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Armenian American Medical Society

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Objectives

- ADA 2018 guidelines for Diabetes or Prediabetes in adults
- New treatments for DM Management
- What to do after Metformin therapy
- Insulin pumps
- What is CGM (Continuous Glucose Monitoring)
- Cases
- Questions

Diabetes Classifications

- Type 1 Diabetes:
  - ✓ due to autoimmune b-cell destruction
  - ✓ accounts for 5-10% of diabetes
  - ✓ usually leading to absolute insulin deficiency
  - ✓ autoimmune markers
    - ✓ GAD 65 (Glutamic Acid Decarboxylase Antibody)
    - ✓ Tyrosine Phosphatases IA-2 and IA-2B
    - ✓ ZnT8Ab (Zinc transporter 8 antibody)
    - ✓ HLA-DR/DQ alleles association
    - ✓ Insulin Antibodies (IAA)

- Idiopathic Type 1 Diabetes:
  - ✓ permanent insulinopenia
  - ✓ prone to DKA
  - ✓ no evidence of B-cell autoimmunity
  - ✓ most are of African or Asian Decent
  - ✓ strong inheritance
  - ✓ no HLA association

American Diabetes Association.

Diabetes Classifications (cont)

- Type 2 diabetes
  - ✓ due to a progressive loss of b-cell insulin secretion
  - ✓ frequently on the background of insulin resistance

- Gestational diabetes mellitus (GDM)
  - ✓ diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation

American Diabetes Association.

Diabetes Classifications (cont)

- Specific types of diabetes due to other causes:
  - Monogenic diabetes syndromes
    - ✓ Neonatal diabetes
    - ✓ Maturity-onset diabetes of the young [MODY]
  - Diseases of the exocrine pancreas
    - ✓ Cystic Fibrosis
    - ✓ Pancreatitis
  - Drug- or chemical-induced diabetes
    - ✓ glucocorticoid use
    - ✓ in the treatment of HIV/AIDS
    - ✓ after organ transplantation

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Testing Criteria for DM or PreDM in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥ 25kg/m^2 or 23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:

   - ✓ First-degree relative with DM
   - ✓ High risk race/ ethnicity (e.g. African American, Latino, Native American, Asian American, Pacific Islander
   - ✓ History of CVD
   - ✓ History of Hypertension (≥ 140/90 mmHg or on tx for HTN)

American Diabetes Association.

Testing Criteria for DM or PreDM in asymptomatic adults (cont)

- ✓ HDL cholesterol level < 35mg/dl and/or Triglyceride levels > 250 mg/dl

- ✓ Women with polycystic ovary syndrome

- ✓ Physical inactivity

- ✓ Other clinical conditions associated with insulin resistance (e.g. severe obesity, acanthosis nigricans)

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Testing Criteria for DM or PreDM in asymptomatic adults (cont)

2. Patients with prediabetes (A1C ≥ 5.7%, IGT, or IFG should be tested yearly

2. Women with GDM should be tested lifelong at least every 3 years

3. For all other patients, testing should begin at age 45 years

4. If results are normal, testing should be repeated at a minimum of 3-yr interval, with consideration of more frequent testing depending on initial results and risk factors

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Staging of Type 1 DM

Table 2.1—Staging of type 1 diabetes (4,5)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

Plasma blood glucose (not A1C) should be used to dx the acute onset of Type 1 Diabetes in patients with symptoms of hyperglycemia

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Diagnosis of Prediabes

- IFG
  - ✓ FPG 100 mg/dL to 125 mg/dL

  OR

- IGT
  - ✓2-h PG during 75-g OGTT 140 mg/dL to 199 mg/dL

  OR

- A1C
  - ✓ 5.7-6.4%

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Criteria for the Diagnosis of DM

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

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Prevention of Type 2 Diabetes

- Metformin treatment should be considered in:
  - ✓With prediabetes, especially for those with BMI ≥ 35 mg/m^2
  - ✓Aged < 60 years
  - ✓Women with prior GDM. (A)

- Metformin long-term use may be associated with Vitamin B12 deficiency
  - ✓ Periodic Vitamin B 12 measurement should be considered
  - ✓In patients on Metformin, especially in those
    - ✓With anemia
    - ✓Peripheral neuropathy (B)

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Diabetes Treatment Goals

Table 6.2—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

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Diabetes Treatment Goals

- Goal of A1C <7% applies to most nonpregnant adults (A)
- A1C < 6.5% can be suggested for selected patients without significant hypoglycemia or polypharmacy (C)
- A1C < 8% may be appropriate for patients with (B):
  - ✓ History of severe hypoglycemia
  - ✓ Limited life expectancy
  - ✓ Advanced micro- or macrovascular complications
  - ✓ Long standing diabetes with difficulty to achieve goal

American Diabetes Association.

Pharmacotherapy Recommendations In Type 2 Diabetes

- When choosing glucose- lowering medications, consider its weight effect in overweight and obese patients (E)
- Metformin is:
  - ✓ Preferred initial choice in adults if no contraindications (A)
  - ✓ First line therapy for children and adolescents (A)
  - ✓ Should be continued when using in combination with other agents, including insulin (if no contraindications) (A)
- Consider Insulin Therapy (with or without additional agent) in newly diagnosed Type 2 who are:
  - ✓ Symptomatic
  - ✓ A1C ≥ 10%
  - ✓ Blood glucose levels ≥ 300 mg/dL (E)

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Pharmacotherapy Recommendations In Type 2 Diabetes (cont)

- Consider initial dual agent therapy with newly diagnosed type 2 diabetes with A1C ≥ 9% (E)
- Drug intensification, including insulin therapy should not be delayed if target blood glucose is not achieved (B)
- With atherosclerotic cardiovascular disease, after metformin and lifestyle changes, consider adding SGLT-2 inhibitor to regimen (C)

Table 8.1 Drug –specific and patients factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

American Diabetes Association.

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Canagliflozin: not recommended with eGFR <45 • Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 • Empagliflozin: contraindicated with eGFR <30	• **FDA Black Box:** Risk of amputation (**canagliflozin**) • Risk of bone fractures (canagliflozin) • DKA risk (all agents, rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	• Exenatide: not indicated with eGFR <30 • Lixisenatide: caution with eGFR <30 • Increased risk of side effects in patients with renal impairment	• **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • ?Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required; can be used in renal impairment	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)

Profiles of Antidiabetic Medications

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m² Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
ASCVD											
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits

Use with caution

Likelihood of adverse effects

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

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Antihyperglycemic Therapy In Adults With Type 2 Diabetes

***If patient does not tolerate or has contraindications to metformin, consider agents from another class in Table 8.1.**

 # GLP-1 receptor agonists and DPP-4 inhibitors should not be prescribed in combination

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

A1C is less than 9%, **consider Monotherapy.**

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Triple Therapy

Triple Therapy — Lifestyle Management + Metformin + Two Additional Agents

Add third agent based on drug-specific effects and patient factors# (See Table 8.1)

A1C at target after 3 months of triple therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)

Combination Injectable Therapy (See Figure 8.2)

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Combination Injectable Therapy For Type 2 Diabetes

Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent

Start: 10 U/day or 0.1–0.2 U/kg/day

Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target

For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%

If A1C not controlled, **consider combination injectable therapy**

Add 1 rapid-acting insulin injection before largest meal

Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount

Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached

For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

If A1C not controlled, **advance to basal-bolus**

Add ≥2 rapid-acting insulin injections before meals ('basal-bolus')

Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount

Adjust: ↑ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target

For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

Add GLP-1 RA

If not tolerated or A1C target not reached, change to 2 injection insulin regimen

If goals not met, **consider changing to alternative insulin regimen**

If goals not met, **consider changing to alternative insulin regimen**

Change to premixed insulin twice daily (before breakfast and supper)

Start: Divide current basal dose into ⅔ AM, ⅓ PM or ½ AM, ½ PM

Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached

For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

If A1C not controlled, **advance to 3rd injection**

Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)

Start: Add additional injection before lunch

Adjust: ↑ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target

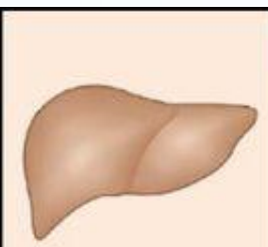
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

American Diabetes Association.

