Prevention, Management and Diagnosis of Diabetes

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- Endocrine Certified Neck Ultrasound
- March 27, 2021
## Disclosure

<table>
<thead>
<tr>
<th>Industry Relationship</th>
<th>Company Name</th>
<th>Role</th>
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<tr>
<td>Advisor/Consultant</td>
<td>Merck</td>
<td>Consultant</td>
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<td>Medtronic</td>
<td>Consultant/Speaker</td>
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<td>Industry Research</td>
<td>Eli-Lilly</td>
<td>PI / Sub-PI</td>
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<td>Enanta Pharmaceuticals</td>
<td>Sub-PI</td>
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<td>Objectives</td>
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<tr>
<td>Know the prevalence of T2DM in Puerto Rico</td>
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<tr>
<td>Review the screening methods for diagnosis prediabetes and diabetes</td>
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<td>Review the current recommendations and standards of care for the management of Prediabetes</td>
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<tr>
<td>Review the current recommendations and standards of care for the management of type 2 diabetes.</td>
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<tr>
<td>Review recent advances in the therapeutic options available for glycemic control including it’s cardiovascular risk reduction</td>
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Question 1

- A 45-year-old Hispanic without medical history comes to the office for evaluation. Her only medication is a multivitamin. She does not have a family history of type 2 diabetes.

- Physical examination
  - BMI: 26
  - BP: 125/82 mmHg
In addition to lifestyle modifications, which is of the following is the next best step management regarding diabetes risk.

- A. Perform screening now
- B. Perform screening in 2 years
- C. No need to perform Diabetes screening.
- D. Perform screening if starts symptoms such as polyuria, polydipsia and polyphagia.
<table>
<thead>
<tr>
<th>Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing should be considered in overweight or obese (BMI ≥ 25 kg/m² or ≥ 23 kg/m² in Asian Americans) adults who have one or more of the following risk factors:</td>
</tr>
<tr>
<td>• First-degree relative with diabetes</td>
</tr>
<tr>
<td>• High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)</td>
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<tr>
<td>• History of CVD</td>
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<tr>
<td>• Hypertension (≥ 140/90 mmHg or on therapy for hypertension)</td>
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<td>• HDL cholesterol level &lt; 35 mg/dL (0.90 mmol/L) and/or a triglyceride level &gt; 250 mg/dL (2.82 mmol/L)</td>
</tr>
<tr>
<td>• Women with polycystic ovary syndrome</td>
</tr>
<tr>
<td>• Physical inactivity</td>
</tr>
<tr>
<td>• Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)</td>
</tr>
<tr>
<td>2. Patients with prediabetes (A1C ≥ 5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.</td>
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<tr>
<td>3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.</td>
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<tr>
<td>4. For all other patients, testing should begin at age 45 years.</td>
</tr>
<tr>
<td>5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.</td>
</tr>
</tbody>
</table>
Criteria for the Diagnosis of Diabetes

- **Fasting plasma glucose (FPG)**
  \[ \geq 126 \text{ mg/dL (7.0 mmol/L)} \]
  
  **OR**

- **2-h plasma glucose**
  \[ \geq 200 \text{ mg/dL (11.1 mmol/L) during an OGTT} \]
  
  **OR**

- **A1C**
  \[ \geq 6.5\% \]
  
  **OR**

- **Random plasma glucose**
  \[ \geq 200 \text{ mg/dL (11.1 mmol/L)} \]
Prediabetes*

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

* For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. Diabetes Care 2019; 42 (Suppl. 1): S13-S28
PREVALENCIA DE DIABETES EN PUERTO RICO, BRFSS, 1996-2010

2011: 13.5%
2016: 16.4%
2020: 16.8%

Standards of Medical Care in Diabetes - 2021
Classification of Diabetes

- Type 1 diabetes
  - β-cell destruction
- Type 2 diabetes
  - Progressive insulin secretory defect
- Gestational Diabetes Mellitus (GDM)

**Other specific types of diabetes due to other causes:**
- Monogenic diabetes syndromes
- Diseases of the exocrine pancreas (cystic fibrosis)
- Drug- or chemical-induced diabetes
Question 2

A 39-year-old obese man is referred after a fingerstick blood glucose measurement at a health screening fair at work was documented to be 115 mg/dL (9.9 mmol/L). He had recently eaten lunch. His medical history is notable for dyslipidemia that is well controlled on simvastatin, gout, and obesity.

On physical examination, his blood pressure is 132/78 mm Hg and his BMI is 41.5 kg/m2. Acanthosis nigricans is present, but there are no other notable findings on physical examination.

