ROAD MAPS TO ACHIEVE GLYCEMIC CONTROL IN TYPE 2 DIABETES MELLITUS

ACE/AACE Diabetes Road Map Task Force

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The accompanying Diabetes Road Maps were created to provide direction for clinicians in achieving the hemoglobin A1c (A1C) glycemic goals established by the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE). The three Road Maps consist of the following: one for treatment-naïve patients (Fig. 1), one for treated patients not at A1C goal (Fig. 2), and a third focusing on the prevention of diabetes (Fig. 3). The Road Maps feature individualized treatment regimens based on the presenting A1C in treatment-naïve patients or the current A1C in treated patients, and they stress the need to advance therapy if the A1C goal is not met within 3 months. The importance of targeting the treatment of postprandial hyperglycemia in the lower A1C ranges is emphasized.

The following should be noted:

1. The evidence base for each of the medications listed in the columns of the Road Maps can be found in the appended bibliography, and the listed resources are annotated with the levels of evidence. Recommendations are based on A1C-lowering data from US Food and Drug Administration (FDA)-approved clinical trials as well as from the large randomized placebo- or comparator-controlled clinical trials published in peer-reviewed journals, and they are consistent with FDA-approved indications.

2. The relative or rank order of the medications listed in the Road Maps is derived from valid comparator trial data that were available. Because of the paucity of such well-designed head-to-head studies, however, the order of medications is provided as a template, is considerably dictated by the preference of the authors, and is based on extensive clinical experience. Therefore, the recommended order of interventions can be categorized primarily as expert opinions of the Diabetes Road Map Task Force.

It is hoped that these Road Maps will be helpful to clinicians in outlining the therapeutic options currently available to achieve the optimal level for glycemic control, as proposed by ACE and AACE.

DISCLOSURE

Dr. Lawrence Blonde has received grant and/or research support from Amylin Pharmaceuticals, Inc., AstraZeneca, Bristol-Myers Squibb Company, Eli Lilly and Company, MannKind Corporation, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Pfizer Inc., and sanofi-aventis. He has received speaker and consultant honoraria from Abbott Laboratories, Amylin Pharmaceuticals, Inc., GlaxoSmithKline, LifeScan, Inc., Eli Lilly and Company, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Pfizer Inc., and sanofi-aventis. He has received consultant honoraria from KOS Pharmaceuticals and U.S. Surgical Corporation. Dr. Blonde has also disclosed that his spouse is a stock shareholder of Amylin Pharmaceuticals, Inc. and Pfizer Inc., in an account that is not part of their community property.

Dr. Jaime A. Davidson has received consultant and/or speaker honoraria from Bristol-Myers Squibb Company, Calixto Medical, CureDM, Inc., Generex Biotechnology Corporation, GlaxoSmithKline, Johnson & Johnson, Eli Lilly and Company, Merck Germany, Merck Sharp & Dohme, Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Pfizer Inc., and sanofi-aventis. He has received consultant honoraria from KOS Pharmaceuticals and U.S. Surgical Corporation. Dr. Blonde has also disclosed that his spouse is a stock shareholder of Amylin Pharmaceuticals, Inc. and Pfizer Inc., in an account that is not part of their community property.

Dr. Daniel Einhorn has received clinical research support from Allergan, Inc., Eli Lilly and Company, Medtronic, Inc., Pfizer Inc., and sanofi-aventis. He has received consultant honoraria from Amylin Pharmaceuticals, Inc., Eli Lilly and Company, MannKind Corporation, Medtronic, Inc., and Takeda Pharmaceuticals America, Inc. He has received speaker honoraria from Amylin Pharmaceuticals, Inc., Merck & Co., Inc., sanofi-aventis, and Takeda Pharmaceuticals America, Inc.

