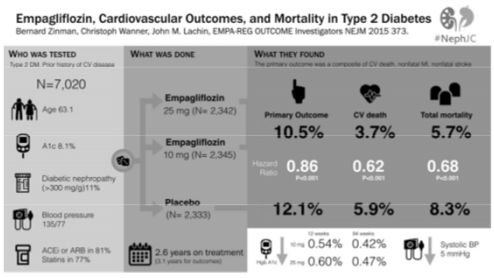

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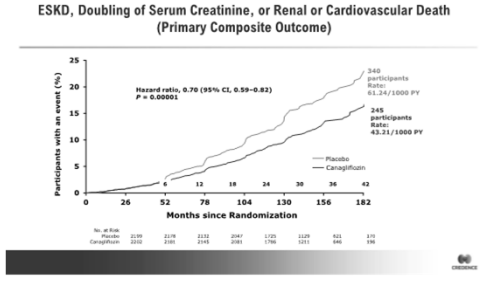

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Patient Adherence

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Education and Adherence

It is not infrequent for patients with long-standing diabetes to not understand

- Relationship of glucose control to complications
- What foods have carbohydrates and why carbohydrates are not "bad", but need to be managed
- Diabetes carries a very high CV risk that is related to their diabetes control
- That the CV risk is still increased if their diabetes is controlled and lipids are "normal"

Patients not understanding the pathophysiology and risks are not motivated

- The volume of bad advice and quick fixes patients are exposed to rivals the physician in basket

Structured education programs cover all this slowly and in detail

- The needed information simply cannot be covered in clinic visits
- Repeating the the program or focused re-education is needed

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Patient Adherence

Financial resources	Limited eye-site and impaired manual skills (neuropathy of the fingers)	Depression
• Not all patients can afford the brand name medications. You may have to ask. • Use the medications that were available for the UKPDS and DCCT (NPH, regular insulin, sulfonylureas) and, maybe, DPP4	• Can they put the strips in the meter? • Can the patient see the insulin dose on syringe or pen?	• Higher incidence and prevalence in patient with chronic diseases, including diabetes • Often not recognized • Some indications that this may be the most common cause of poor control and adherence

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Instructions to the Patient and Adherence

Patient interpretation of our instructions can be surprising

We use words that convey specifics to us but may different meanings to the patient

- We mean bedtime basal insulin to be at the same time. Some patient's bedtimes vary by 6 hours
- "At night" can mean before supper, after supper or at "bedtime"
- Daily can mean anytime of the day, but some medications like SGLT2s or sulfonylureas are better taken before the first meal
- "Mealtime" insulin may be given at the Noon "mealtime" when the patient doesn't eat lunch
- Scaled insulin may be given 3 times daily based on the FBS

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Write Instructions with Greatest Specificity Possible

Does dinner mean Noon or the last meal of the day?

Based on glucose checked before which meal?

- Fasting is "before meal"
- I have had patients use the FBS to guide insulin by scale for every meal

How long before the meal should insulin or medications be given (some may need max and min times)

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Monitoring in patients with diabetes mellitus

Intervention	Frequency	Notes
History and physical examination		
Height, weight, and BMI	Every visit	
Smoking cessation counseling	Every visit	For smokers only.
Blood pressure	Every visit	Goal systolic pressure 125 to 130 mmHg.*
Dilated eye examination	Annually.¶	Begin at onset of type 2 diabetes, 3 to 5 years after onset of type 1 diabetes. Examine yearly (or more frequently) if retinopathy present, every 2 to 3 years if there is no evidence of retinopathy.
Comprehensive foot examination	Annually	Every visit if peripheral vascular disease or neuropathy.
Dental examination	Annually	Periodontal disease is more severe but not necessarily more prevalent in patients with diabetes.
Laboratory studies		
Lipid profile	Initially, as indicated	In people without dyslipidemia and not on cholesterol-lowering therapy, testing may be infrequent.
A1C	Every 3 to 6 months	Goal ≤ 7% (may be lower or higher in selected patients).
Urinary albumin-to-creatinine ratio	Annually	Begin 3 to 5 years after onset of type 1 diabetes and at diagnosis in patients with type 2 diabetes; protein excretion should also be monitored if persistent albuminuria is present.
Serum creatinine	Initially, as indicated	Typically annually; more often in the presence of chronic kidney disease.
Vaccinations		
Pneumococcal • PPSV23	1 dose, ages 19 to 64 years	Once the patient is ≥65 years (and ≥1 year after PCV13 and ≥5 years after previous dose of PPSV23), give a second dose of PPSV23. Revaccinate every 10 years.
• PCV13	1 dose at age ≥65 years	Once the patient is ≥65 years (and ≥1 year after PPSV23), give PCV13.
Influenza	Annually	
Hepatitis B	3-dose series	Administer to unvaccinated adults who are ages 19 to 59 years. For older patients, administer based upon risk of acquiring hepatitis B, including the need for assisted blood glucose monitoring and the likelihood of an adequate immune response to vaccination.
Provide other routine vaccinations for adults with diabetes according to age-related recommendations.		
Education, self-management review	Annually	More often at onset of diabetes and when there is a change in regimen.