You reassess his glycemic status:

- Fasting plasma glucose (laboratory) = 119 mg/dL (70-99 mg/dL) (SI: 6.6 mmol/L [3.9-5.5 mmol/L])
- Hemoglobin A1c = 6.3% (4.0%-5.6%) (SI: 49 mmol/mol [20-38 mmol/mol])
What is the next best step of management

- A. Lifestyle Modifications with target of 7% weight loss
- B. Start Metformin 500 mg once daily
- C. Start dapagliflozin 10 mg once daily
- D. None of the above
Progression to Type 2 Diabetes

Impaired Glucose Tolerance
Impaired Fasting Glucose
Prediabetes
Diabetes

Or both
Pathophysiologic Progression of Type 2 Diabetes and Its Vascular Complications

Relative function

Insulin resistance

Insulin secretion

β-cell failure

Postprandial glucose

Fasting glucose

DM diagnosis

OBESITY/ METAB SYND

IFG

IGT

T2DM

UNCONTROLLED HYPERGLYCEMIA

Glucose (mg/dL)

Relative function

MACROVASCULAR COMPLICATIONS

MICROVASCULAR COMPLICATIONS

Time (years)

-10

-5

0

5

10

15

20

25

30

0%

50%

100%

150%

200%

250%

300%

350%


IFG = impaired fasting glucose

IGT = impaired glucose tolerance

T2DM = type 2 diabetes mellitus

IFG = impaired fasting glucose

IGT = impaired glucose tolerance

T2DM = type 2 diabetes mellitus

Association between preDM & all-cause mortality and CVD

**Studies:**
129

**People:**
10,069,955

**Follow-up:**
9.8 yrs

In those with ASCVD, preDM was associated with a greater relative risk (over 3.2 yrs) for:
- ALL CAUSE DEATH: RR 1.36 (1.21-1.54)
- COMPOSITE CVD: RR 1.37 (1.23-1.53)

A similarly increased relative risk for:
- CHD: RR 1.15 (1.02-1.29)

But not for:
- STROKE 1.05 (0.81-1.36)
### T2DM Doubles the Risk for Macrovascular Outcomes

Meta-Analysis of 102 Prospective Studies

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>HR (95% CI)</th>
<th>( P ) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary heart disease</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26,505</td>
<td>2.00 (1.83-2.19)</td>
</tr>
<tr>
<td><strong>Coronary death</strong></td>
<td>11,556</td>
<td>2.31 (2.05-2.60)</td>
</tr>
<tr>
<td><strong>Nonfatal MI</strong></td>
<td>14,741</td>
<td>1.82 (1.64-2.03)</td>
</tr>
<tr>
<td><strong>Stroke subtypes</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td>3,799</td>
<td>2.27 (1.95-2.56)</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>1,183</td>
<td>1.56 (1.19-2.05)</td>
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<tr>
<td><strong>Unclassified stroke</strong></td>
<td>4,973</td>
<td>1.84 (1.59-2.13)</td>
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<tr>
<td><strong>Other vascular deaths</strong></td>
<td>3,826</td>
<td>1.73 (1.51-1.98)</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Includes both fatal and nonfatal events. Emerging Risk Factors Collaboration. *Lancet.* 2010;375:2215-22
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>N</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Duration</th>
<th>RRR</th>
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<tbody>
<tr>
<td>Da Qing</td>
<td>1997</td>
<td>577</td>
<td>IGT</td>
<td>Lifestyle</td>
<td>~6 years</td>
<td>32%</td>
</tr>
<tr>
<td>Finnish DPS</td>
<td>2001</td>
<td>522</td>
<td>IGT</td>
<td>Lifestyle</td>
<td>3.2 years</td>
<td>58%</td>
</tr>
<tr>
<td>US DPP</td>
<td>2002</td>
<td>3234</td>
<td>IGT</td>
<td>Lifestyle</td>
<td>2.8 years</td>
<td>58%</td>
</tr>
<tr>
<td>US DPP</td>
<td>2002</td>
<td>3234</td>
<td>IGT</td>
<td>Metformin (biguanide)</td>
<td>2.8 years</td>
<td>31%</td>
</tr>
<tr>
<td>STOP NIDDM</td>
<td>2002</td>
<td>1418</td>
<td>IGT</td>
<td>Acarbose (AGI)</td>
<td>3.3 years</td>
<td>25%</td>
</tr>
<tr>
<td>XENDOS</td>
<td>2004</td>
<td>3305</td>
<td>IGT</td>
<td>Orlistat (lipase inhibitor)</td>
<td>~4 years</td>
<td>37%</td>
</tr>
<tr>
<td>DREAM</td>
<td>2006</td>
<td>5269</td>
<td>IGT/IFG</td>
<td>Rosiglitazone (TZD)</td>
<td>3.0 years</td>
<td>62%</td>
</tr>
<tr>
<td>NAVIGATOR</td>
<td>2010</td>
<td>9031</td>
<td>IGT + high CV risk</td>
<td>Nateglinide (meglitinide)</td>
<td>5.0 years</td>
<td>NS</td>
</tr>
<tr>
<td>ACT NOW</td>
<td>2011</td>
<td>602</td>
<td>IGT</td>
<td>Pioglitazone (TZD)</td>
<td>2.4 years</td>
<td>72%</td>
</tr>
<tr>
<td>ORIGIN*</td>
<td>2012</td>
<td>1456</td>
<td>IGT + high CV risk</td>
<td>Glargine (basal insulin)</td>
<td>6.2 years</td>
<td>20%</td>
</tr>
<tr>
<td>CONQUER*</td>
<td>2014</td>
<td>866</td>
<td>Pre-DM / MetS</td>
<td>Phentermine/Topiramate</td>
<td>~2 years</td>
<td>79%</td>
</tr>
<tr>
<td>IRIS*</td>
<td>2016</td>
<td>3876</td>
<td>Stroke + insulin resistance</td>
<td>Pioglitazone (TZD)</td>
<td>4.8 years</td>
<td>52%</td>
</tr>
<tr>
<td>SCALE</td>
<td>2017</td>
<td>2254</td>
<td>Obesity + prediabetes</td>
<td>Liraglutide (GLP-1 RA)</td>
<td>~3 years</td>
<td>79%</td>
</tr>
<tr>
<td>CAMELLIA*</td>
<td>2018</td>
<td>12,000</td>
<td>Overweight + high CV risk</td>
<td>Lorcaserin (serotonergic)</td>
<td>3.3 years</td>
<td>19%</td>
</tr>
</tbody>
</table>

