Hemoglobin A1c Targets for Glycemic Control with Pharmacologic Therapy in Non-Pregnant Adults with Type 2 Diabetes Mellitus:

A Guidance Statement from the American College of Physicians

Timothy J. Wilt, MD, MPH, MACP for the ACP Clinical Guidelines Committee
Disclosure

- I am chair of the ACP Clinical Practice Guideline Committee
Objectives

- Describe Purpose & Methods of ACP-Guidance Statements
- Highlight findings from review process of HbA1c target guidelines
- Summarize evidence included in HbA1c target guidelines
- Discuss ACP-Guidance Statements & Rationale
  - Emphasize role of age, comorbidities, value of care in HbA1c targets
- Describe newer glucose lowering agents and their healthcare value
- Emphasize importance & challenges of clinician driven cost-conscious health care delivery
Hemoglobin A\textsubscript{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

Amir Qasem, MD, PhD, MHA; Timothy J. Wilt, MD, MPH; Devan Kanagas, MD, MCR; Carrie Horwitz, MD, MPH; Michael J. Barry, MD; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians

**Description:** The American College of Physicians developed this guidance statement to guide clinicians in selecting targets for pharmacologic treatment of type 2 diabetes.

**Methods:** The National Guideline Clearinghouse and the Guidelines International Network library were searched (May 2017) for national guidelines, published in English, that addressed hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) targets for treating type 2 diabetes in nonpregnant outpatient adults. The authors identified guidelines from the National Institute for Health and Care Excellence and the Institute for Clinical Systems Improvement. In addition, 4 commonly used guidelines were reviewed, from the American Association of Clinical Endocrinologists and American College of Endocrinology, the American Diabetes Association, the Scottish Intercollegiate Guidelines Network, and the U.S. Department of Veterans Affairs and Department of Defense. The AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument was used to evaluate the guidelines.

**Guidance Statement 1:** Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.

**Guidance Statement 2:** Clinicians should aim to achieve an HbA\textsubscript{1c} level between 7% and 8% in most patients with type 2 diabetes.

**Guidance Statement 3:** Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA\textsubscript{1c} levels less than 6.5%.

**Guidance Statement 4:** Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA\textsubscript{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.

Ann Intern Med. doi: 10.7326/M17-0939
An online article. For author affiliations, see end of text.
This article was published at Annals.org on 6 March 2018.
Purpose & Methods: Guidance Statements

- Critically review & reconcile available guidelines and included evidence
  - Topic areas where several guidelines exist but recommendations may vary
  - Do not include evidence quality assessment or strength of recommendation

- Evaluate benefits & harms of targeting lower vs. higher HbA1c targets
  - Glycemic targets influence clinical decisions and practice policy
  - Did not assess newer DM drugs studied as “add on” w/o regard to HbA1c level or target
Guidelines Overview

- Included 6 guidelines by national level organizations:
  - NICE, SIGN, ICSI, VA/DOD: Scored highest.  
    *(ADA, AACE/ACE scored low)*
  - ACP: “recommended” or “recommended with modification”

- HbA1c targets varied by guideline and patient population

- All guidelines recommend “individualizing HbA1c targets” based on patient characteristics such as comorbidities and hypoglycemia risk
  - Less intensive targets: older, sicker adults; higher medication harms
HbA1c treatment target?

*Adult with Type 2 DM*

A. <6%
B. 6-7%
C. 7-8%
D. 9%
E. Treat to minimize symptoms rather than achieve HbA1c target
F. It depends; I need more information
HbA1c treatment target?

*Adult with Type 2 DM*

A. <6%
B. 6-7%
C. 7-8%
D. 9%
E. Treat to minimize symptoms rather than achieve HbA1c target
F. It depends; I need more information

ACP Guidance Statement 1

- Clinicians should personalize goals for glycemic control in patients with type 2 diabetes based on a discussion of benefits and harms of pharmacotherapy, patients’ preferences, patients’ general health and life expectancy, treatment burden, and costs of care.