BMI: body mass index; A1C: glycated hemoglobin.
* When manual auscultatory method is used to measure blood pressure.
¶ Less frequent screening (every 2 to 3 years) may be appropriate for some patients (eg, patients with little or no retinopathy and near-normal A1C levels).

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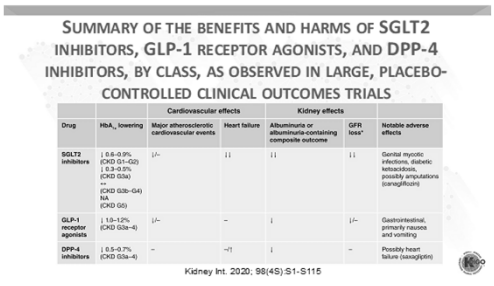
SUMMARY OF THE BENEFITS AND HARMS OF SGLT2 INHIBITORS, GLP-1 RECEPTOR AGONISTS, AND DPP-4 INHIBITORS, BY CLASS, AS OBSERVED IN LARGE, PLACEBO-CONTROLLED CLINICAL OUTCOMES TRIALS

		Cardiovascular effects		Kidney effects		
Drug	HbA_{1c} lowering	Major atherosclerotic cardiovascular events	Heart failure	Albuminuria or albuminuria-containing composite outcome	GFR loss*	Notable adverse effects
SGLT2 inhibitors	↓ 0.6–0.9% (CKD G1–G2) ↓ 0.3–0.5% (CKD G3a) ↔ (CKD G3b–G4) NA (CKD G5)	↓/–	↓↓	↓↓	↓↓	Genital mycotic infections, diabetic ketoacidosis, possibly amputations (canagliflozin)
GLP-1 receptor agonists	↓ 1.0–1.2% (CKD G3a–4)	↓/–	–	↓	↓/–	Gastrointestinal, primarily nausea and vomiting
DPP-4 inhibitors	↓ 0.5–0.7% (CKD G3a–4)	–	–/↑	↓	–	Possibly heart failure (saxagliptin)

Kidney Int. 2020; 98(4S):S1-S115

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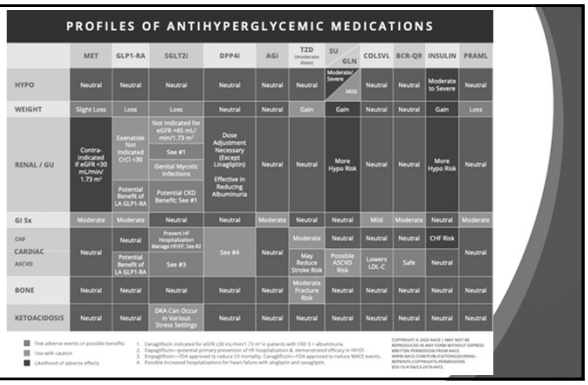

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Wrap up

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Summary

- Glucose control prevents complications from diabetes
- New insulins and monitoring tools have increased the ability to improve control without hypoglycemia since the original trials on benefits of glucose control
- Several non-insulin therapies have significant benefits for renal and CV complications
- The keys to managing complications are:
  - Visits specifically for diabetes every 3-6 months (6 months only if controlled and not on insulin)
  - Trying to improve control at each visit (better control lowers incidence, decreases progression, and improves outcomes from other interventions for diabetic complications)
  - Use of medications documented to positively influence complications
  - Regular screening and monitoring for complications
  - Early referrals to specialists in ophthalmology, cardiology, or podiatry when complications are discovered or progressing

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Notes