* Not primary outcome

Long-term follow-up of the DPP participants: DPP-OS

- 1996-2001
- 3234 persons with preDM (IGT + FPG >95)
- Interventions: Lifestyle change (7% body wt loss, 150 min exercise/wk) vs. metformin (850 mg BID), vs. placebo
- 2.8 yrs follow-up
- mean age, 51 yrs
- mean BMI, 34
- 45% minority groups
- DPPOS: Ongoing follow-up after randomized component of trial completed

DPP Research Group. Lancet 2009;374:1677-86
DPP Research Group. Lancet Diabetes Endocrinol 2015;3:86-75
Long-term follow-up of the DPP participants: DPP-OS

- **Microvascular outcomes**

Participants who did **not** develop T2D during DPP/DPPOS had a 28% lower (RR 0.72, p=0.01) aggregate microvascular disease prevalence than those who did develop T2D - for all treatment groups combined.

In women, the prevalence of aggregate microvascular outcome was 22% lower (RR 0.78, p=0.02) lower in the lifestyle group vs. metformin and 21% lower (RR 0.79, p=0.03) vs. placebo.

Long-term (10-years) follow-up of the DPP participants: DPP-OS

- **Macrovascular outcomes**
  - Major improvements in SBP (↓ 2-3 mmHg) and DBP (↓ 5-6 mmHg) for LDL-C (↓ 18-21 mg/dl), HDL-C (↑ 5-6 mg/dl), and TGs (↓ 16-28 mg/dl) in all groups, with no between-group differences.
  - Lipid ($P < 0.012$) and BP ($P < 0.09$) med use, however, was lower for the lifestyle group during DPP-OS.

Long-term (10-years) follow-up:

**New Data from DPP-OS Shows Persistent Reduction of T2D Development Over 22-Year Average Follow-Up**

- Prevention effects in original lifestyle group and metformin groups remain after 22 years: 25% & 18% ↓ risk of T2D, respectively, vs. placebo.
- Those who did not develop T2D had a significant 57% and 37% ↓ risk of retinopathy and nephropathy, respectively.

**MACE.**
- Despite the benefits seen with DM prevention overall, no significant benefit seen with the individual interventions for these outcomes.
- However, there were favorable trends with metformin in stroke reduction and for MACE in the subgroup of people before age 45.

Nathan DM. *80th Scientific Sessions of the ADA*, June 2020
DAPA-HF Design

**Inclusion:**
- NYHA class II-IV
- LVEF ≤40%
- NT-proBNP ≥600 pg/ml*

**Exclusion:**
- eGFR <30 ml/min/1.73 m²
- SBP <95 mmHg
- Type 1 diabetes

**Visit Schedule:**
- Visit 1: Day -14
- Visit 2: Day 0
- Visit 3: Day 14
- Visit 4: Day 60
- Visit 5: Day 120
- Visit 6 etc.: Every 120 days

**Randomization:**
- N=2371
- Placebo

**Treated:**
- N=2373
- Dapagliflozin 10 mg once daily

**≥844 Primary outcomes**
- Composite of:
  - CV death
  - HF hospitalization
  - Urgent HF visit

*≥400 pg/ml if HF hospitalization within ≤12 months; ≥900 pg/ml if atrial fibrillation/flutter
Dapagliflozin reduced worsening HF or CV death in patients with HFrEF

CV Death/HF hospitalization/Urgent HF visit

**HR 0.74 (0.65, 0.85)**  
**p=0.00001**  
**NNT=21**


---

**Similar benefit in patients with and without T2DM**

**HR (95% CI)**  
All patients: **0.74 (0.65, 0.85)**  
T2D at baseline*  
   - Yes: **0.75 (0.63, 0.90)**  
   - No: **0.73 (0.60, 0.88)**

