2021 ADA Guidelines – Updates in T2DM Care

Simon Newsom, PGY3
None
Overview

- Major takeaways from 2021 guidelines and differences from previous years
- Epidemiology, prevention strategies and glycemic targets
- Evolving use of technology in individualized DM management
- Care for older adults
- Cardiovascular outcomes
- Updated treatment guidelines
- Impact of guidelines
What Will Not Be Discussed

Management of T1DM
Management of diabetes in children or pregnant patients
Inpatient management of DM
Comorbidities (retinopathy, neuropathy)
HTN/ Lipid/ Aspirin Guidelines
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Epidemiology

>4000 new cases of DM in the United States per day

>122 million Americans have DM or preDM

¼ of older adults have DM, and ½ have preDM
ADA Guidelines

Developed by the ADA’s multidisciplinary Professional Practice Committee

Updated and published annually since 1989

Includes most current evidence based recommendations for diagnosis and management of DM

Includes 15 domains of DM
<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
</table>
| A                | Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including:  
- Evidence from a well-conducted multicenter trial  
- Evidence from a meta-analysis that incorporated quality ratings in the analysis  
Compelling nonexperimental evidence, i.e., “all or none” rule developed by the Centre for Evidence-Based Medicine at the University of Oxford  
Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including:  
- Evidence from a well-conducted trial at one or more institutions  
- Evidence from a meta-analysis that incorporated quality ratings in the analysis  |
| B                | Supportive evidence from well-conducted cohort studies:  
- Evidence from a well-conducted prospective cohort study or registry  
- Evidence from a well-conducted meta-analysis of cohort studies  
Supportive evidence from a well-conducted case-control study  |
| C                | Supportive evidence from poorly controlled or uncontrolled studies:  
- Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results  
- Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls)  
- Evidence from case series or case reports  
Conflicting evidence with the weight of evidence supporting the recommendation  |
| E                | Expert consensus or clinical experience  |
Improving Care and Promoting Health in Populations

Outcomes

- ½ of adult diabetics reported financial stress
- ⅕ reported food insecurity

2x risk of developing DM in those with food insecurity
Higher risk of medication non-adherence

Social determinants of health, cost-related non-adherence, and cost-reducing behaviors among adults with diabetes: findings from the National Health Interview Survey

Minal R. Patel, Ph.D, M.P.H.

Recommendations

1.5 Assess food insecurity, housing insecurity/homelessness, financial barriers, and social capital/social community support and apply that information to treatment decisions. A

1.6 Refer patients to local community resources when available. B

1.7 Provide patients with self-management support from lay health coaches, navigators, or community health workers when available. A
3.6 Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI $\geq 35$ kg/m$^2$, those aged <60 years, and women with prior gestational diabetes mellitus. A
LADA (Latent Autoimmune Diabetes in Adulthood)

- Autoimmune destruction of pancreatic beta cells
- Adults have higher reserve of insulin secretory capacity than children
- May or may not appear phenotypically like T2DM
- Most will become insulin deficient and will require insulin therapy sooner
Glycemic Targets

A1c is now retitled “Glycemic Assessment”

Glycemic goals:

1. A1c < 7% for most non pregnant adults
2. Time in range >70%, with time below range <4% for those using continuous glucose monitoring (CGM)
3. Less stringent A1C goals (A1c <8%) for pt with limited life expectancy, or when risk of ASE is greater than anticipated benefits
Glycemic Targets

ACCORD, ADVANCE, VADT Trials

**Aim:**

Evaluate effect of intensive glucose control (A1c <6) on cardiac outcomes in patients with T2DM and CVD or cardiac risk factors

**Outcome:**

1. Lower A1c associated with reduced onset/ progression of microvascular complications
2. Increased mortality in the intensive group in the ACCORD trial (HR1.22)
3. Increased rate of weight gain, severe hypoglycemia
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Diabetes Technology

