General

Guideline Title
Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians.

Bibliographic Source(s)

Guideline Status
Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

Recommendations

Major Recommendations
Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

The strength of the evidence (high, moderate, low, or insufficient evidence to determine benefits or risks) and strength of recommendations (strong, weak) are defined at the end of the "Major Recommendations" field.

Recommendation 1: The American College of Physicians (ACP) recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia (Grade: strong recommendation; high-quality evidence).

Initiation of oral pharmacologic therapy is an important approach to effective management of type 2 diabetes. There are no data on the best time to add oral therapies to lifestyle modifications; thus, to avoid an unacceptable burden on patients, other complicating factors should be considered, such as life expectancy of the patient, presence or absence of microvascular and macrovascular complications, risk for adverse events related to glucose control, and patient preferences. The goal for hemoglobin A1c (HbA1c) should be based on individualized assessment of risk for complications from diabetes, comorbidity, life expectancy, and patient preferences. An HbA1c level less than 7% based on individualized assessment is a reasonable goal for many but not all patients.

Recommendation 2: ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes (Grade: strong recommendation; high-quality evidence).

The effectiveness, adverse effect profiles, and costs of various oral pharmacologic treatments vary. Metformin is more effective than other pharmacologic agents in reducing glycemic levels and is not associated with weight gain. In addition, metformin aids in decreasing weight and
reduces low-density lipoprotein (LDL) cholesterol and triglyceride levels. Metformin was also associated with slightly lower all-cause mortality and cardiovascular mortality compared with sulfonylureas. Finally, metformin is associated with fewer hypoglycemic episodes and is cheaper than most other pharmacologic agents. Therefore, unless contraindicated, metformin is the drug of choice for patients with type 2 diabetes, in addition to lifestyle modification. Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart failure, and any condition that might lead to lactic acidosis.

Physicians and patients should discuss adverse event profiles before selecting a medication. Compared with baseline values, most diabetes medications (metformin, thiazolidinediones, and sulfonylureas) reduced baseline HbA1c by about 1 percentage point 3 or more months after the initiation of treatment. For adverse effects, metformin is associated with an increased risk for gastrointestinal side effects, sulfonylureas and meglitinides are associated with an increased risk for hypoglycemia, and thiazolidinediones are associated with an increased risk for heart failure (with no conclusive evidence for any increase in ischemic cardiovascular risk). However, in comparing the effectiveness of various agents, the evidence shows that metformin is the most efficacious agent as monotherapy and in combination therapy.

Recommendation 3: ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia (Grade: strong recommendation; high-quality evidence).

All dual-therapy regimens were more efficacious than monotherapies in reducing the HbA1c level in patients with type 2 diabetes by about 1 additional percentage point. Combination therapies with more than 2 agents were not included in the evidence review. No good evidence supports one combination therapy over another, even though some evidence shows that the combination of metformin with another agent generally tends to have better efficacy than any other monotherapy or combination therapy. However, combination therapies are also associated with an increased risk for adverse effects compared with monotherapy. Generic sulfonylureas are the cheapest second-line therapy; however, adverse effects are generally worse with combination therapies that include a sulfonylurea.

Although this guideline addresses only oral pharmacological therapy, patients with persistent hyperglycemia despite oral agents and lifestyle interventions may need insulin therapy.

Definitions:

<table>
<thead>
<tr>
<th>The American College of Physicians’ Guideline Grading System*</th>
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<tbody>
<tr>
<td><strong>Quality of Evidence</strong></td>
</tr>
<tr>
<td>Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits</td>
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<tr>
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*Adopted from the classification developed by the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) workgroup.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Type 2 diabetes mellitus
Guideline Category

Treatment

Clinical Specialty

Endocrinology
Family Practice
Internal Medicine

Intended Users

Advanced Practice Nurses
Physician Assistants
Physicians

Guideline Objective(s)

To present the evidence and provide clinical recommendations on the comparative effectiveness and safety of type 2 diabetes medications

Target Population

Adults with type 2 diabetes

Interventions and Practices Considered

1. Treatment with metformin when lifestyle changes fail to control hyperglycemia
2. Treatment with metformin plus a second agent* when monotherapy provides inadequate control

Note: Secondary agents include thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, and glucagon-like peptide-1 (GLP-1) inhibitors.

Major Outcomes Considered

- All-cause mortality
- Changes in hemoglobin A1c levels
- Cardiovascular morbidity and mortality
- Weight change
- Cerebrovascular morbidity
- Changes in plasma lipid levels
- Incidence of neuropathy, nephropathy, retinopathy
- Adverse effects of treatment

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The literature search included studies identified by using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The studies that were selected included observational studies and trials published in the English language from 1966 through April 2010. In addition, the MEDLINE search was updated to December 2010 for long-term clinical outcomes (all-cause mortality, cardiovascular morbidity and mortality, cerebrovascular morbidity, nephropathy, neuropathy, and retinopathy). Reference lists, US Food and Drug Administration (FDA) medical reviews, European Public Assessment Reports, Health Canada Product Monographs, unpublished data from pharmaceutical companies, and public registries of clinical trials were also reviewed.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

This guideline rates the evidence and recommendations by using the American College of Physicians (ACP) guideline grading system, which is based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (see the "Rating Scheme for the Strength of the Recommendations" field).