---

*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrolment and randomization visits.
Distribution of Patients by Glycemic Status: HFrEF Population

N=4744

- No diabetes (55%)
- History of diabetes (42%)
- Undiagnosed diabetes (3%)

**History of diabetes (n=1983)**
- Provided by investigators

**Undiagnosed diabetes (n=156)**
- HbA1c ≥6.5% at Visits 1 and 2 in paVents without diabetes history

**No diabetes (n=2605)**
- HbA1c <6.5% at Visits 1 and 2

Petrie MC et al. JAMA 2020;323:1353-68
Results:
Incidence of new onset T2D in dapa vs. placebo groups

Placebo: 93/1307 (7.1%; 5.0/100 pt-yrs)
Dapa: 64/1298 (4.9%; 3.4/100 pt-yrs)

HR = 0.68 (95% CI, 0.50-0.94); p=0.019

32% ↓ in new onset DM2

Median follow-up:
18.2 months (IQR, 14.2-21.5)

Number at Risk
Dapagliflozin 1298 1266 1233 1208 1147 895 666 366 123
Placebo 1307 1268 1225 1198 1127 874 642 358 125

Fine & Gray: HR 0.69 (0.50-0.95)
LR adjusted for baseline HbA1c: OR 0.72 (0.51, 1.02)
Type 2 Diabetes - a Chronic Degenerative Disease: Potential for Intervention

Most trials have captured brief vignettes in a chronic life-long disease.

IGT          Type 2 DM  Early  Complications  Morbidity/Mortality

Current Diagnosis

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CVD safety studies-Median F-U
- EMPA-Reg 3.1  CANVAS  2.4
- LEADER  3.8  EXCSEL  3.2
- SUSTAIN  2.1  CAROLINA  6.3
- ACCORD  4.2  DECLARE  2.6
- ADVANCE  1.3  EXCSEL  3.2
- ELIXA  2.1  CANVAS  2.4
- VERTIS  3.0  EMPA-Reg  3.1

Mean DM duration ~11-14 years

Mean DM duration ~11-14 years

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Most strongly established rationale for controlling glycemia in T2DM is the reduction in microvascular complications.

Reduction in microvascular complications roughly proportional to A1c reduction.
Relationship between Glycemia and Microvascular Complications

DCCT (Type 1) and UKPDS (Type 2)

Although lower is better for microvascular complications in both type 1 and 2 diabetes, A1c of 7% was selected as the target as:

1) 7% was the A1c achieved in DCCT and UKPDS;
2) Absolute risks for complications quite low at HbA1c under 7%;
3) Balances benefits, risks and costs.
Scope of the Problem: Therapeutic Inertia

Summary of Scope of Problem

- Not all patients with type 2 reach appropriate metabolic goals
- Clinicians are slow to change therapy
GLYCEMIC CONTROL ALGORITHM

INDIVIDUALIZE GOALS

A1C ≤6.5%
For patients without concurrent serious illness and at low hypoglycemic risk

A1C >6.5%
For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY AND ONGOING GLUCOSE MONITORING (CGM preferred)

INDEPENDENT OF GLYCEMIC CONTROL, IF ESTABLISHED OR HIGH ASCVD RISK AND/OR CKD, RECOMMEND SGLT2i AND/OR LA GLP1-RA

Entry A1C ≥7.5% - 9.0%

DUAL THERAPY
- GLP1-RA
- SGLT2i
- DPP4i
- TZD
- SU/GLN
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi

TRIPLE THERAPY
- GLP1-RA
- SGLT2i
- TZD
- SU/GLN
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi

3 MONTHS

3 MONTHS

ENTRY A1C <7.5%

MONOTHERAPY
- Metformin
- GLP1-RA
- SGLT2i
- DPP4i
- TZD
- AGi
- SU/GLN

Independent of glycemic control, if established ASCVD or high risk. CKD 3, or HFrEF, start LA GLP1-RA or SGLT2i with proven efficacy

Entry A1C >9.0%

SYMPTOMS

NO
DUAL Therapy
OR
TRIPLE Therapy

YES
ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

SYMBOLS

- Few adverse events and/or possible benefits
- Use with caution

LEGEND

PROGRESSION OF DISEASE

1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation
2 If not at goal in 3 months, proceed to next level therapy

CKD 3: canagliflozin; HFrEF: dapagliflozin
CKD 3 = stage 3 chronic kidney disease; HFrEF = heart failure with reduced ejection fraction; LA = long-acting (624 hour duration)
ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

- **A1C <8%**
  - TDD 0.1–0.2 U/kg

- **A1C >8%**
  - TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:
- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG >180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
  - If hypoglycemia, reduce TDD by:
    - BG <70 mg/dL: 10% – 20%
    - BG <40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

*Glycemic Goal:*
- <7% for most patients with T2D; fasting and premeal BG <110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

INTENSIFY (Prandial Control)

- Add GLP1-RA
  - Or SGLT2i
  - Or DPP4i

- Add Prandial Insulin

- Basal Plus 1, Plus 2, Plus 3
  - Begin prandial insulin before largest meal
  - If not at goal, progress to injections before 2 or 3 meals
  - Start: 10% of basal dose or 5 units

- Basal Bolus
  - Begin prandial insulin before each meal
  - 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
  - Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:
- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently >140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently <70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG <40 mg/dL: 20% - 40%

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Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals.