- **Rationale:** All guidelines recommend personalizing HbA1c goal. Benefits vs. harms finely balanced & vary.
HbA1c treatment target?
60 year old, Type 2 DM, HTN

A. <6%
B. 6-7%
C. 7-8%
D. 9%
E. Treat to minimize symptoms rather than HbA1c target
Benefits & Harms: “Treat to Target”
5 large long-term RCTs
Benefits

- **Intensive** (HbA1c: 6.4%-7.4%) vs **Less intensive** (HbA1c: 7.0% to 8.4%):
  - *Small/inconsistent reductions in microvascular surrogate events:*
    - Retinopathy: *screen detected*; Nephropathy: *albuminuria*; Neuropathy: *reflexes*
  - Achieving HbA1c <7% did not reduce:
    - *clinical microvascular events* (impaired vision, ESRD, painful neuropathy)
    - *macrovascular events* (mortality, MI, stroke, amputations, heart failure)
- UKPDS-34 (overweight adults):
  - “intensive” control (HbA1c 7.4% vs. 8.0%) w/metformin: → reduced mortality (ARD<1%) but not macrovascular events
- Remainder showed little to no clinical benefit through 10+ years
Harms

- More intensive HbA1c targets:
  - Greater healthcare burden & costs:
    - Increased patient & glucose monitoring
    - Higher doses & more hypoglycemic medications
  - Increased adverse events
    - Hypoglycemia, Hospitalizations, Weight gain, Water retention, Dyspnea, “Non-hypoglycemic” serious AE, Death
- Very intensive HbA1c level (6.4%) $\rightarrow$ increased death (ACCORD)
ACP Guidance Statement 2

- Clinicians should aim to achieve a HbA1c between 7% and 8% in most patients with type 2 diabetes.

- **Rationale:** Treating to ≤7% vs. about 8% did not reduce mortality or macrovascular events over 5-10 years, but resulted in substantial harms including, but not limited to, hypoglycemia. Reductions in microvascular events, were inconsistent, small in absolute terms, and typically surrogate measures NOT clinical outcomes.
HbA1c treatment target/strategy?

*HbA1c* = 6.3

*Metformin, Glipizide, Sitagliptin, Glargine*

A. Add/increase medication to achieve normal HbA1c (≤ 6%)
B. Maintain current meds & dose: HbA1c optimal
C. De-intensify DM meds: Harms exceed benefits
D. Discontinue all DM meds: treat to minimize symptoms rather than achieve HbA1c target
ACP Guidance Statement 3

- Clinicians should consider de-intensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA1c levels less than 6.5%.

- **Rationale:** No trials showed that targeting HbA1c <6.5% improves clinical outcomes. There are substantial harms & costs of pharmacologically treating to HbA1c <6.5%.
HbA1c treatment target/strategy?

78 yo with COPD, CHF, CKD

A. <6%
B. 6-7%
C. 7-8%
D. 9%
E. Treat to minimize symptoms & avoid targeting HbA1c level
ACP Guidance Statement 4

- Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting a HbA1c level in patients with a life expectancy less than 10 years due to advanced age (80 years or older) or chronic conditions (such as dementia, cancer, end stage kidney disease, severe COPD or CHF, patients residing in nursing homes) as the harms outweigh the benefits.

- **Rationale:** All guidelines recommend “relaxing targets”. There is long lag-time to any small benefit and there are substantial treatment harms, burden, & costs.
Areas of uncertainty and future research needs

- **Long-term benefits/harms/costs**
  - HbA1c targets between 6.5%-7%
    - Young, newly diagnosed individuals

- **Newer agents (DPP-4, SGLT-2i, GLP-1 receptor agonists ...)**
  - Treat to HbA1c target
  - “Risk-based” add-on therapy (established CVD vs. “increased risk”)
  - 1<sup>st</sup> or 2<sup>nd</sup> line option in average risk or “limited life expectancy”
    - Alternative to insulin (especially analogs)
High-Value Care

Oral pharmacologic therapy with metformin (unless contraindicated) is an effective management strategy. It is cheaper and more effective than most other pharmacologic agents and is associated with fewer adverse effects; of note, it does not result in weight gain.
High-Value Care

Oral pharmacologic therapy with metformin (unless contraindicated) is an effective management strategy. It is cheaper and more effective than most other pharmacologic agents and is associated with fewer adverse effects; of note, it does not result in weight gain.