American Diabetes Association Dia Care 2018;41:S73-S85

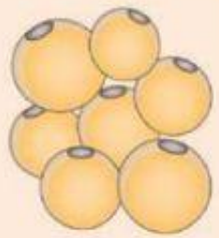
New DM Medications

1. DPP-4 inhibitors
2. GLP-1 receptor agonists
3. SGLT2 inhibitors
4. Modern insulins
5. Combinations of Insulins and GLP-1 receptor agonists



Liver

- Excessive glucose production
- Increased lipid storage



Adipose tissue

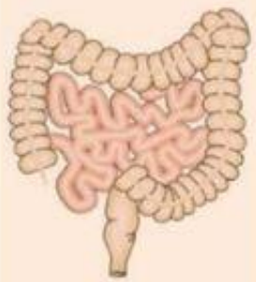
- Increased lipid storage
- Inflammation

Brain

- Impaired activation of satiety centers
- Central insulin resistance

Muscle

- Impaired glucose uptake
- Impaired glucose storage and metabolism

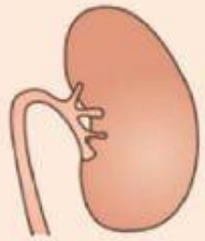


Gut

- Impaired incretin effect
- Change in microbiome composition

Pancreas

- Impaired insulin secretion and loss of β-cell mass
- Excessive glucagon secretion
- Impaired incretin effect



Kidney

- Increased glucose reabsorption
- Increased gluconeogenesis

Metformin

GLP-1RA

DPP-4

TZD

GLP-1RA

DPP-4

SU

GLP-1RA

SGLT2i

Insulin

DPP-4

GLP-1RA

Metformin

Blood glucose

Lifestyle, diet, and exercise

Figure 1-Pathophysiology and drug targets

Diabetes Care 2018;41:1543-1556

① DPP-4 Inhibitors

DPP-4 Inhibitors

1. Januvia (sitagliptin)
    - ☑ 25mg - 100 mg based on creatine
2. Tradjenta (linogliptin)
    - ☑ 5 mg
    - ☑ no dose adjustment needed with renal function
3. Onglyza (saxagliptin)
    - ☑ 2.5 - 5 mg based on creatine
4. Nesina (alogliptin):
    - ☑ 12.5 mg - 25 mg based on creatine function
    - ☑ Generic now

DPP-4 Inhibitors

Benefits:

- ✓ Weight neutral
- ✓ Decrease of A1C by 0.5-0.8%
- ✓ Usually no hypoglycemia with treatment by itself
- ✓ Usually well tolerated
- ✓ Can be used in ESRD (Januvia 25 mg or Tradjenta)

There are combinations with Metformin, Jardiance, and Pioglitazone

DPP4- Inhibitors

Risks:

- ✓ Pancreatitis
- ✓ Nausea
- ✓ Rash
- ✓ Nasopharyngitis
- ✓ Headache
- ✓ URI
- ✓ ? Pancreatic cancer (ADA and ESE did not find enough evidence to confirm increase risk of pancreatic cancer with use of DPP-4 inhibitors and GLP-1 receptor agonist)
- ✓ ? Increase in HF and hospitalization (only with Onglyza (Saxagliptin)

② GLP-1 Receptor Agonists

GLP-1 Receptor Agonists

1. Victoza (Liraglutide)
2. Trulicity (Dulaglutide)
3. Ozempic (Semaglutide)
4. Byetta/Bydureon (Exenatide)
5. Soliqua 100/33 (Glargine /Lixisenatide)
6. Xultophy 100/3.6 (Degludec/Liraglutide).

GLP-1 Receptor Agonists

Benefits:

- ✓ Weight loss
- ✓ No hypoglycemia (unless is used with other agents to cause hypoglycemia)
- ✓ Decrease in bs postprandial and fasting: A1c decrease of 0.5 -1.6 on the average about 1.
- ✓ Decreases gastric emptying
- ✓ Decreases post-meal glucagon release

GLP-1 Receptor Agonists

Benefits (continue):

- ✓ Decrease in gastric emptying and effect of GLP-1 Receptor agonists on appetite center in the brain can help to decrease weight even in patients who do not have nausea/emesis

- ✓ Decrease in CVD outcomes in patients with Diabetes and CVD with Victoza (liraglutide) and Trulicity (dulagtutide)

GLP-1 Receptor Agonists

Risks:

- ✓ Nausea/emesis
- ✓ Diarrhea
- ✓ Pancreatitis
- ✓ ? Pancreatic cancer
- ✓ Medullary thyroid cancer (C-Cell Tumors in rodents)
- ✓ Renal (not able to use in patients GFR<30 ml/min)
- ✓ Immunogenicity

LEADER Study of GLP-1 Receptor Agonist

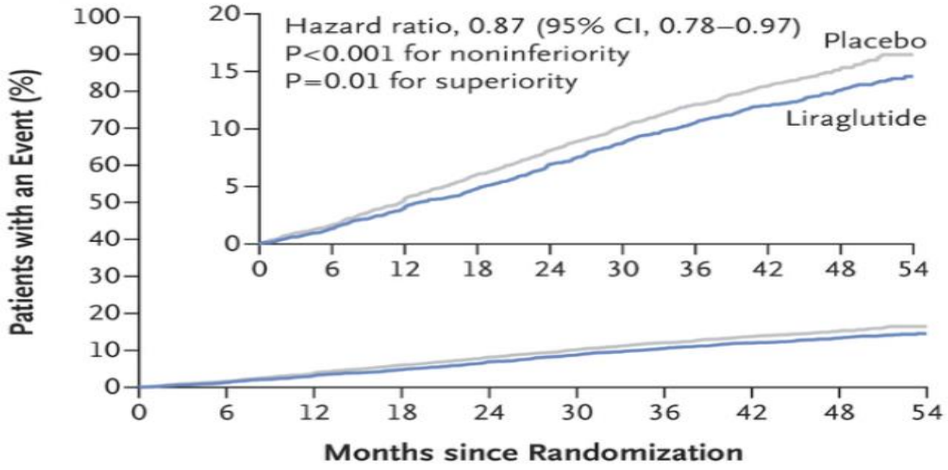
Victoza (liraglutide)

GLP-1 Receptor Agonists Benefits

Victoza (liraglutide) (LEADER Trial):

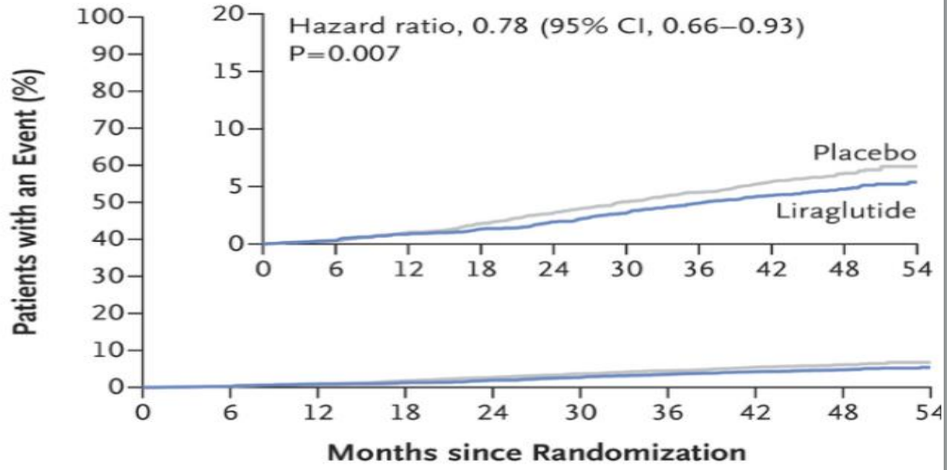
- ✓ Approved by FDA: reduces risk of cardiovascular events
- ✓ Reduction in cardiovascular death, nonfatal MI and nonfatal stroke (13%)with absolute risk reduction of 1.9%
- ✓ Cardiovascular death reduction (22%)
- ✓ All-cause mortality reduction (15%)

A Primary Outcome



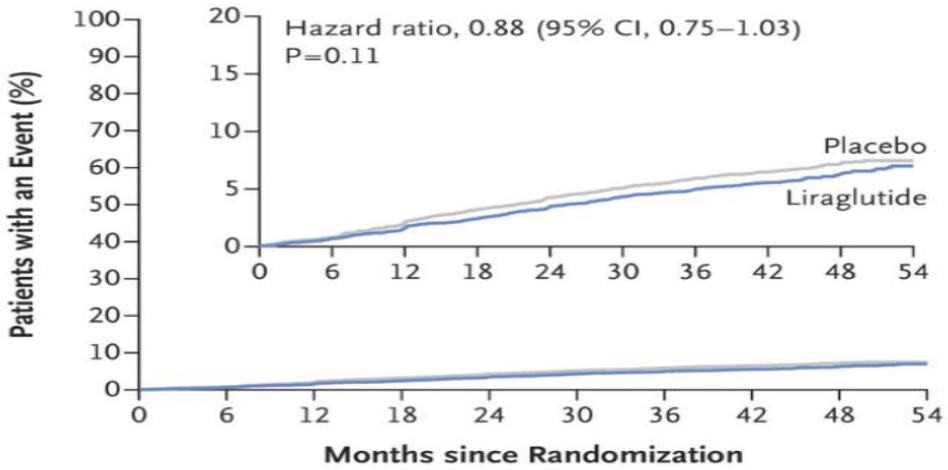
No. at Risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