If injectable therapy is needed to reduce A1C

Consider GLP-1 RA in most patients prior to insulin

**INITIATION**: Initiate appropriate starting dose for agent selected (varies within class)

**TITRATION**: Titration to maintenance dose (varies within class)

If above A1C target

Add basal insulin

Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to *Table 9.3* for insulin cost information.

Add basal analog or bedtime NPH insulin

**INITIATION**: Start 10 IU a day OR 0.1-0.2 IU/kg a day

**TITRATION**:
- Set FPG target (see Section 6: Glycemic Targets)
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10-20%

Assess adequacy of basal insulin dose

Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose >0.5 IU/kg, elevated bedtime-morning and/or post-prandial differential, hypoglycemia [aware or unaware], high variability).

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred

*TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)*
PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

If above A1C target

Consider GLP-1 RA if not already in regimen
For addition of GLP-1 RA, consider lowering insulin dose dependent on current glycemic assessment and patient factors

Add prandial insulin
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

INITIATION:
- 4 IU a day or 10% of basal insulin dose
- If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose

TITRATION:
- Increase dose by 1-2 IU or 10-15% twice weekly
- For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10-20%

If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is one possible approach:

INITIATION:
- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:
- Titrate based on individualized needs

If above A1C target

Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)

Proceed to full basal-bolus regimen
(i.e., basal insulin and prandial insulin with each meal)

Consider self-mixed/split insulin regimen
Can adjust NPH and short/rapid-acting insulins separately

INITIATION:
- Total NPH dose = 80% of current NPH dose
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 IU of short/rapid-acting insulin to each injection or 10% of reduced NPH dose

TITRATION:
- Titrate each component of the regimen based on individualized needs

Consider twice daily premix insulin regimen

INITIATION:
- Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs

TITRATION:
- Titrate based on individualized needs
SHOULD ANTIHYPERGLYCEMIC THERAPY BE FOCUSED ON REDUCING CARDIOVASCULAR RISK?
Diabetes and Cardiovascular Risk

MI, myocardial infarction.
Intensive Glycemic Control Reduces Long-term Macrovascular Risk

**DCCT**
T1D, 5-6 years duration
(N=1441)

**UKPDS**
T2D, newly diagnosed
(N=4209)

42% risk reduction
\(P=0.02\)

15% risk reduction
\(P=0.01\)

CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; T1D, type 1 diabetes; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.

**Timeline of Major Diabetes Outcomes Trials**

Blue = Intensive vs standard control using same set of glucose-lowering agent(s)

Purple = Intensive control with a specific agent vs standard care

Red = Placebo- or active-controlled study

* = FDA-mandated cardiovascular safety trial

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CANVAS, Canagliflozin Cardiovascular Assessment Study; DCCT, Diabetes Control and Complications Trial; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG, EMPA-REG OUTCOME trial; EXEN; Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; PROActive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; SUSTAIN, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Sitagliptin in Subjects with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.
Cardiovascular Outcomes Trials: A Brief History

- 2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs
  - Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo
    - Some study designs tested for superiority if noninferiority criteria were met
  - Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke
    - Some primary endpoints included additional components

MACE = major adverse cardiovascular events; RCTs, randomized controlled trials.
### Large CV Outcomes Trials in Diabetes (Non-Insulin)

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4-i</td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>lama</td>
<td>placebo</td>
<td>place</td>
<td>sulfonylurea</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>16,560</td>
<td>14,500</td>
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<tr>
<td>Results</td>
<td>2016</td>
<td>2015</td>
<td>2016</td>
<td>2018</td>
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<table>
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<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUSTAIN 6</th>
<th>EXCSEL</th>
<th>REWIND</th>
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<tbody>
<tr>
<td>GLP1-RA</td>
<td>liraglutide</td>
<td>lixisenatide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>place</td>
<td>placebo</td>
<td>place</td>
</tr>
<tr>
<td>N</td>
<td>14,000</td>
<td>6,000</td>
<td>5,400</td>
<td>8,300</td>
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<td>2016</td>
<td>2018</td>
<td>2018</td>
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</table>

<table>
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<tr>
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<th>EMPA-REG</th>
<th>CANVAS</th>
<th>DECLARE</th>
<th>NCT01986881</th>
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</thead>
<tbody>
<tr>
<td>SGLT-2-i</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>place</td>
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<td>N</td>
<td>7,080</td>
<td>4,380</td>
<td>3,280</td>
<td>3,900</td>
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<tr>
<td>Results</td>
<td>2015</td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
</tr>
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</table>