No one size fits all approach

Patient and provider interest and comfort highly variable

Insurance coverage lags behind device availability

Recommendation

7.1 Use of technology should be individualized based on a patient’s needs, desires, skill level, and availability of devices. E
Self Monitored Blood Glucose (SMBG)

May offer insight into impact of diet, exercise and medication management

Can lower A1c when combined with structured medication titration

No effect on A1c when used alone
Continuous Glucose Monitoring

7.11 In patients on multiple daily injections and continuous subcutaneous insulin infusion, real-time continuous glucose monitoring (CGM) devices should be used as close to daily as possible for maximal benefit. A Intermittently scanned CGM devices should be scanned frequently, at a minimum once every 8 h.

Help maintain A1c and reduce hypoglycemic episodes in patients on continuous insulin \( A \), or other forms of subq insulin \( C \)

Do not need to be on insulin therapy

Useful for medication titration

Education is essential

Realistic expectations
6.4 Time in range (TIR) is associated with the risk of microvascular complications, should be an acceptable end point for clinical trials moving forward, and can be used for assessment of glycemic control. Additionally, time below target (<70 and <54 mg/dL [3.9 and 3.0 mmol/L]) and time above target (>180 mg/dL [10.0 mmol/L]) are useful parameters for reevaluation of the treatment regimen.
GLUCOSE STATISTICS AND TARGETS

14 days
% Sensor Time

Glucose Ranges   Targets [% of Readings (Time/Day)]
Target Range 70–180 mg/dL ...... Greater than 70% (16h 48min)
Below 70 mg/dL..........................Less than 4% (58min)
Below 54 mg/dL..........................Less than 1% (14min)
Above 180 mg/dL .....................Less than 25% (6h)
Above 250 mg/dL .....................Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose
Glucose Management Indicator (GMI)
Glucose Variability
Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

Type 1 & Type 2 Diabetes

<table>
<thead>
<tr>
<th>Range</th>
<th>Target</th>
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<tbody>
<tr>
<td>&gt;250 mg/dL</td>
<td>&lt;5%</td>
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<td>&gt;180 mg/dL</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>Target Range: 70–180 mg/dL (3.9–10.0 mmol/L)</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>&lt;70 mg/dL (3.9 mmol/L)</td>
<td>&lt;4%</td>
</tr>
<tr>
<td>&lt;54 mg/dL (3.0 mmol/L)</td>
<td>&lt;1%</td>
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>¼ of patients over 65 have DM, ½ are prediabetic

Higher rates of premature death, functional disability, accelerated muscle loss, and coexisting illnesses, such as HTN, CAD, and stroke, than those without DM

Greater risk for geriatric syndromes (polypharmacy, cognitive impairment, depression, urinary incontinence, falls, persistent pain)
Older Adults

Glycemic targets

- Healthy patients >65 with few coexisting chronic illness and intact cognition→ aim for A1c<7-7.5 C
- Medically complex/ poor overall health status→ avoid reliance on A1c, instead focus on avoiding hypoglycemia and symptomatic hyperglycemia C

Medication classes with low risk of hypoglycemia are preferred. B

Overtreatment of diabetes is common in older adults and should be avoided. B

Deintensify therapy to reduce hypoglycemia and polypharmacy if possible B
Consider CGM in older adults at risk of hypoglycemia (T1DM, insulin/sulfonylurea therapy) A

**Wireless Innovation in Seniors with Diabetes Mellitus (WISDM) trial**

- 2017-2019, 200 pt >60 years old with T1DM
- Pt with T1DM randomized to CGM or standard glucose glucose monitoring
- Over 6 months, CGM resulted statistically significant reduction in time spent in hypoglycemia compared to standard care
- Extrapolated - CGM may be an option for older patients with type 2 diabetes using multiple daily injections of insulin
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- **Cardiovascular outcomes**
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Few major changes aside from more robust evidence supporting previous recommendations:

- AECi/ARB for HTN
- Statin guidelines
- ASA therapy
- GLP-1 agonists and SGLT-2 inhibitors
In patients with T2DM who have established ASCVD or established kidney disease:

- an SGLT2I or GLP-1RA is recommended as part of the comprehensive CV risk reduction and/or glucose-lowering regimens

- a GLP-1RA is recommended to reduce the risk of major adverse cardiovascular events

In patients with T2DM and HFrEF:

- An SGLT2 inhibitor is recommended to reduce risk of worsening HF and CV death.