B Death from Cardiovascular Causes



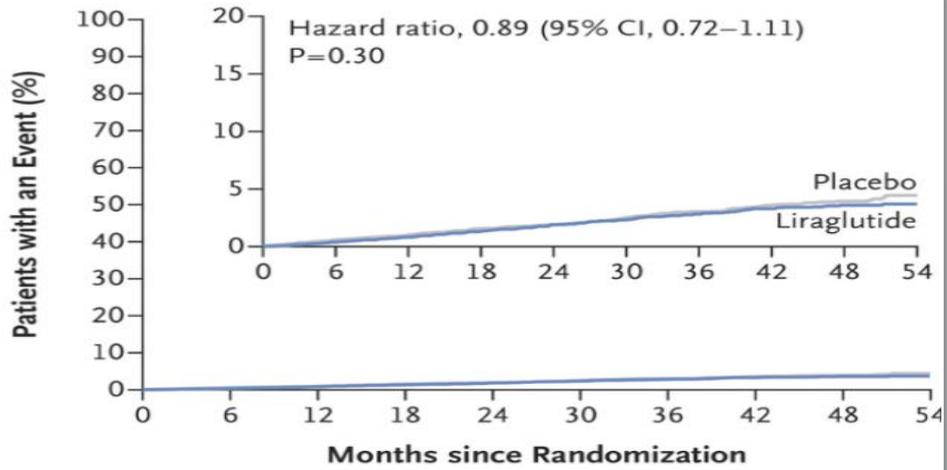
No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	48
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	46

C Nonfatal Myocardial Infarction



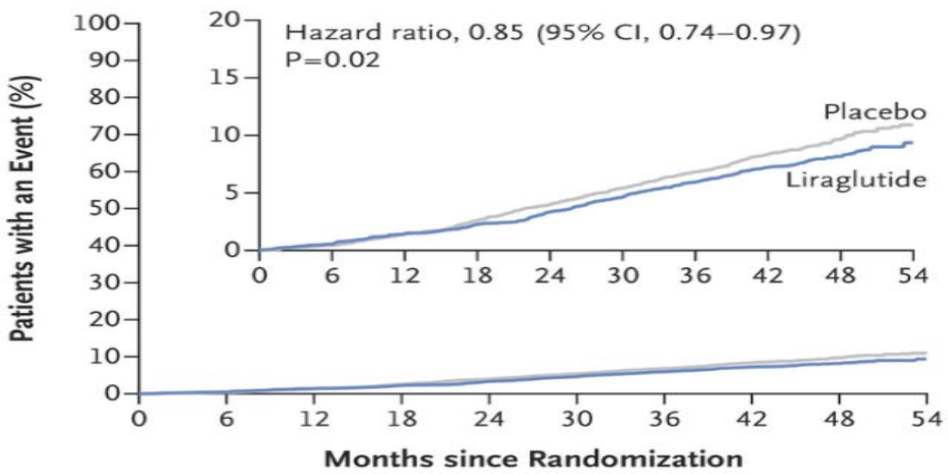
No. at Risk										
Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

D Nonfatal Stroke



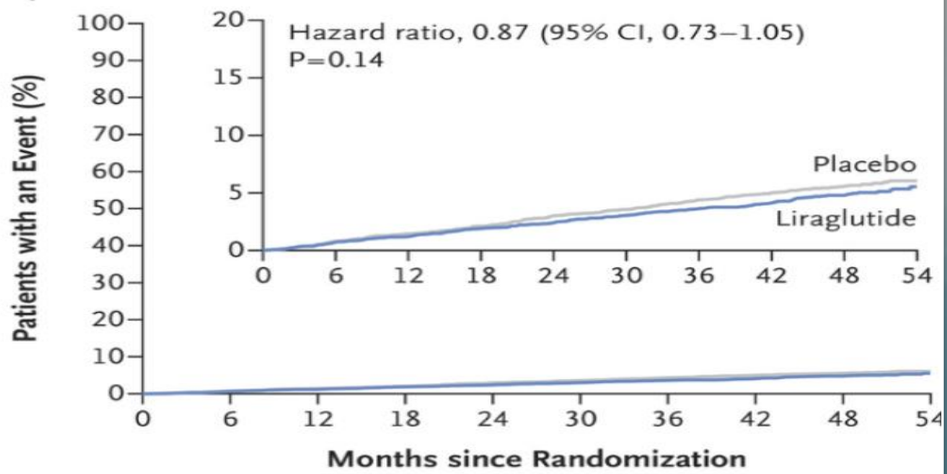
No. at Risk										
Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	46
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	44

E Death from Any Cause



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

F Hospitalization for Heart Failure



No. at Risk										
Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	46
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	44

AWARD-7 Trial
GLP-1 Receptor Agonist
Trulicity (dulaglutide)

GLP-1 Receptor Agonist Benefits

AWARD-7 Trial:

1. Trulicity (dulaglutide) + bolus insulin vs Lantus + bolus insulin
2. Trulicity (dulaglutide) + prandial insulin
    - Greater weight loss (2.3 Kg loss) and 1 Kg gain with basal insulin group
    - fewer episodes of hypoglycemia
        - 50% Truliicty 1.5 mg
        - 59 % Trulicity 0.75 mg
        - 75% Glargine/basal insulin group
    - Similar to the group of basal/bolus regimen to achieve comparable Alc results
    - Greater albuminuria reduction
    - Markedly reduced eGFR decline
        - -0.8 % Trulicity 1.5 mg
        - -3.3 % Trulicity 0.75 mg
        - -7.7% Lantus/basal insulin group

③ SGLT-2 Inhibitors

SGLT-2 Inhibitors

1. Canagliflozin (Invokana): 100 & 300 mg
2. Dapagliflozin (Farxiga): 5 & 10 mg
3. Empagliflozin (Jardiance): 10 & 25mg
4. Ertugliflozin (Steglatro): 5mg & 15mg
5. Glyxambi (combination of Tradjenta /Jardiance)
6. Steglujan (combination of Ertugliflozin /Januvia)
7. Invokamet (combination of Metformin/Invokana)
8. Synjardy (combination of Metformin/Jardiance)
9. Segluromet (combination of Ertugliflozin/Metformin)
10. Xigduo (combination of Metformin/Farxiga)
11. Qtern (combination of Onglyza and Farxiga)

NEW BENEFITS WITH SGLT-2 INHIBITORS

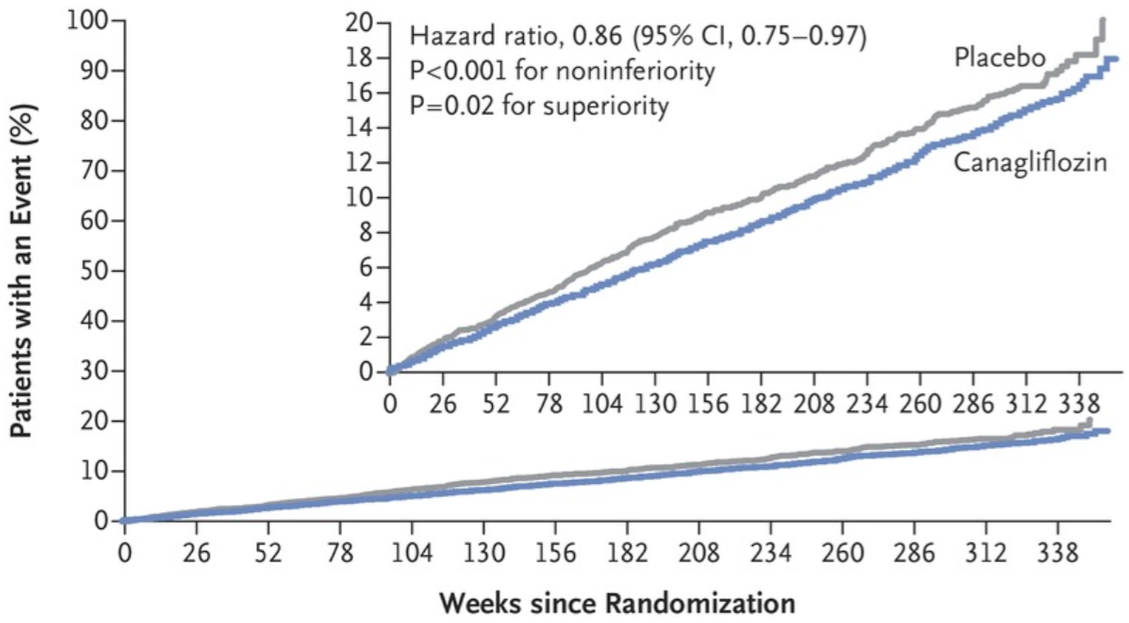
- ✓ Decrease in composite of death from cardiovascular causes (38%)
- ✓ Decrease in nonfatal MI
- ✓ Decrease in nonfatal stroke
- ✓ Primary Outcome
- ✓ Decrease in all cause mortality (32% reduction)
- ✓ “The reductions were unchanged when adjusted for control of blood pressure, LDL cholesterol and HgA1C during the study” (David Fitchett, M.D.)