Dr. George Grunberger has received grant/research support from Eli Lilly and Company, Mitsubishi, Pfizer Inc., and sanofi-aventis. He has received speaker honoraria from Amylin Pharmaceuticals, Inc., AstraZeneca, GlaxoSmithKline, Eli Lilly and Company, Merck & Co., Inc., Novo Nordisk Inc., Pfizer Inc., and sanofi-aventis.
**Road Map to Achieve Glycemic Goals: Naïve to Therapy (Type 2)**

<table>
<thead>
<tr>
<th>Initial A1C%</th>
<th>Achieve ACE Glycemic Goals (FPG, PPG, and A1C)</th>
<th>Continuous Titration of Rx (2-3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>Assess FPG and PPG</td>
<td>Monitor/adjust Rx to maximal effective dose to meet ACE Glycemic Goals</td>
</tr>
<tr>
<td>7-8</td>
<td>Target: PPG and FPG</td>
<td>Monitor/adjust Rx to maximal effective dose to meet ACE Glycemic Goals</td>
</tr>
<tr>
<td>8-9</td>
<td>Target: FPG and PPG</td>
<td>Monitor/adjust Rx to maximal effective dose to meet ACE Glycemic Goals</td>
</tr>
<tr>
<td>&gt;10</td>
<td>Insulin Therapy</td>
<td>Monitor/adjust Rx to maximal effective dose to meet ACE Glycemic Goals</td>
</tr>
</tbody>
</table>

**Interventions**
- **Initial Therapy**
  - Preferred:
    - Metformin®
    -TZD<sup>1</sup>,<sup>11</sup>
    -AGI
    -DPP-4 inhibitor
  - Alternatives:
    - Glinides
    - SU (low dose)
    - Prandial insulin<sup>2</sup>,<sup>3</sup>

**Alternatives**
- Prandial insulin<sup>2</sup>,<sup>3</sup>
- Premixed insulin preparations<sup>2</sup>,<sup>3</sup>
- NPH
- Other approved combinations

**Lifestyle Modification**
- Intensify or combine Rx including incretin mimetic<sup>1</sup>
- Intensify or combine Rx, including incretin mimetic with SU, TZD, and/or metformin
- Initiate or intensify insulin therapy or add incretin mimetic<sup>1</sup>

**Abbreviations in Road Maps:**
- ACE = American Association of Clinical Endocrinologists
- A1C = hemoglobin A1c
- AGI = α-glucosidase inhibitor
- DPP-4 = dipeptidyl peptidase-4
- FDA = US Food and Drug Administration
- FPG = fasting plasma glucose
- HDL = high-density lipoprotein
- IFG = impaired fasting glucose
- IGT = impaired glucose tolerance
- MNT = medical nutrition therapy
- OGTT = oral glucose tolerance test
- PPG = postprandial glucose
- RX = treatment
- SU = sulfonylurea
- TZD = thiazolidinediones

**References**
- Lawrence Blonde, MD, FACP, FACE; Richard Hellman, MD, FACP, FACE; Harold Lebovitz, MD, FACE;
- George Grunberger, MD, FACP, FACE; Yehuda Handelsman, MD, FACP, FACE;
- Jaime A. Davidson, MD, FACE, Co-Chair
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Road Map to Achieve Glycemic Goals: Treated Patients (Type 2)

**Abbreviations in Road Maps:**
AACE = American Association of Clinical Endocrinologists; A1C = hemoglobin A1c; ACE = American College of Endocrinology; AGI = α-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; FDA = US Food and Drug Administration; FPG = fasting plasma glucose; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; MNT = medical nutrition therapy; OGTT = oral glucose tolerance test; PPG = postprandial glucose; Rx = treatment; SU = sulfonylurea; TZD = thiazolidinedione

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### Current A1C%

<6.5%

**Current Therapy**

- Monotherapy or Combination Therapy

**Intervention**

- Continue current therapy if all ACE glycemic goals are met
- Adjust therapy as needed to meet ACE FPG and PPG goals

**Continuous Titration of Rx (2-3 months)**

- Monitor/adjust Rx to maintain ACE Glycemic Goals†

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6.5-8.5

**Continue Lifestyle Modification**

**Monotherapy:**

- Glinides, SU, AGI, metformin, TZD, DPP-4, premixed insulin preparations, prandial or basal insulin

**Intensity Lifestyle Modification**

- Initiate Combination Therapy

**Incretin Mimetic**

- Incretin mimetic + metformin and/or TZD

**Basal or Premixed Insulin**

- Basal or premixed insulin preparations

**Amylin Analog**

- Amylin analog with prandial insulin

**Other approved combinations including approved oral agents with insulin.**

- Monitor/adjust Rx to meet ACE Glycemic Goals†

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>8.5%

**Current Therapy**

- Monotherapy or Combination Therapy

**Intervention**

- Intensify Lifestyle Modification

**Initiate Insulin Therapy (Basal-Bolus)**

- Basal + prandial insulin

- Premixed insulin preparations

**Combine with approved oral agents**

- Monitor/adjust Rx to meet ACE Glycemic Goals†

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Road Map to PREVENT Type 2 Diabetes