- an SGLT2I is recommended to reduce the risk of HF hospitalization
Consider initiating an SGLT2 Inhibitor in all patients with T2DM and evidence of diabetic kidney disease.

GLP-1 receptor agonists slow progression of kidney disease in patients with CKD who are at higher risk of CV events.
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FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF?

CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

+ASCVD/Indicators of High Risk
- Established ASCVD
- Indicators of high ASCVD risk (e.g., ≥5 years with coronary, carotid, or lower-extremity artery stenosis ≥60%, or LVEF)

+HF
- Particularly HF/EF (LVEF ≤40%)

+CKD
- DDK and Albuminuria

SGLT2i with proven benefit in this population

GLP-1 RA with proven CV benefit

If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:
- For patients on a GLP-1 RA, consider adding SGLT2i with proven CV benefit and vice versa
- TZD
- DPP-4i if not on GLP-1 RA

If A1C above target

If A1C above target

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

GLP-1 RA with good efficacy for weight loss

SGLT2i

GLP-1 RA

DPP-4i

TZD

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss

SGLT2i

IF A1C ABOVE TARGET

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IF A1C ABOVE TARGET

INSULIN therapy
- Basal insulin with lowest acquisition cost
- Consider other therapies based on cost

COST IS A MAJOR ISSUE

SU

TZD

SU

TZD

SU
Metformin

9.4 Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A

9.5 Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. A
Dual therapy

Consider dual therapy when A1c > 8.5, or when A1c not at goal after 3 months on MFM monotherapy.

VERIFY TRIAL (2019 Lancet)

- 2001 patients, 18-70 yo with T2DM, A1c 6.5-7.0
- Early combination therapy with MFM+DPP-4 Vildagliptin vs standard therapy (MFM alone)
- Primary endpoint: time to treatment failure (two consecutive A1c > 7)
- Outcome: initial combination therapy had overall slower decline in glycemic control

Results have not proven to be generalizable

Should still consider if A1c 1.5-2.0% above goal

Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial

David R Matthews 1, 2, Páivi M Paldánius 1, 3, Pieter Proot 1, Yann-Tong Chiang 1, Michael Stumvoll 1, Stefano Del Prato 1, 2, VERIFY study group
GLP-1 Agonists
- Semaglutide (Ozempic, Rybelsus*)
- Exenatide (Byetta, Bydureon)
- Liraglutide (Victoza)

MOA
1. Stimulate insulin production
2. Inhibition of glucagon secretion
3. Inhibit gastric emptying
4. Decrease appetite

Benefits
- Reduce A1c by 1-2%
- 5-10lb wt loss
- Proven cardiovascular and renal benefits

Downsides
- Primarily injectables
- Mainly GI upset
GLP-1 Agonists

When compared to insulin

- Similar reduction in A1c
- Lower risk of hypoglycemia
- Beneficial effect on body weight
- *more GI side effects

High costs and tolerability issues remain barriers to widespread use
SGLT2 Inhibitors
- Empagliflozin (Jardiance)
- Dapagliflozin (Farxiga)
- Canagliflozin (Invokana)

MOA
Inhibit sodium-glucose transporter in the proximal tubule → decreased glucose reabsorption

Benefits
- Do not lead to hypoglycemia
- Reduce A1c 0.5-1.0%
- 4-6 lb wt loss, small reduction in blood pressure
- Significant cardiovascular and renal benefit