HARMONY
Albiglutide
Final 2018
9,463
Preliminary
<table>
<thead>
<tr>
<th>Drug</th>
<th>Subjects with Established CVD</th>
<th>Non-Fatal MI</th>
<th>Non-Fatal CVA</th>
<th>CV Death</th>
<th>3-Pt MACE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide LEADER</td>
<td>~81%</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Positive</td>
<td>Positive</td>
<td>3-Pt MACE Driven by significant ↓ in CV death Relative risk reduction ~22%</td>
</tr>
<tr>
<td>9340 Patients</td>
<td></td>
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<tr>
<td>Semaglutide SQ SUSTAIN-6 Study</td>
<td>~83%</td>
<td>Neutral</td>
<td>Positive</td>
<td>Neutral</td>
<td>Positive</td>
<td>3-Pt MACE Driven by significant ↓ in non-fatal CVA Relative risk reduction ~39%</td>
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<td>3297 Patients</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Semaglutide PO PIONEER-6 Study</td>
<td>~85%</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Positive</td>
<td>Positive</td>
<td>3-Pt MACE Driven by significant ↓ in CV death Relative risk reduction ~51%</td>
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<tr>
<td>3183 Patients</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Lixisenatide ELIXA STUDY</td>
<td>100%</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>NA</td>
</tr>
<tr>
<td>6068 Patients</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide EXCEL Study</td>
<td>~73%</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>3-Pt MACE Barely missed significance, HR 0.91 (p=0.06) Relative risk reduction ~9%</td>
</tr>
<tr>
<td>14752 Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alboglutide HARMONY Study</td>
<td>100%</td>
<td>Positive</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Positive</td>
<td>3-Pt MACE Driven by significant ↓ in fatal and non-fatal MI Relative risk reduction ~25%</td>
</tr>
<tr>
<td>9463 Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulaglutide REWIND Study</td>
<td>~31%</td>
<td>UNK</td>
<td>UNK</td>
<td>UNK</td>
<td>Positive</td>
<td>Full results not released/published</td>
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<tr>
<td>9901 Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

Hupfer C, Mudaliar S. Diab Obes Metab, 2019
<table>
<thead>
<tr>
<th>MACE Events in CVOTs with SGLT2 Inhibitors</th>
<th>Cardiovascular Benefits</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Subjects with Established CVD</strong></td>
<td><strong>Non-Fatal MI</strong></td>
<td><strong>Non-Fatal CVA</strong></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>100%</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>EMPA-REG</strong></td>
<td>7020 Patients</td>
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<tr>
<td>Canagliflozin</td>
<td>66%</td>
<td>Neutral</td>
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<tr>
<td><strong>CANVAS Program</strong></td>
<td>10142 Patients</td>
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<tr>
<td>Dapagliflozin</td>
<td>41%</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>DECLARE-TIMI</strong></td>
<td>17160 Patients</td>
<td></td>
</tr>
</tbody>
</table>

Hupfer C, Mudaliar S. Diab Obes Metab, 2019
Canagliflozin (Invokana) Gets FDA Nod for CV Protection

Megan Brooks  
October 31, 2018

The US Food and Drug Administration (FDA) has approved the sodium-glucose cotransporter type 2 (SGLT2) inhibitor canagliflozin (Invokana, Janssen) to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes who have established cardiovascular disease (CVD).

With FDA approval of the supplemental new drug application, canagliflozin becomes the first oral diabetes drug indicated to reduce the risk of myocardial infarction (MI), stroke, or death due to a cardiovascular cause, the company said in a news release.
Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

https://doi.org/10.2337/dc18-0033
SGLT2i: empagliflozin, canagliflozin
GLP1: liraglutide > semaglutide > exenatide LAR

Now in SGLT2i:
Empagliflozin: CV death
Canagliflozin: nonfatal MI, nonfatal stroke and CV death
Dapagliflozin: Hospitalizations for HF
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

In those WITHOUT established ASCVD OR CKD

Use principles in Figure 1

First-line therapy is metformin
If HbA\(_1c\) is ≥17 mmol/mol (1.5%) above individualized HbA\(_1c\) target consider early combination therapy

If HbA\(_1c\) above target

EITHER/ OR

GLP-1 RA with good efficacy for weight loss\(^1\)
SGLT2i if eGFR adequate\(^2\)

If HbA\(_1c\) above target

SGLT2i if eGFR adequate\(^2\)
GLP-1 RA with good efficacy for weight loss\(^1\)

If HbA\(_1c\) above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
- SU\(^1\) + TZD\(^2\) + Basal insulin

Implement strategies for maximizing weight loss

General lifestyle advice
- Medical nutritional therapy
- Eating patterns
- Physical activity