NEW RISKS WITH SGLT-2 INHIBITORS

- ✓ Increased risk of Lower Limb amputation (toe and mid foot) was noted during study with canagliflozin
  - ✓ 5.9 and 2.8 per 1000 patient-years (5.7 years)
  - ✓ 7.5 and 4.2 per 1000 patient-years (2.1 years)
- ✓ Increased risk of bladder cancer (noted only with dapagliflozin (Farxiga)
- ✓ Euglycemic (Plasma glucose <250 mg/dL) DKA
- ✓ Increased bone fractures (noted with cangliflozine) but bone loss noted as a class effect

CANVAS Study of SGLT-2 Inhibitor Invokana (canagliflozin)

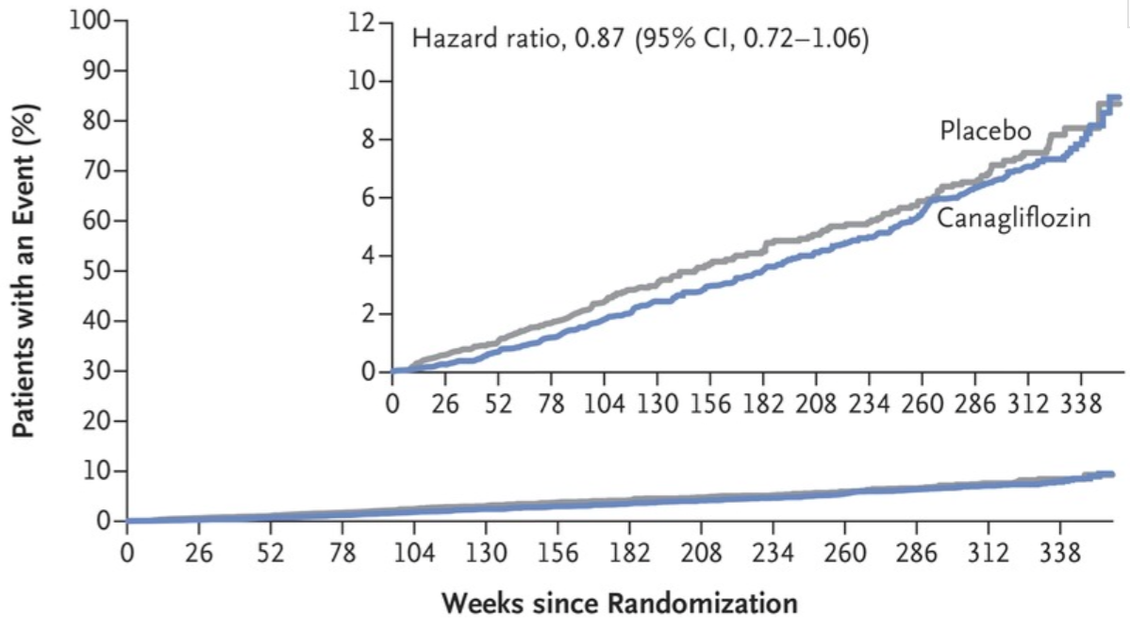
A Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke



No. at Risk

Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448

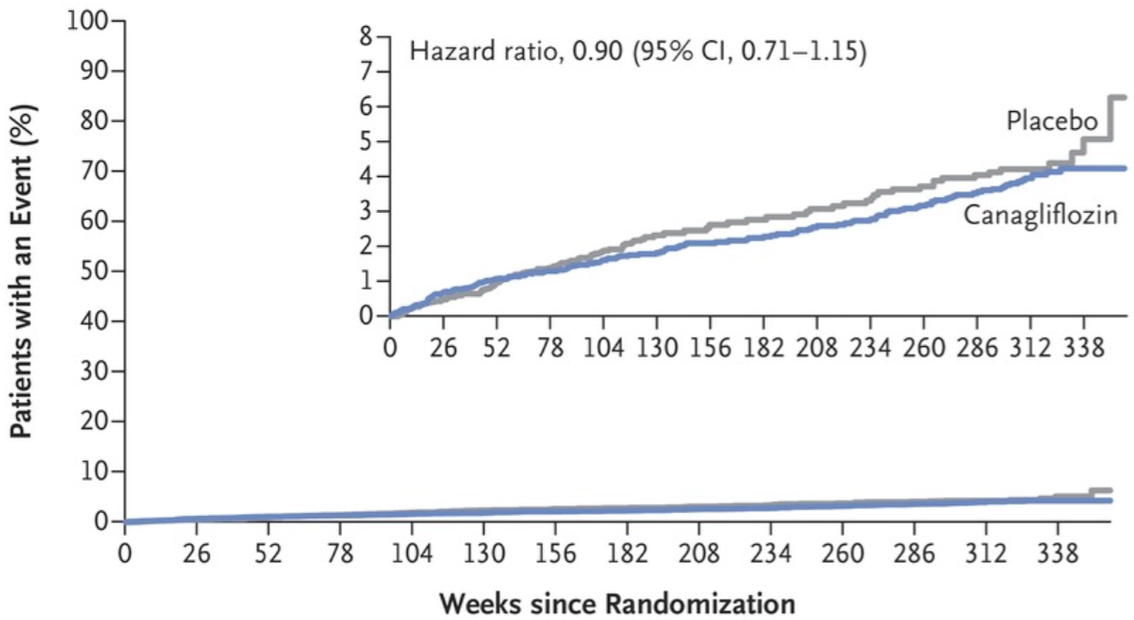
B Death from Cardiovascular Causes



No. at Risk

Placebo	4347	4316	4279	4236	3119	1759	1356	1344	1328	1310	1292	1280	924	258
Canagliflozin	5795	5768	5723	5679	4576	3182	2761	2736	2710	2687	2651	2615	1904	532

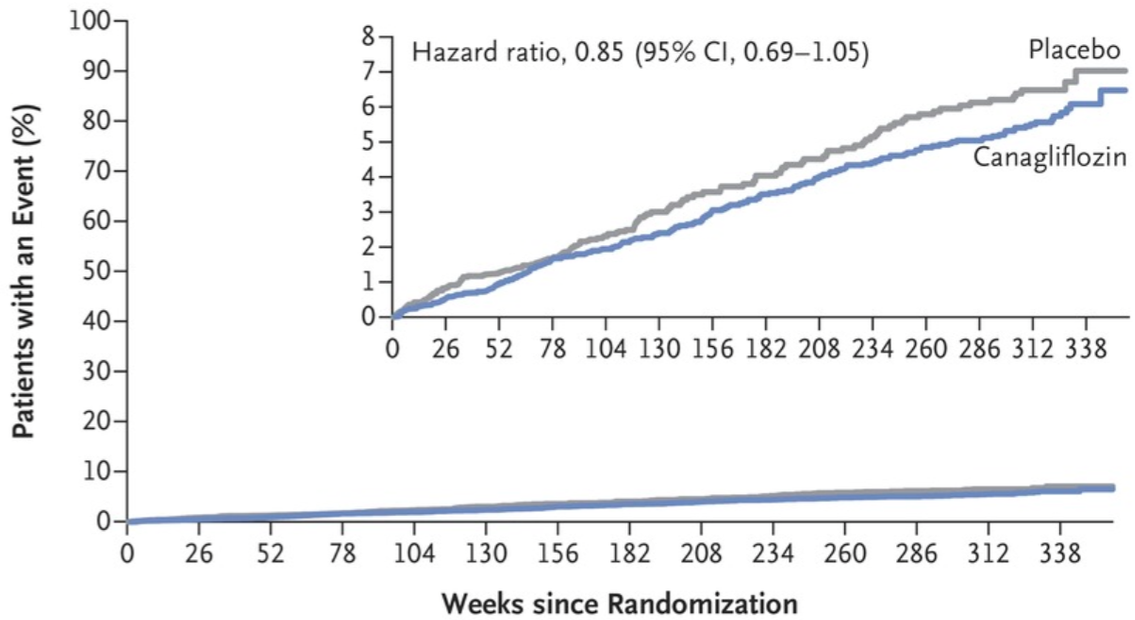
C Nonfatal Stroke



No. at Risk

Placebo	4347	4270	4197	4123	3004	1667	1274	1255	1232	1208	1177	1155	829	232
Canagliflozin	5795	5702	5615	5530	4414	3043	2621	2588	2543	2511	2464	2415	1751	481