ASE
- Hypovolemia
- GU/yeast infections
- DKA

Less effective as GFR decreases, so CI if GFR <30
<table>
<thead>
<tr>
<th>Class</th>
<th>Compound(s)</th>
<th>Dosage strength/product (if applicable)</th>
<th>Median AWP (min, max)$^a$</th>
<th>Median NADAC (min, max)$^a$</th>
<th>Maximum approved daily dose*</th>
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<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>850 mg (IR), 1,000 mg (ER)</td>
<td>$108 ($66, $109)</td>
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<td>Sulfonylureas (2nd generation)</td>
<td>Glimepiride</td>
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<td>Glipizide</td>
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<td>Glyburide</td>
<td>6 mg (micronized)</td>
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<td>$10</td>
<td>12 mg (micronized)</td>
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<td>Thiazolidinediones</td>
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<td>α-Glucosidase inhibitors</td>
<td>Acarbose</td>
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<td>Repaglinide</td>
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<td>DPP-4 inhibitors</td>
<td>Alogliptin</td>
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<td>Canagliflozin</td>
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<td>GLP-1 RAs</td>
<td>Exenatide (extended release)</td>
<td>2 mg powder for suspension or pen</td>
<td>$882</td>
<td>$105</td>
<td>2 mg**</td>
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<td>Dulaglutide</td>
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<td>$957</td>
<td>$766</td>
<td>4.5 mg**</td>
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<td>Semaglutide</td>
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<td>$973</td>
<td>$779</td>
<td>1 mg**</td>
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<td>Bile acid sequestrant</td>
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<td>$710 ($674, $712)</td>
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<tr>
<td></td>
<td>N/A</td>
<td>3.75 g suspension</td>
<td>$804</td>
<td>$318</td>
<td>3.75 g</td>
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<tr>
<td>Dopamine-2 agonist</td>
<td>Bromocryptine</td>
<td>0.8 mg</td>
<td>$960</td>
<td>$772</td>
<td>4.8 mg</td>
</tr>
</tbody>
</table>
| Amylin mimetic              | Pramlintide                  | 120 µg pen                             | $2,702                    | $2,097                       | 120 µg/injection††
FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF

NO

CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE

+ASCVD/Indicators of High Risk
  - Established ASCVD
  - Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

+HF
  - Particularly HREF (LVEF <45%)

+CKD
  - DKK and Albuminuria
  - SGLT2i with proven benefit in this population

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

- GLP-1 RA with proven CVD benefit
- SGLT2i with primary evidence of reducing CKD progression

IF A1C above target
- Either/or
- DPP-4i
- GLP-1 RA
- SGLT2i
- TZD

COMPPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

- GLP-1 RA with good efficacy for weight loss
- SGLT2i

IF A1C above target
- Either/or
- SU
- TZD

COST IS A MAJOR ISSUE

- If A1C above target
  - SU
  - TZD

Insulin therapy with lowest acquisition cost

OR

Consider other therapies based on cost
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Financial Hardship

41 million Americans live below federal poverty line

28 million Americans did not have health insurance. Among the insured, 43% reported that they struggled to meet their deductible

¼ of adults reported difficulty affording medications

40% of Americans could not afford a $400 emergency.

Risk factors for difficulty affording medications

- Low income
- Poor health status
- Prescribed 4 or more medications
2021 editorial in the AMA Journal of Ethics

Consequences of cost pathway

- Creates appearance of evidence based quality for inferior care
- Creation of social hierarchy

What do we do if financial hardship is identified?