Consider medication for weight loss

Consider metabolic surgery

Non-surgical energy restriction for weight loss
Weight loss of 15 kg can lead to remission of T2DM in patient ~6 years' duration, consider evidence-based weight loss programs
## Algorithm for Individualizing Glycemic Targets

<table>
<thead>
<tr>
<th>Most intensive</th>
<th>Less intensive</th>
<th>Least intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0%</td>
<td>7.0%</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

### Psychosocioeconomic considerations
- Highly motivated, adherent, knowledgeable, excellent self-care capacities, and comprehensive support systems
- Less motivated, nonadherent, limited insight, poor self-care capacities, and weak support systems

### Hypoglycemia risk
- Low
- Moderate
- High

### Patient age, years
- 40
- 45
- 50
- 55
- 60
- 65
- 70
- 75

### Disease duration, years
- 5
- 10
- 15
- 20

### Other comorbid conditions
- None
- Few or mild
- Multiple or severe

### Established vascular complications
- None
- Cardiovascular disease
- Early microvascular
- Advanced microvascular

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT
10.4 For individuals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >15%), a blood pressure target of <130/80 mmHg may be appropriate, if it can be safely attained.

10.5 For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year atherosclerotic cardiovascular disease risk <15%), treat to a blood pressure target of <140/90 mmHg.
### Goal BP and Initial Therapy in Diabetes to Reduce CV / Renal Risk?

<table>
<thead>
<tr>
<th>Group</th>
<th>Goal BP (mmHg)</th>
<th>Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA (2018)</td>
<td>&lt;140/90; high risk</td>
<td>ACE Inhibitor/ARB (only if nephropathy or heart failure present)</td>
</tr>
<tr>
<td>ACC/AHA BP (2017)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>KDIGO/KDOQI (NKF) (2013)</td>
<td>&lt;140/90</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>KDOQI (NKF) (2004)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>JNC 7 (2003)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Am. Diabetes Assoc (2003)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Canadian HTN Soc. (2002)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Am. Diabetes Assoc (2002)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor*</td>
</tr>
<tr>
<td>British HTN Soc. (1999)</td>
<td>&lt;140/80</td>
<td>ACE Inhibitor</td>
</tr>
<tr>
<td>JNC VI (1997)</td>
<td>&lt;130/85</td>
<td>ACE Inhibitor</td>
</tr>
</tbody>
</table>

* Indicates use with diuretic
INTENSIVE BLOOD PRESSURE MANAGEMENT MAY SAVE LIVES

WHAT'S THE BEST WAY TO TREAT HIGH BLOOD PRESSURE IN PATIENTS 50 AND OLDER? The SPRINT trial enrolled more than 9,300 participants at UAB and other locations to find out. Investigators divided them into two groups:

STANDARD TREATMENT

TARGET: 140 mmHg
Systolic BP

THERAPY: Avg. 2 different blood pressure medications

RESULTS: ABOUT 30% lower rates of heart attack, heart failure, and other cardiovascular events

INTENSIVE TREATMENT

TARGET: 120 mmHg
Systolic BP

THERAPY: Avg. 3 different blood pressure medications

RESULTS: ABOUT 25% lower risk of death among participants receiving intensive treatment
Weight loss
Sodium intake less than 2,300 mg /day
Increase consumption of fruits and vegetables
• 8-10 servings per day
Alcohol intake
• 2 for men
• 1 for women
Low fat dairy products
• 2-3 servings per day
Table 10.2—Recommendations for statin and combination treatment in adults with diabetes

<table>
<thead>
<tr>
<th>Age</th>
<th>ASCVD or 10-year ASCVD risk ≥20%</th>
<th>Recommended statin intensity^ and combination treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>No</td>
<td>None†</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#</td>
</tr>
<tr>
<td>≥40 years</td>
<td>No</td>
<td>Moderate‡</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#</td>
</tr>
</tbody>
</table>
Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia → statin

Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dl (≥4.1 mmol/L)

Age 40-75 y and LDL-C ≥70-<190 mg/dl (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dl (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

Risk discussion:
Emphasize lifestyle to reduce risk factors (Class I)

<5%
"Low Risk"

5% - <7.5%
"Borderline Risk"

≥7.5% - <20%
"Intermediate Risk"

Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

≥20%
"High Risk"

Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

Risk discussion:
Initiate statin to reduce LDL-C ≥50% (Class I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = 0 (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

LDL-C ≥190 mg/dl (≥4.9 mmol/L)
No risk assessment; High-intensity statin (Class I)

Diabetes mellitus and age 40-75 y
Moderate-intensity statin (Class I)

Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin (Class IIa)

Age >75 y
Clinical assessment, Risk discussion

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/dl, ≥2.0 mmol/l)

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L.
- Lp(a) levels >50 mg/dl or >125 nmol/L
- apoB ≥130 mg/dl.
- Ankle-brachial index (ABI) <0.9
Table 5. Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