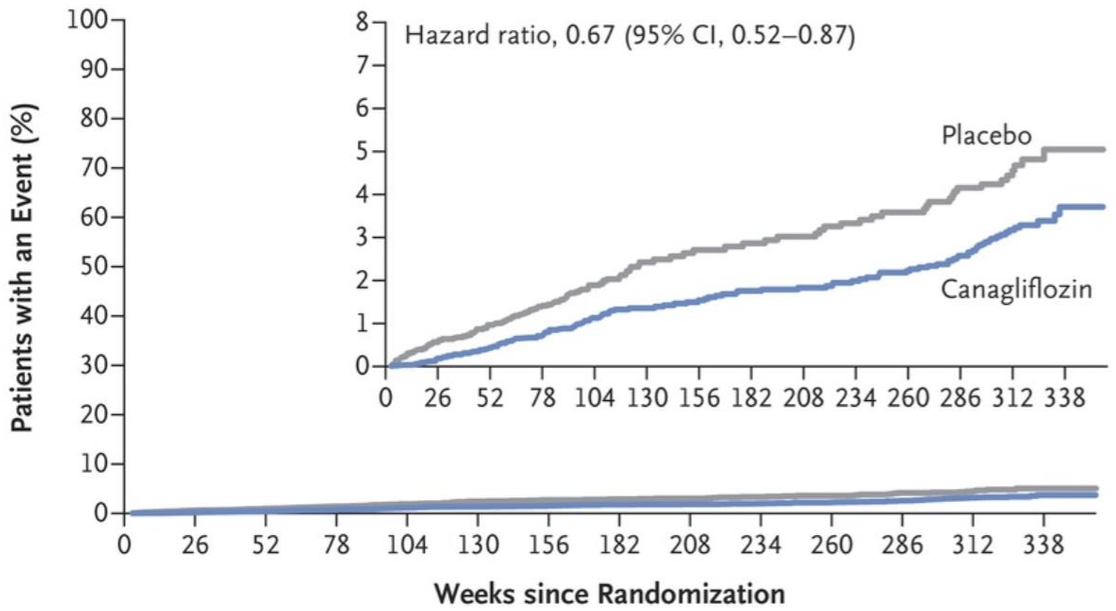
D Nonfatal Myocardial Infarction



No. at Risk

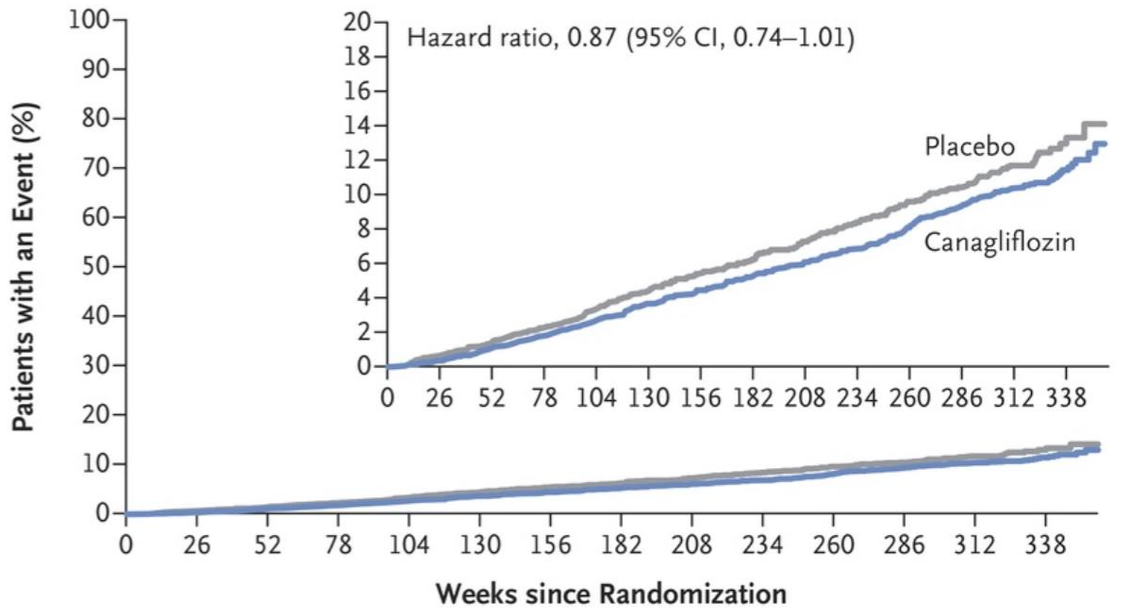
Placebo	4347	4256	4187	4109	2986	1647	1255	1233	1207	1179	1146	1126	812	223
Canagliflozin	5795	5711	5625	5513	4405	3029	2602	2565	2516	2476	2425	2382	1728	468

A Hospitalization for Heart Failure



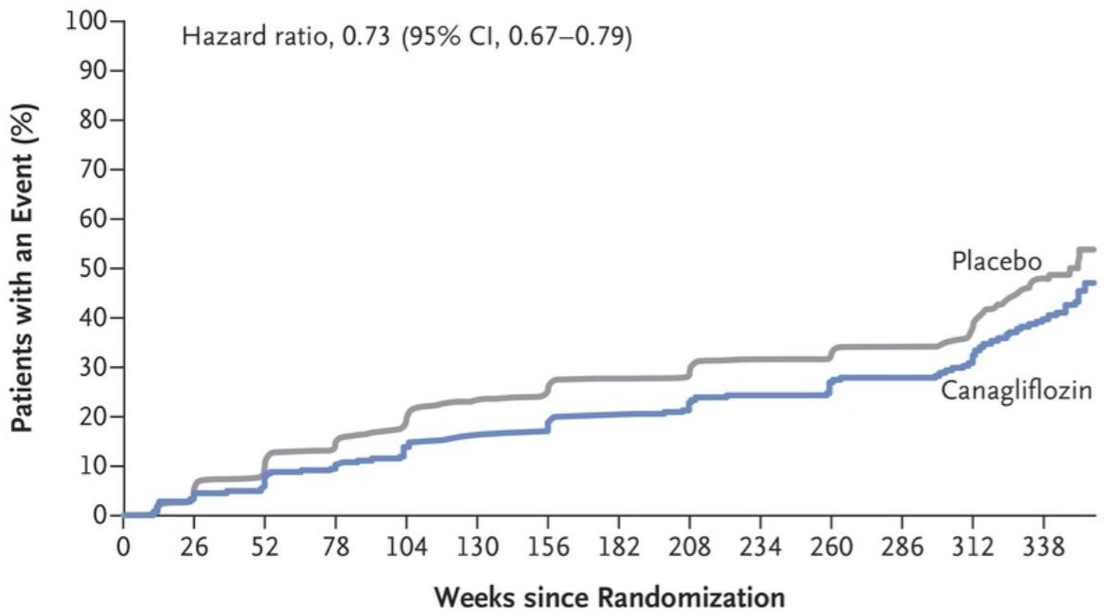
No. at Risk															
Placebo	4347	4267	4198	4123	3011	1667	1274	1256	1236	1210	1180	1158	829	233
Canagliflozin	5795	5732	5653	5564	4437	3059	2643	2610	2572	2540	2498	2451	1782	490