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Standardized forms were used for data abstraction, and each article underwent double review. Quality of randomized, controlled trials (RCTs) was assessed by using the Jadad criteria, and quality of observational studies was assessed as recommended in the Guide for Conducting Comparative Effectiveness Reviews. The $I^2$ statistic was used to determine study heterogeneity. Further details about the methods and inclusion and exclusion criteria applied in the evidence review are available in the full Agency for Healthcare Research and Quality (AHRQ) report (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The evidence report informing this guideline reviewed data for 11 US Food and Drug Administration (FDA)-approved, unique classes of drugs for the treatment of hyperglycemia in type 2 diabetes (see Appendix Table 1 in the original guideline document). This guideline is based on a systematic evidence review that addressed the following key questions:
• Key question 1: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options for the intermediate outcomes of glycemic control (in terms of hemoglobin A1c [HbA1c]), weight, or lipids?

• Key question 2: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options in terms of the following long-term clinical outcomes: all-cause mortality, cardiovascular mortality, cardiovascular and cerebrovascular morbidity (for example, myocardial infarction and stroke), retinopathy, nephropathy, and neuropathy?

• Key question 3: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative safety of these treatment options in terms of the following adverse events and side effects: hypoglycemia, liver injury, congestive heart failure, severe lactic acidosis, cancer, severe allergic reactions, hip and nonhip fractures, pancreatitis, cholecystitis, macular edema or decreased vision, and gastrointestinal side effects?

• Key question 4: Do safety and effectiveness of these treatment options differ across subgroups of adults with type 2 diabetes, in particular for adults aged 65 years or older, in terms of mortality, hypoglycemia, and cardiovascular and cerebrovascular outcomes?

The systematic evidence review was conducted by the Johns Hopkins Evidence-based Practice Center. This review updates a 2007 systematic review on the same topic and focuses on head-to-head comparisons rather than placebo-controlled trials.

This guideline rates the recommendations by using the American College of Physicians (ACP) guideline grading system, which is based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. Details of the ACP guideline development process can be found in ACP's methods paper. This guideline focuses on results that were statistically significant, and details on non-statistically significant results are available in the full Agency for Healthcare Research and Quality (AHRQ) report (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

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Insufficient evidence to determine net benefits or risks

*Adopted from the classification developed by the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) workgroup.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was approved by the American College of Physicians (ACP) Board of Regents on 19 November 2011.

Evidence Supporting the Recommendations
Type of Evidence Supporting the Recommendations
The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits
Appropriate pharmacologic treatment of patients with type 2 diabetes mellitus

Potential Harms
Adverse effects of medications

Contraindications

Contraindications
- Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart failure, and any condition that might lead to lactic acidosis.
- Thiazolidinediones are associated with an increased risk for heart failure, and both rosiglitazone and pioglitazone are contraindicated in patients with serious heart failure.

Qualifying Statements

Qualifying Statements
- Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians’ judgment.
- The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the U.S. Department of Veterans Affairs.

Implementation of the Guideline

Description of Implementation Strategy
An implementation strategy was not provided.

Implementation Tools
Mobile Device Resources
Patient Resources
For information about availability, see the Availability of Companion Documents and Patient Resources fields below.
Institute of Medicine (IOM) National Healthcare Quality Report

Categories

IOM Care Need
Living with Illness

IOM Domain
Effectiveness
Patient-centeredness
Safety

Identifying Information and Availability

Bibliographic Source(s)


Adaptation
Not applicable: The guideline was not adapted from another source.

Date Released
2012 Feb 7

Guideline Developer(s)
American College of Physicians - Medical Specialty Society

Source(s) of Funding
American College of Physicians

Guideline Committee
Clinical Guidelines Committee

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Financial Disclosures/Conflicts of Interest

Any financial and nonfinancial conflicts of interest of the group members were declared, discussed, and resolved. A record of conflicts of interest is kept for each Clinical Guidelines Committee meeting and conference call and can be viewed at www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm. Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-2857.

Guideline Status

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

Guideline Availability

Available from the Annals of Internal Medicine Web site.

Print copies: Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106; e-mail, aqaseem@acponline.org.

Availability of Companion Documents

The following are available:


Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

A collection of Recommendation Summaries for all current American College of Physicians Clinical Guidelines is now available for Personal Digital Assistant (PDA) download from the American College of Physicians Web site.

Patient Resources

The following is available:


Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

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NGC Status

This NGC summary was completed by ECRI Institute on March 30, 2012. This summary was updated by ECRI Institute on April 4, 2014 following the U.S. Food and Drug Administration (FDA) advisory on Rosiglitazone-containing Diabetes Medicines. This summary was updated by ECRI Institute on September 15, 2015 following the U.S. Food and Drug Administration (FDA) advisory on DPP-4 Inhibitors for Type 2 Diabetes. This summary was updated by ECRI Institute on April 12, 2016 following the U.S. Food and Drug Administration (FDA) advisory on Diabetes Medications Containing Saxagliptin and Alogliptin. This summary was updated by ECRI Institute on April 15, 2016 following the U.S. Food and Drug Administration advisory on Metformin-containing Drugs.

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