Adding a second agent to metformin may provide additional benefits; however, the increased cost may not always support the added benefit, particularly for the more expensive, newer medications.
...intended for settings with limited health system resources where the health care budget can be quickly exhausted with widespread use of expensive brand-name medications...apply to high-income countries where patients with limited resources need evidence-based care that takes into account costs and value.
Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes
A Meta-analysis

Sueotiona C. Palmer, PhD; Dimitris Mavridis, PhD; Antonio Nicolucci, MD; David W. Johnson, PhD; Marcello Tonelli, MD; Jonathan C. Craig, PhD; Jasjot Maggo, MMed; Vanessa Gray, MSc; Giorgia De Berardis, MSC; Marinella Rusopo, MSc; Patrizia Natale, MSC; Valeria Saglimbene, MSc; Sunil V. Badve, MD; Yeoungjee Cho, PhD; Annie-Claire Nadeau-Fredette, MD; Michael Burke, MD; Labib Faruque, MSc; Anita Lloyd, MSc; Nasreen Ahmad, BSc; Yuanchen Liu; Sophanny Tiv, BSc; Natasha Wiebe, MMath; Giovanni F. M. Strippoli, PhD

Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes
A Systematic Review and Meta-analysis

Sean L. Zheng, BCh, MA, MRCP; Alistair J. Roddick, BSc; Rochan Aghar-Jaffar, BMedSci, BMBBS, MRCP; Matthew J. Shun-Shin, BM BCh, MRCP; Darrel Francis, MB BChir, FRCP, MD; Nick Oliver, MBBS, FRCP; Karim Meenan, MBBS, MD, FRCP, FRCPath
“Risk-based, add-on therapy” for CVD prevention:

GLP1a & SGLT2i
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven R. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lars E. Ravn, M.D., Ph.D., William M. Steinhberg, M.D., Mette Stockbrügge, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D.,

for the LEADER Steering Committee on behalf of the LEADER Trial Investigators

ARD = 1.9%

ARD = 1.4%
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,
David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D.,
Michaela Matheus, Dipl. Biomath., Theresa Devins, Dr. P.H.,
Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D.,
and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

A Primary Outcome

ARD = 1.6%

Hazard ratio, 0.66 (95% CI, 0.74–0.99)

P=0.04 for superiority

No. at Risk
Empagliflozin 4687 4680 4455 4328 3851 2821 2359 1594 370
Placebo 2333 2256 2194 2112 1875 1380 1161 741 166

C Death from Any Cause

ARD = 2.6%

Hazard ratio, 0.68 (95% CI, 0.57–0.82)

P<0.001

No. at Risk
Empagliflozin 4687 4651 4608 4556 4128 3079 2617 1722 414
Placebo 2333 2303 2280 2243 2012 1503 1281 825 177
Weight change

A. Weight

Liraglutide: -2.3kg (3%)

Empagliflozin: -1.7kg (2%)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>10mg</th>
<th>25mg</th>
<th>10mg</th>
<th>25mg</th>
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<tr>
<td></td>
<td>1015</td>
<td>2215</td>
<td>2156</td>
<td>1506</td>
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<td>2263</td>
<td>1891</td>
<td>2250</td>
<td>1079</td>
<td>1555</td>
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<tr>
<td>52</td>
<td>425</td>
<td>483</td>
<td>483</td>
<td>483</td>
<td>483</td>
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</tbody>
</table>
Insulin: Analogs vs. Human
Comparative Effectiveness, Safety, & Cost

Insulin Comparisons

• Analog vs. Human Insulin: Meta-analyses of RCTs:
  • HbA1c differences small (0.1-0.3%)
  • Small differences in “nocturnal hypoglycemia”
  • Small to no difference in severe hypoglycemia (10 if on SFU & HbA1c <7%)

• National clinical data bases
  • No difference in HbA1c, or ED visits or hospitalizations for hypoglycemia

• Human vs. Basal Analogs: Cost & Convenience
  • Analogs in pens cost 6x more than NPH & Regular in vials
  • High concentration cost 2-4x more than regular concentration
  • NPH & analog pens cost similar
  • Pens more convenient than vials; very small difference in satisfaction, ?QOL
  • Analogs not cost-effective

• Conversions feasible, safe, effective, cost saving
Are the benefits worth harms & costs?