B Death from Any Cause



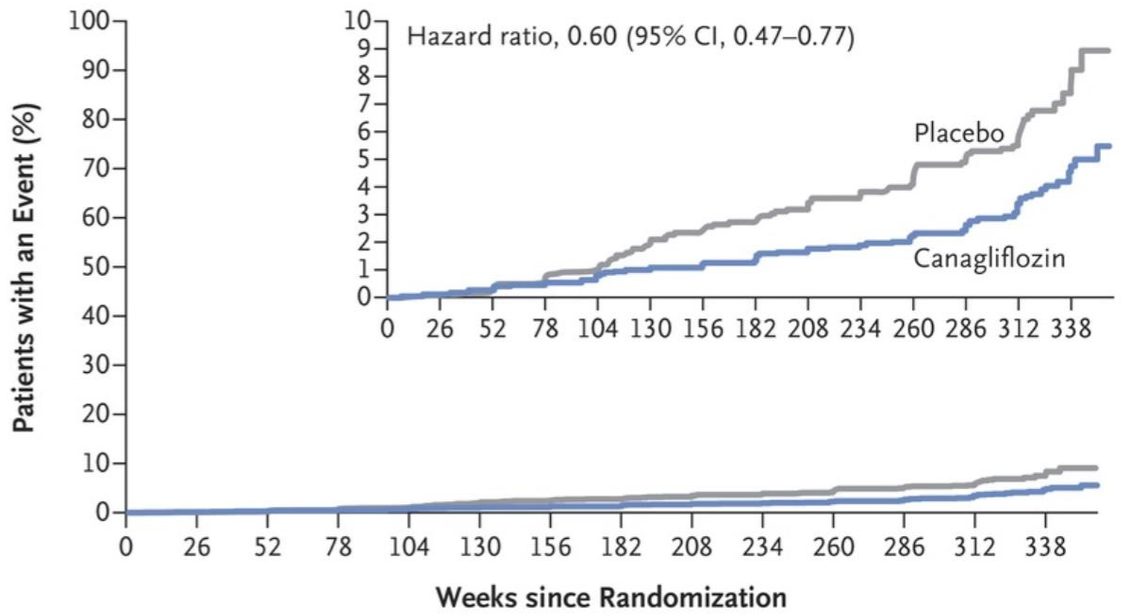
No. at Risk															
Placebo	4347	4316	4279	4236	3119	1759	1356	1344	1328	1310	1292	1280	924	258
Canagliflozin	5795	5768	5723	5679	4576	3182	2761	2736	2710	2687	2651	2615	1904	532

C Progression of Albuminuria



No. at Risk															
Placebo	3819	3473	3096	2700	1690	877	724	652	626	565	548	485	303	67
Canagliflozin	5196	4791	4475	4027	2968	1951	1730	1593	1528	1408	1354	1213	775	185

D Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy, or Death from Renal Causes

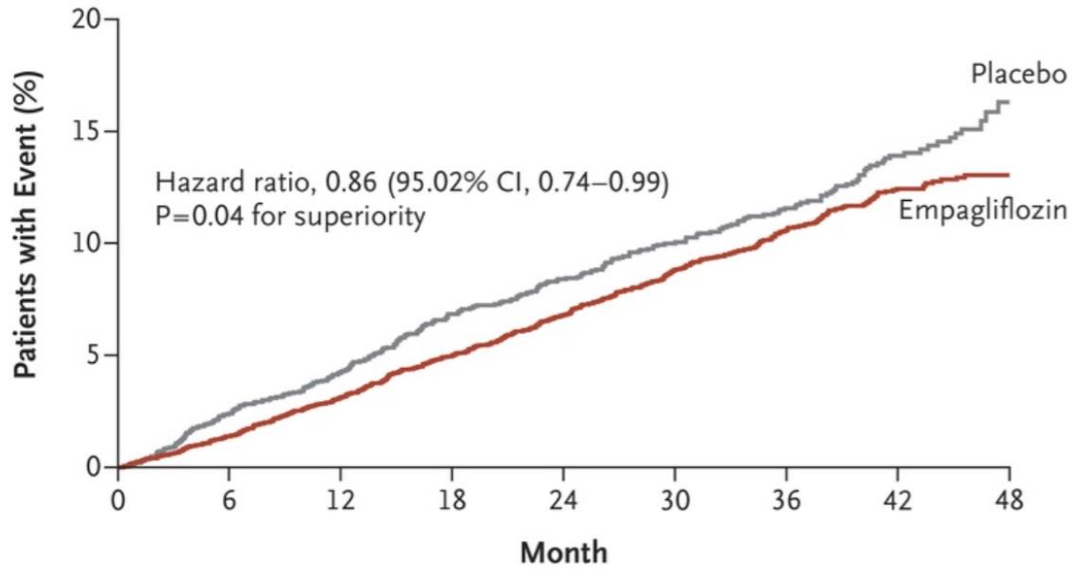


No. at Risk															
Placebo	4347	4287	4227	4151	3029	1674	1274	1253	1229	1202	1173	1148	819	229
Canagliflozin	5795	5737	5664	5578	4454	3071	2654	2623	2576	2542	2495	2450	1781	493

EMPAG Study of SGLT-2 Inhibitor

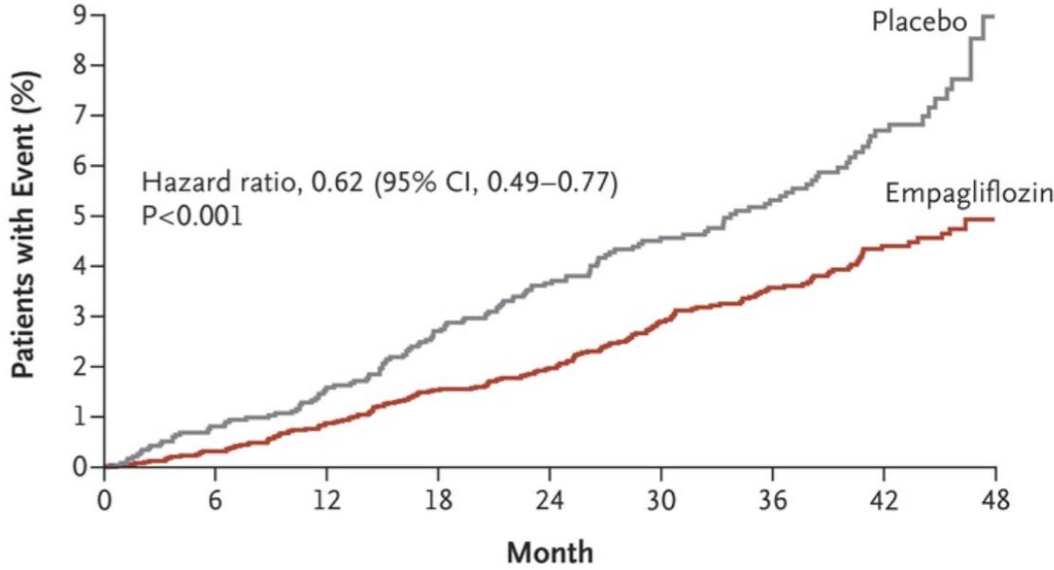
Jardiance (empagliflozin)

A Primary Outcome



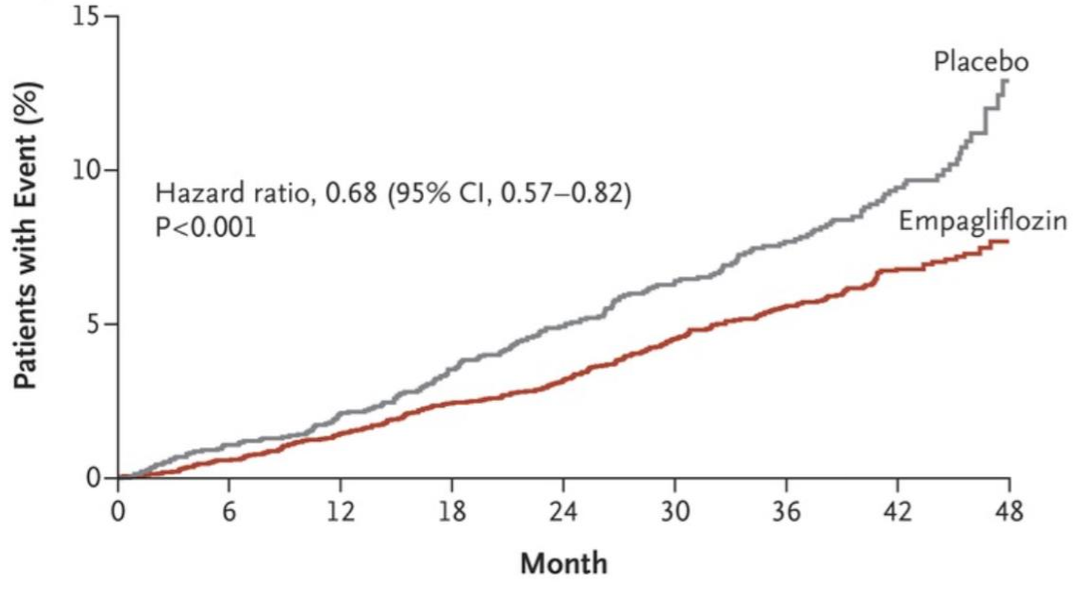
No. at Risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