FPG or 2-h OGTT is the recommended screening procedure

Age 30 or above for populations at high risk:
- Family history of diabetes
- Cardiovascular disease
- Overweight
- Sedentary lifestyle
- Latino/Hispanic, African American, Native American, or Pacific Islander
- Previously identified IGT or IFG
- Hypertension
- Elevated triglycerides, low HDL, or both
- History of gestational diabetes
- Delivery of a baby weighing more than 9 lbs
- Severe psychiatric illness

Early Identification

Lifestyle Modification
- Medical Nutrition Therapy (MNT)
- Physical Fitness Program
- Weight Loss
- 5-7% reduction in body weight (if overweight)
- 30 minutes exercise, 5 times per week at the equivalent of brisk walking

Pharmacologic
- Non-FDA Approved*
  - TZD**
  - Metformin
  - Orlistat
  - AGI

Persistent Monitoring of Glucose and Risk Reduction Measures
- Hypertension
- Dyslipidemia
- Physical Fitness
- Weight Control

* Shown to be effective in delaying the onset of type 2 diabetes in clinical studies
** A recent report (NEJM; 6/14/07) suggests a possible link of rosiglitazone to cardiovascular events that requires further evaluation

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AACE = American Association of Clinical Endocrinologists; A1C = hemoglobin A1c; ACE = American College of Endocrinology; AGI = α-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase-4; FDA = US Food and Drug Administration; FPG = fasting plasma glucose; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; MNT = medical nutrition therapy; OGTT = oral glucose tolerance test; PPG = postprandial glucose; Rx = treatment; SU = sulfonylurea; TZD = thiazolidinedione

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Dr. Yehuda Handselman has received speaker honoraria from Abbott Laboratories, Amylin Pharmaceuticals, Inc., AstraZeneca, Bristol-Myers Squibb Company, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, and sanofi-aventis and consultant honoraria from Abbott Laboratories, GlaxoSmithKline, and sanofi-aventis. He has also received grant support for research from sanofi-aventis.

Dr. Richard Hellman has received speaker honoraria from Daiichi Sankyo, Inc. and Pfizer Inc. as well as research grants from Abbott Laboratories, Medtronic, Inc., and Pfizer Inc.

Dr. Paul S. Jellinger has received speaker honoraria from GlaxoSmithKline, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., and Takeda Pharmaceuticals America, Inc.

Dr. Harold Lebovitz has received speaker honoraria from GlaxoSmithKline and sanofi-aventis. He has received advisory board honoraria from Amlin Pharmaceuticals, Inc., LifeScan, Inc., and Novartis Pharmaceuticals Corporation. He is a shareholder of Amlin Pharmaceuticals, Inc., Bristol-Myers Squibb Company, and sanofi-aventis stocks.

Dr. Philip Levy has received speaker honoraria from Abbott Laboratories, Amlin Pharmaceuticals, Inc., GlaxoSmithKline, Eli Lilly and Company, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Novo Nordisk Inc., Pfizer Inc., and sanofi-aventis. He has also received research grants from Amlin Pharmaceuticals, Inc., GlaxoSmithKline, MannKind Corporation, Novo Nordisk Inc., Pfizer Inc., and sanofi-aventis.

Dr. Victor L. Roberts has received speaker honoraria from GlaxoSmithKline, Eli Lilly and Company, Merck & Co., Inc., Novo Nordisk Inc., Pfizer Inc., and sanofi-aventis and has been a speaker for Bristol-Myers Squibb Company and Takeda Pharmaceuticals America, Inc.

BIBLIOGRAPHY

General

Combination Orally Administered Agents

α-Glucosidase Inhibitors
1. Acarbose (Precose) [package insert]. West Haven, CT: Bayer Pharmaceuticals, 2004. (Not rated)
Incretin Mimetic, Dipeptidyl Peptidase-4 Inhibitors, Amylin Analogue


Insulin


7. 50% NPL/50% lispro (lispro mix 50/50) [package insert]. Indianapolis, IN: Eli Lilly and Company, 2006. (Not rated)


**Insulin Secretagogues**


**Metformin**


**Postprandial Glucose**


Self-Monitoring of Blood Glucose


Thiazolidinediones