- Bias towards inferior care?
- Physician burnout
- Harm provider - patient relationship

Professional ethics vs real world financial constraints
Reviewed the major takeaways from 2021 ADA guidelines and changes from previous years

- Discussed evolving use of technology in individualized DM management
- Updated pharmacologic management
- Societal impact of these changes


Blood Pressure Management

BP goal:
- ASCVD risk <15% → less than 140/90 A
- ASCVD risk >15% → less than 130/80 C

First line agent should be ACEi/ARB A
- Maximize these prior to initiating second agent if evidence of proteinuria
- Not indicated for diabetic pts without evidence of HTN, CKD or proteinuria A

Those not controlled on three or more medications should be considered for mineralocorticoid receptor antagonist therapy. B
Blood Pressure Management

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

ACCORD Trial

- Almost 5000 patients with T2DM
- Randomized to standard BP goal (<140 SBP) or intensive goal (<120)
- Primary endpoint: nonfatal MI, stroke, death from CV events.
- Results:
  a. Reduction in nonfatal stroke rate (HR 0.59)
  b. Increased death from any cause (HR 1.07)
  c. Increased rate of ASE (3.3% vs 1.3%)

Did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.
Lipid Management

All patients should undergo lifestyle modifications A

### Primary Prevention

- Age 40–75 without ASCVD → initiate moderate-intensity statin A
- Age 50-70 or with multiple ASCVD risk factors → initiate high intensity statin B
- Age 20-39 with ASCVD risk factors → consider initiating statin therapy (does not specify intensity) C
- If ASCVD >20% → consider ezetimibe in addition to max statin to reduce LDL by >50% C

### Table 10.2—High-intensity and moderate-intensity statin therapy*

<table>
<thead>
<tr>
<th>High-intensity statin therapy</th>
<th>Moderate-intensity statin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(lowers LDL cholesterol by ≥50%)</td>
<td>(lowers LDL cholesterol by 30–49%)</td>
</tr>
<tr>
<td>Atorvastatin 40–80 mg</td>
<td>Atorvastatin 10–20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20–40 mg</td>
<td>Rosuvastatin 5–10 mg</td>
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<tr>
<td></td>
<td>Simvastatin 20–40 mg</td>
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<td>Pravastatin 40–80 mg</td>
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<td></td>
<td>Lovastatin 40 mg</td>
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<td></td>
<td>Fluvastatin XL 80 mg</td>
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<td>Pitavastatin 1–4 mg</td>
</tr>
</tbody>
</table>

*Once-daily dosing. XL, extended release.
Lipid Management

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</tbody>
</table>

*Once-daily dosing. XL, extended release.

Secondary Prevention

- All patients should be on high intensity statin in addition to lifestyle mods A

- If LDL >70 and with other ASCVD risk factors → consider additional LDL lowering agent (ezetimibe or PCSK9 inhibitor). A

- For patients with DM and >75, if already on statin therapy, reasonable to continue statin B
Diabetic Risk with Statin Use?

2012 Meta-analysis of 13 RCT (91,140 participants) published in Lancet

- OR 1.09 for a new diagnosis of diabetes
- On average, treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes
- Statins simultaneously prevented 5.4 vascular events among those 255 patients

Cardiovascular Benefits and Diabetes Risks of Statin Therapy in Primary Prevention

Paul M Ridker, MD, Aruna Pradhan, MD, Jean G. MacFadyen, BA, Peter Libby, MD, and Robert J Glynn, ScD

Center for Cardiovascular Disease Prevention (PMR, AD, JM, GJG) and the Division of Cardiovascular Medicine (PMR, PL), Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA
Aspirin

Indicated as a secondary prevention strategy in those with diabetes and a history of ASCVD. A

Consider as primary prevention strategy in patients 50-70yo with DM who are at increased CV risk, after discussion of risk/ benefit A

Not recommended for those at low risk of ASCVD, as the low benefit is likely to be outweighed by the risks of bleeding.
Self Monitored Blood Glucose (SMBG)

7.5 Although self-monitoring of blood glucose in patients on noninsulin therapies has not consistently shown clinically significant reductions in A1C, it may be helpful when altering diet, physical activity, and/or medications (particularly medications that can cause hypoglycemia) in conjunction with a treatment adjustment program. E

May offer insight into impact of diet, exercise and medication management

Can lower A1c when combined with structured medication titration

No effect on A1c when used alone