B Death from Cardiovascular Causes



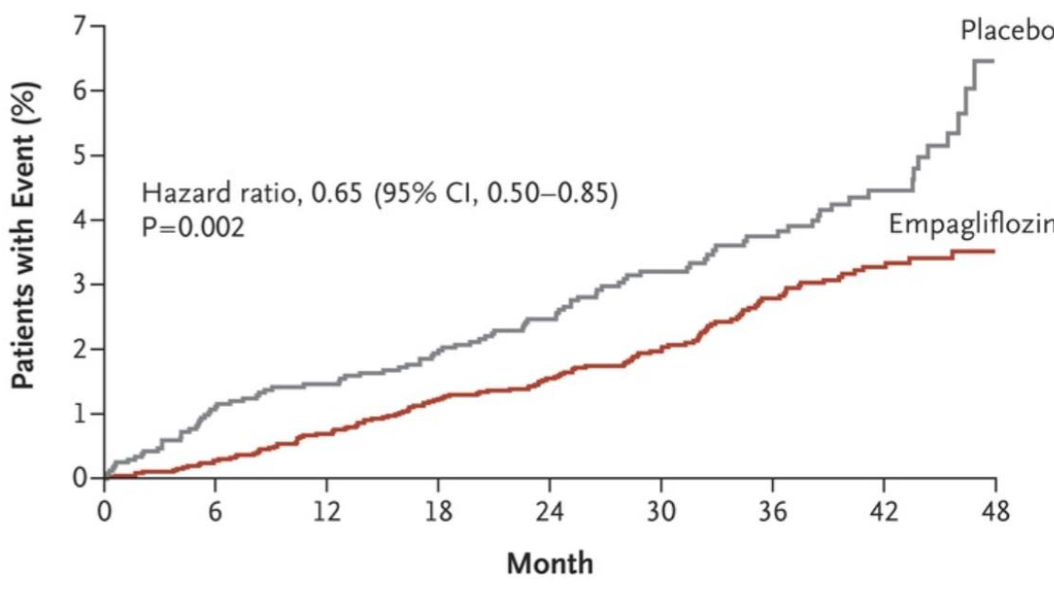
No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

C Death from Any Cause



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

D Hospitalization for Heart Failure



No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Insulin pumps (CSII): Continuous Subcutaneous Insulin Infusion

- ☑ Medronics
- ☑ T-Slim
- ☑ OmniPod
- ☑ AccuCheck (not available now)
- ☑ Animas (not available now)

Insulin Pump Benefits

- ✓ Need to change usually every 3 days (injection every 3 days)
- ✓ Uses only one insulin (short acting/rapid insulin)
- ✓ Basal (continuous insulin given every hour)
  - ☑ can have temporary basal for exercise routine
  - ☑ can suspend pump to decrease risk of hypoglycemia

Insulin Pump Benefits (cont)

- ✓ Bolus insulin for meals (I:C ratio) and correction insulin (CF)
  - ☑ decreases the need for calculation
  - ☑ can give boluses at different rates and times
- ✓ Insulin on board (IOB) (minimizes stacking of the insulin)
- ✓ Can give lower increments of insulins for meals and corrections
- ✓ Easy to give insulin (no need to look for insulin pen or vial)

Glucose Monitoring With Insulin Therapy

- Patients on Intensive Insulin Regimens (MDI or insulin pump therapy) should do:
  - ✓ Self- monitoring of blood glucose (SMBG) prior to:
    - Meals and snacks
    - At bedtime
    - Occasionally postprandially
    - Prior to exercise
    - Anytime with suspected low blood glucose
    - After treatment for hypoglycemia episode
    - Prior to driving or other critical tasks (B)

Glucose Monitoring With Insulin Therapy (cont)

- Continuous glucose monitoring (CGM) with intensive insulin regimens is useful tool to lower A1C in adults with Type 1 Diabetes who are not at goal. (A)
- CGM maybe useful tool for patients with hypoglycemia unawareness and/or frequent hypoglycemia episodes. (C)
- With use of CGM, robust diabetes education, training and support are required (E)
- Patients who have been successful with CGM should continue to use it after they turn 65 years of age. (E)

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Insulin Pump Risks

Pump failure:

- ☑ Bad site
- ☑ Scarring of the sites
- ☑ Issues with Tubing (except OmniPod: tubeless)
- ☑ Failure of insulin delivery

Back Up Plan (ALWAYS):

- ☑ Carry insulin pens (long acting and short acting)
- ☑ Call PUMP company for EMERGENCY SUPPLIES AND PUMP MALFUNCTION

Classification of Hypoglycemia

Level	Glycemic criteria	Description
Hypoglycemia alert value (level 1)	≤70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	<54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

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CGM (Continuous Glucose Monitoring)

- ✓ Medronics
- ✓ Dexcom
- ✓ Eversense (implantable: approved for 90 days in USA and 180 days in Europe)
- ✓ Libre (Flash CGM: only when you check). No alarms. Covered by Medicare for Type 1 and Type 2 on insulin therapy

CGM (cont)

- ✓ Need to change every 7-10 days and 90-180 days for implantable (Eversense)
- ✓ Dexcom G6 and Libre were approved by FDA direct treatment without fingerstick verification.
- ✓ Medronics and Eversense require 2 calibrations per day
- ✓ Information can be send to receiver or compatible smart device (I-Phone and Android) and shared through app with family and doctors
- ✓ Trend arrows allow to make decisions about insulin and hypoglycemia treatment easier
- ✓ Alarms to notify of increasing or decreasing blood sugars

CGM (cont)

DIAMOND and GOLD studies:

- ✓ CGM can reduce also HgA1C and hypoglycemia in patients with T1D with MDI instead of conventional SMBG
- ✓ Patients with T1D when switched from MDI/CGM to CSII/CGM further improvement of glycemic control
  - ☑ but also increase in biochemical hypoglycemia was noted

Blood Pressure Treatment Goals In Patients With Diabetes

- Most patients should be treated to < 140/90 mmHg (A)
- ACEI or ARB is not recommended for primary prevention of diabetic kidney disease in patients with:
  - ✓ normal pressure
  - ✓ Normal urinary albumin-to-creatinine ratio (<30 mg/g creatinine)
  - ✓ Normal eGFR (B)
- ACEI or ARB is recommended for those with:
  - ✓ Elevated urinary albumin-to-creatinine ratio (30 - 299 mg/g creatinine) (B)
  - ✓ Strongly recommended for albumin-to-creatinine ratio ≥ 300 mg/g creatinine (A)

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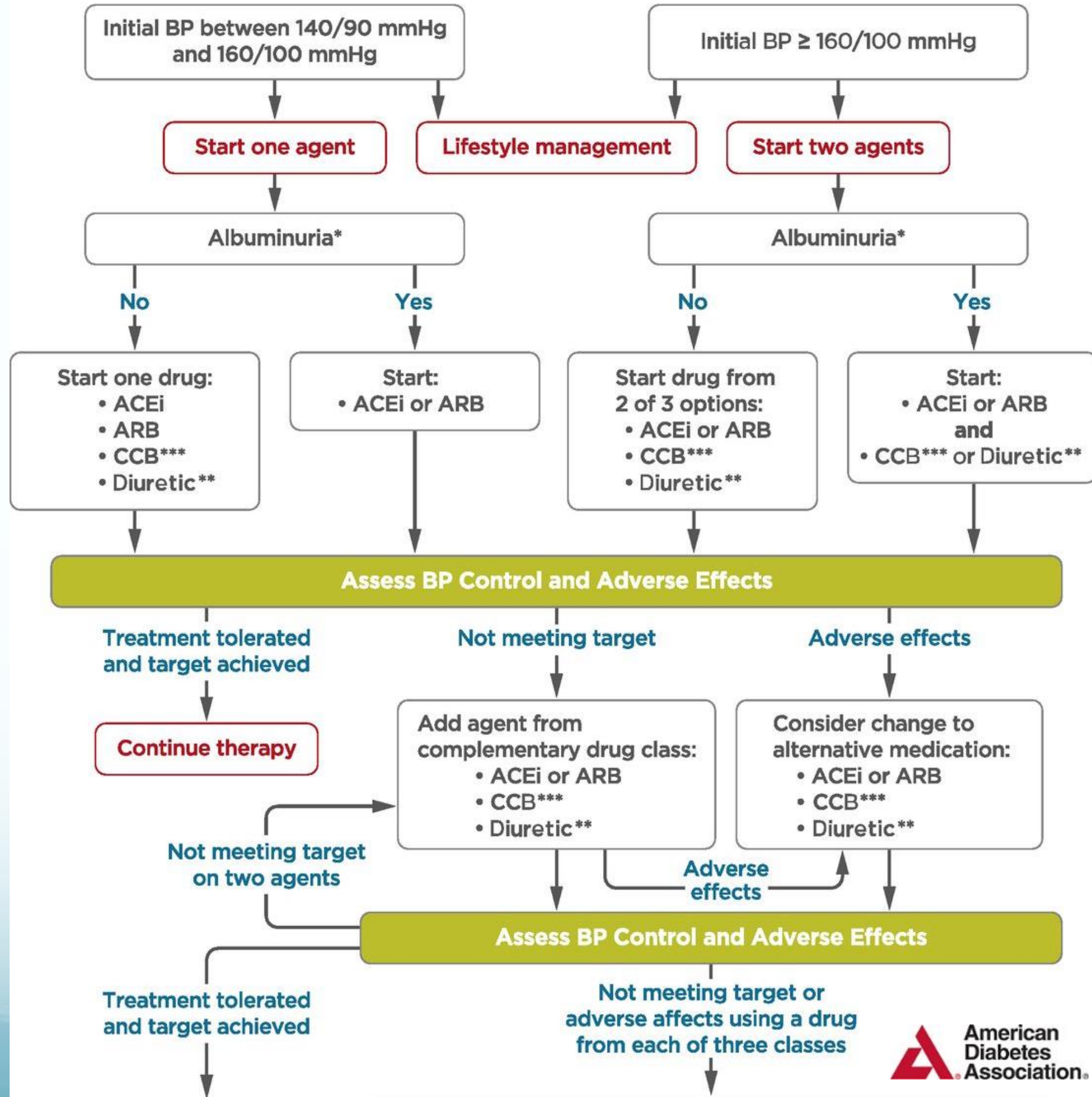
Recommendations for Treatment of confirmed Hypertension in People with Diabetes