*Are newer higher cost options High Value?*
### National Trends in Drug Expenditures: Top 25 Prescription Drugs by $

<table>
<thead>
<tr>
<th>Drug</th>
<th>2017 Expenditures ($ Thousands)</th>
<th>Percent Change From 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>17,106,721</td>
<td>20.6</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>9,382,979</td>
<td>-3.7</td>
</tr>
<tr>
<td>Etanercept</td>
<td>8,828,006</td>
<td>8.9</td>
</tr>
<tr>
<td>Ledipasvir-sofosbuvir</td>
<td>6,091,534</td>
<td>-38.7</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>5,633,123</td>
<td>16.8</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5,544,901</td>
<td>4.5</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>5,340,837</td>
<td>10.0</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>5,055,719</td>
<td>8.4</td>
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<tr>
<td>Fluticasone-salmeterol</td>
<td>4,910,787</td>
<td>-3.7</td>
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<tr>
<td>Pregabalin</td>
<td>4,909,142</td>
<td>14.5</td>
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<td>Apixaban</td>
<td>4,752,043</td>
<td>55.9</td>
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<tr>
<td>Cladiramer</td>
<td>4,370,331</td>
<td>-0.8</td>
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<tr>
<td>Pegfilgrastim</td>
<td>4,315,216</td>
<td>-0.4</td>
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<tr>
<td>Rivaroxaban</td>
<td>4,300,573</td>
<td>23.5</td>
</tr>
<tr>
<td>Rituximab</td>
<td>4,043,783</td>
<td>3.5</td>
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<tr>
<td>Emtricitabine-tenofovir disoprol</td>
<td>3,987,201</td>
<td>18.7</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>3,936,921</td>
<td>20.2</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>3,814,417</td>
<td>0.0</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>3,676,817</td>
<td>43.7</td>
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<tr>
<td>Cobimetast-eztrevir-salvematin</td>
<td>3,610,546</td>
<td>125.5</td>
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<tr>
<td>Insulin detemir</td>
<td>3,332,309</td>
<td>-6.5</td>
</tr>
<tr>
<td>Lisdexametidine</td>
<td>3,327,777</td>
<td>10.1</td>
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<tr>
<td>Albuterol</td>
<td>3,319,066</td>
<td>3.0</td>
</tr>
<tr>
<td>Interferon beta-1a</td>
<td>3,204,554</td>
<td>-5.9</td>
</tr>
<tr>
<td>Tiotropium bromide</td>
<td>3,152,383</td>
<td>-4.2</td>
</tr>
</tbody>
</table>

6/25 = DM meds: $33,000,000,000

2018 MVAMC DM Drug Costs: $7,000,000

Schumock GT et al. AM J Health Syst Pharm 2018
Drug Cost: ARP

<table>
<thead>
<tr>
<th>Glucose Lowering Drug</th>
<th>Annual Retail Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SFU: Glipizide</td>
<td>$206</td>
</tr>
<tr>
<td>• Biguanide: Metformin</td>
<td>$327</td>
</tr>
<tr>
<td>• TZD: Pioglitazone</td>
<td>$2483</td>
</tr>
<tr>
<td>• DPP-4: Sitagliptin</td>
<td>$6486</td>
</tr>
<tr>
<td>• SGLT2i: Empagliflozin</td>
<td>$6600</td>
</tr>
<tr>
<td>• GLP1a: Liraglutide</td>
<td>$12,844</td>
</tr>
<tr>
<td>• Insulin: NPH/Reg (vials)</td>
<td>$288</td>
</tr>
<tr>
<td>• Insulin: Glargine (pens)</td>
<td>$3339</td>
</tr>
</tbody>
</table>
Cost Per Cardiovascular Event Prevented