<table>
<thead>
<tr>
<th>Risk Enhancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Long duration (≥10 years for type 2 diabetes mellitus)</td>
</tr>
<tr>
<td>• Albuminuria ≥30 mcg of albumin/mg creatinine</td>
</tr>
<tr>
<td>• eGFR &lt;60 mL/min/1.73 m²</td>
</tr>
<tr>
<td>• Retinopathy</td>
</tr>
<tr>
<td>• Neuropathy</td>
</tr>
<tr>
<td>• ABI &lt;0.9</td>
</tr>
<tr>
<td>Risk category</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Extreme risk</td>
</tr>
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<tr>
<td>Very high risk</td>
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<tr>
<td>High risk</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
</tr>
<tr>
<td>Low risk</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.
Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD, Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD, Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD, Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, Christie M. Ballantyne, MD, on Behalf of the REDUCE-IT Investigators
Key Inclusion Criteria – REDUCE-IT

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) or ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*

3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

Key Secondary End Point:
CV Death, MI, Stroke

Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P = 0.0000006

## Prespecified Hierarchical Testing

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio (95% CI) RRR P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite (ITT)</td>
<td></td>
<td>705/4089 (17.2%)</td>
<td>801/4090 (22.0%)</td>
<td>0.75 (0.68–0.83) 25%▼ &lt;0.001</td>
</tr>
<tr>
<td>Key Secondary Composite (ITT)</td>
<td></td>
<td>459/4089 (11.2%)</td>
<td>606/4090 (14.8%)</td>
<td>0.74 (0.65–0.83) 26%▼ &lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Death or Nonfatal Myocardial Infarction</td>
<td></td>
<td>392/4089 (9.6%)</td>
<td>507/4090 (12.4%)</td>
<td>0.75 (0.66–0.86) 25%▼ &lt;0.001</td>
</tr>
<tr>
<td>Fatal or Nonfatal Myocardial Infarction</td>
<td></td>
<td>250/4089 (6.1%)</td>
<td>355/4090 (8.7%)</td>
<td>0.69 (0.58–0.81) 31%▼ &lt;0.001</td>
</tr>
<tr>
<td>Urgent or Emergent Revascularization</td>
<td></td>
<td>216/4089 (5.3%)</td>
<td>321/4090 (7.8%)</td>
<td>0.65 (0.55–0.78) 35%▼ &lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td></td>
<td>174/4089 (4.3%)</td>
<td>213/4090 (5.2%)</td>
<td>0.80 (0.66–0.98) 20%▼ 0.03</td>
</tr>
<tr>
<td>Hospitalization for Unstable Angina</td>
<td></td>
<td>108/4089 (2.6%)</td>
<td>157/4090 (3.8%)</td>
<td>0.68 (0.53–0.87) 32%▼ 0.002</td>
</tr>
<tr>
<td>Fatal or Nonfatal Stroke</td>
<td></td>
<td>98/4089 (2.4%)</td>
<td>134/4090 (3.3%)</td>
<td>0.72 (0.55–0.93) 28%▼ 0.01</td>
</tr>
<tr>
<td>Total Mortality, Nonfatal Myocardial Infarction or Nonfatal Stroke</td>
<td></td>
<td>549/4089 (13.4%)</td>
<td>690/4090 (16.9%)</td>
<td>0.77 (0.69–0.86) 23%▼ &lt;0.001</td>
</tr>
<tr>
<td>Total Mortality</td>
<td></td>
<td>274/4089 (6.7%)</td>
<td>310/4090 (7.6%)</td>
<td>0.87 (0.74–1.02) 13%▼ 0.09</td>
</tr>
</tbody>
</table>

RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago. Icosapent Ethyl Better Placebo Better

Updated ADA SOC March 27 2019 on Lipid management for CV Risk Reduction

- Based on the outcome of Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT)

- The Standards of Care now include a recommendation that icosapent ethyl be considered for patients with diabetes and atherosclerotic cardiovascular disease (ASCVD) or other cardiac risk factors on a statin with controlled LDL-C, but with elevated triglycerides (135-499) to reduce cardiovascular risk.
Antiplatelet Agents: Recommendations

- Use aspirin therapy (75-162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD. A

- For patients with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. B

- Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome A and may have benefits beyond this period. B
Antiplatelet Agents: Recommendations

- Aspirin therapy (75–162mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a discussion with the patient on the benefits versus increased risk of bleeding. C
Conclusion

◊ Effective ways to prevent diabetes include both lifestyle modification and drug therapy tailored to the individual.

◊ Although a new approach regarding management is pursued, glycemic control is still a main target.

◊ Patient with presence of ASCVD, Diabetic Kidney Disease and Heart Failure therapy should include medications with benefits regardless A1c

◊ Lipid lowering therapy should be always included in the diabetic patient.
NEVER SAY NEVER, BECAUSE LIMITS, LIKE FEARS, ARE OFTEN JUST AN ILLUSION

Michael Jordan