***An ACE inhibitor (ACEi) or ARB is suggested to treat hypertension for patients with UACR 30–299 mg/g creatinine and strongly recommended for patients with UACR ≥300 mg/g creatinine.**

****Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred.**

*****Dihydropyridine calcium channel blocker**



Statin and Combination Treatment Recommendations

- Combination therapy (statin/ fibrate)
  - ✓ Has not been shown to improve atherosclerotic cardiovascular disease outcomes
  - ✓ Generally not recommended (A)
- Combination therapy (statin/ niacin)
  - ✓ Has not been shown to provide additional cardiovascular benefit above statin alone
  - ✓ May increase risk of stroke with additional side effects
  - ✓ Generally not recommended (A)
- Combination therapy (statin / fish oil: DHA, EPA)
  - ✓ Has not been shown to provide additional cardiovascular benefit above statin alone (ASCEND Trial)
- Combination therapy (statin / fish oil: EPA)
  - ✓ Pending results of REDUCE-IT Trial in Sept of 2018

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Statin and Combination Treatment Recommendations

Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

*In addition to lifestyle therapy. ^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

Statin Treatment Recommendations (cont)

Table 9.3—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30% to 50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

*Once-daily dosing. XL, extended release.

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Treatment of Other Lipoprotein Fractions or Targets

- For patients with fasting triglyceride levels ≥ 500 mg/dL:
  - ✓ Evaluate for secondary causes of hypertriglyceridemia
  - ✓ Consider medical treatment to reduce risk of pancreatitis (C)

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Diabetic Peripheral Neuropathy (DPN)

- All patients should be assessed for DPN
- DPN is diagnosis of exclusion
- Nondiabetic neuropathies maybe present in patient with diabetes and may be treatable
  - ✓ Toxins (alcohol)
  - ✓ Neurotoxic medications (chemotherapy)
  - ✓ Vitamin B 12 deficiency
  - ✓ Hypothyroidism
  - ✓ Renal disease
  - ✓ Malignancies (Multiple Myeloma, Bronchogenic Carcinoma)
  - ✓ Infections / HIV
  - ✓ Vasculitis

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Treatment Of Diabetic Peripheral Neuropathy (DPN)

- Optimize glucose control:
  - ✓ In Type 1 to prevent or delay the development of DPN (A)
  - ✓ In Type 2 to slow the progression of DPN (B)

- Either Lyrica (pregabalin) or Cymbalta (duloxetine) are recommended as initial treatment for neuropathic pain in diabetes

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Recommendations for Diabetic Retinopathy

- Screening with initial dilated and comprehensive eye exam in adult patients should be done:
  - ✓ Type 1 Diabetes within 5 years after the onset of Diabetes (B)
  - ✓ Type 2 Diabetes at the time of Diabetes diagnosis (B)
- To reduce the risk or slow the progression of diabetic retinopathy optimize:
  - ✓ Glycemic control
  - ✓ Blood pressure
  - ✓ Lipid control (A)
- Women with preexisting Type 1or 2 Diabetes, should be counseled on risk of development / progression of DR in pregnancy
  - ✓ Eye exam:
    - Before pregnancy or in the first trimester
    - Every trimester
    - One 1 year post postpartum

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Treatment of Diabetic Retinopathy

- Refer patients to ophthalmologist (A):
  - ✓ With any macular edema
  - ✓ Severe nonproliferative diabetic retinopathy
  - ✓ Any proliferative diabetic retinopathy
- Traditional standard treatment (A)
  - ✓ Panretinal laser photocoagulation therapy
- New Treatment intravitreous injections of antivascular endothelial growth factor ranibizumab
  - ✓ Indicated for central- involved diabetic macular edema beneath the foveal center (A)
- Aspirin therapy is not contraindicated for cardioprotection in the presence of retinopathy (A)

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Case #1

DL is a 66 year old female with:

- hx of DM type 2 for >10 years.
- Has been on oral medications for her DM type 2 management
- For the past 5- 6 days noted to have some dyspnea, nausea and emesis
- Bs had been in 120- 220s range
- Was seen in ED 2 days and was send home after IV hydration
- Came back with worsening of the dyspnea, change of mental status and N/V

Case #1

PMH: T2DM; Hypothyroidism; Hyperlipidemia

Social: Quit tobacco 15 yrs ago (20 year hx of tobacco use); social alcohol; no IVDU; lives with family at home. No recent travel outside of USA

Medications:

1) Janumet 50/500 mg twice a day
2) Glipizide 5 mg once a day
3) Invokana 300 mg per day
4) Lipitor 20 mg
5) Losartan 50 mg per day
6) Levothyroxine 75 mcg per day

Case # 1

PE:

- vitals: 100/60; 95; 98.7; 92% on RA
- RRR
- CTAB
- Abd: soft; BS+; mild tenderness (nonspecific)
- ext: no c/c/edema
- neck: + nodular thyroid

Case #1

Labs:

- Na: 135; CL: 96; CO2: 7; Cr: 1.4; BUN: 40; K: 5.0; BS: 185; AG: 32
- UA: Ketones: 80; +Leuk; (culture requested)
- ABG: ph: 7.1
- Hemoglobin: 12.1
- WBC: 15

Chest X-ray : good

Case # 1

What is the reason of patient condition and what treatment were initiated.

On discharge ....

Case #2

MH is 42 year old obese female with

- hx of T2DM was started on metformin therapy and her A1C improved to <7 but could not tolerate metformin due to fatigue and muscle pain. She was sure it was from metformin and improved when stopped it but now her bs were in 200s.
- Pt was not pregnant and not planning for pregnancy.

Case # 2

Meds:

1) Lisinopril 5 mg
2) Lipitor 10 mg
3) LT4 50 mcg
4) Metformin 500 mg twice a day (not taking)

PE: Unremarkable except for obesity

Vitals: 125/75; 80; 98.5; 96% RA. BS: 285 in the office (2 hours after breakfast)

Labs: Na: 135; CO2: 25; K: 4.5; BUN: 22; Creatine: 0.9; H/H: good; HgAiC: 8.5

What to do?

Case #3

DL is 80 year old Hispanic male with

- hx of T2DM for >10 years and was on diet and metformin.
- His bs were controlled until about 5 months ago when suddenly started to rise and now bs were mostly in 200-300s.
- Pt was started on glipizide by primary and bs were still elevated.

ROS: polyuria/polydipsia; weight loss; abdominal pain/discomfort

Case # 3

Vitals:

- ✓ 110/75; 78; 97% on RA; BS: 320 in the ffice (1 hour after lunch)

Labs:

- ✓ A1C: 10 and it was <7 about 6 months ago. Na: 134; K: 4.6; Cr: 0.8; BUN: 18

What to do?

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 (Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

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

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

 DOI 10.4158/CS-2017-0153

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 Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP-1 RA

Or SGLT-2i
Or DPP-4i

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%

***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

 DOI 10.4158/CS-2017-0153