• **Liraglutide** ($12,844/year)
  • NNT @ 3 years = 52
  • $ per CV event avoided: $2,034,315

• **Empagliflozin** ($6,660/year)
  • NNT @ 3 years = 62
  • $ per CV event avoided: $1,248,750

• **Insulin Analog (Pens) vs. NPH/Reg (Vials)**
  • No mortality or CV event difference
  • $ per hypoglycemia event avoided: ?
  • $ for convenience: ???
Cost and Health Care Decisions

• Considering costs while caring for patients can seem ethically murky
  • Convenience of higher cost options: important but difficult to quantify
• Challenging when health system/society rather than patient paying

• Is it ethical?
• Is it necessary?
• Whose role is it?
• What are the consequences of considering and not considering costs?
“Physicians have a responsibility to practice effective and efficient healthcare and to use healthcare resources responsibly. Parsimonious care that utilizes the most efficient means to effectively diagnose a condition and treat a patient respects the need to use resources wisely and to help ensure that resources are equitably available.”

American College of Physicians Ethics Manual, Sixth Edition
...understand the need for stewardship of resources or for practicing in a cost-conscious fashion
“... physicians are required to provide healthcare that is based on the wise and cost-effective management of limited clinical resources. They should be committed to working with other physicians, hospitals, and payers to develop guidelines for cost-effective care.”

American Board of Internal Medicine Professionalism Charter
ACGME “Cost-effective-HVC Milestones”

<table>
<thead>
<tr>
<th>Critical Deficiencies</th>
<th>Lacks awareness of external factors (e.g. socioeconomic, cultural, literacy, insurance status) that impact the cost of health care and the role that external stakeholders (e.g. providers, suppliers, financers, purchasers) have on the cost of care</th>
<th>Recognizes that external factors influence a patient’s utilization of health care and may act as barriers to cost-effective care</th>
<th>Consistently works to address patient specific barriers to cost-effective care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ignores cost issues in the provision of care</td>
<td>Does not consider limited health care resources when ordering diagnostic or therapeutic interventions</td>
<td>Minimizes unnecessary diagnostic and therapeutic tests</td>
<td>Teaches patients and healthcare team members to recognize and address common barriers to cost-effective care and appropriate utilization of resources</td>
</tr>
<tr>
<td>Demonstrates no effort to overcome barriers to cost-effective care</td>
<td></td>
<td>Possesses an incomplete understanding of cost-awareness principles for a population of patients (e.g. screening tests)</td>
<td>Actively participates in initiatives and care delivery models designed to overcome or mitigate barriers to cost-effective high quality care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incorporates cost-awareness principles into standard clinical judgments and decision-making, including screening tests</td>
<td></td>
</tr>
</tbody>
</table>

10. Identifies forces that impact the cost of health care, and advocates for, and practices cost-effective care. (SBP3)
HbA1c treatment target/strategy: Improving healthcare value

$HbA1c=6.3$

Metformin, Glipizide, Sitagliptin, Glargine

- Annual Cost of DM Meds: $10,358
- Deprescribe to improve healthcare value
  - DC Sitagliptin; Change Glargine (Pens) $\rightarrow$ NPH/Reg (Vials)
  - Target HbA1c: 7-8%
    - Metformin, Glipizide, NPH/Reg in Vials
    - HbA1c: 7.3%
    - Medication Cost: $821
Summary-ACP HgbA1c Target Guidance

- Emphasize “healthy life style” in all patients
- Individualize HgbA1c pharmacologic targets
  - Optimize balance of benefits, harms, burden, & costs
    - HgbA1c: 7%-8% in most
    - Less intensive HgbA1c targets in many
    - De-intensify pharmacologic treatment for repeated HgbA1c <6.5%
- Better health outcomes; Lower costs/burden; Higher value
High Value Care Conclusions

• Cost conscious care is ethical, important, and encouraged by most clinical professional organizations

• Treatment decisions should:
  • Balance clinical benefits with harms and burden
  • Include cost of care to the patient, health care system, & society

• Clinicians have a leading role & responsibility in Defining, Discovering, & Delivering High Value Care