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Ohio Cardiovascular and Diabetes Health Collaborative

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Type 2 Diabetes in the context of cardiovascular risk

Thursday, December 3, 2020

Disclosure Statements

- The following planners, speakers, moderators, and/or panelists of the CME activity have financial relationships with commercial interests to disclose:
  - Kathleen Dungan, MD, MPH receives consulting fees from Eli Lilly and Tolerion, institutional research fees from Eli Lilly, Novo Nordisk, and Sanofi Aventis, and presentation honoraria from Nova Biomedical, Integritas, and Uptodate.
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  - Jackson T. Wright, Jr., MD, PhD reports research support from the NIH and Ohio Department of Medicaid and consulting with NIH, AHA, and ACC.
  - These financial relationships are outside the presented work.
- All other planners, speakers, moderators, and/or panelists of the CME activity have no financial relationships with commercial interests to disclose.

Type 2 diabetes in the context of cardiovascular risk

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Learning Objectives

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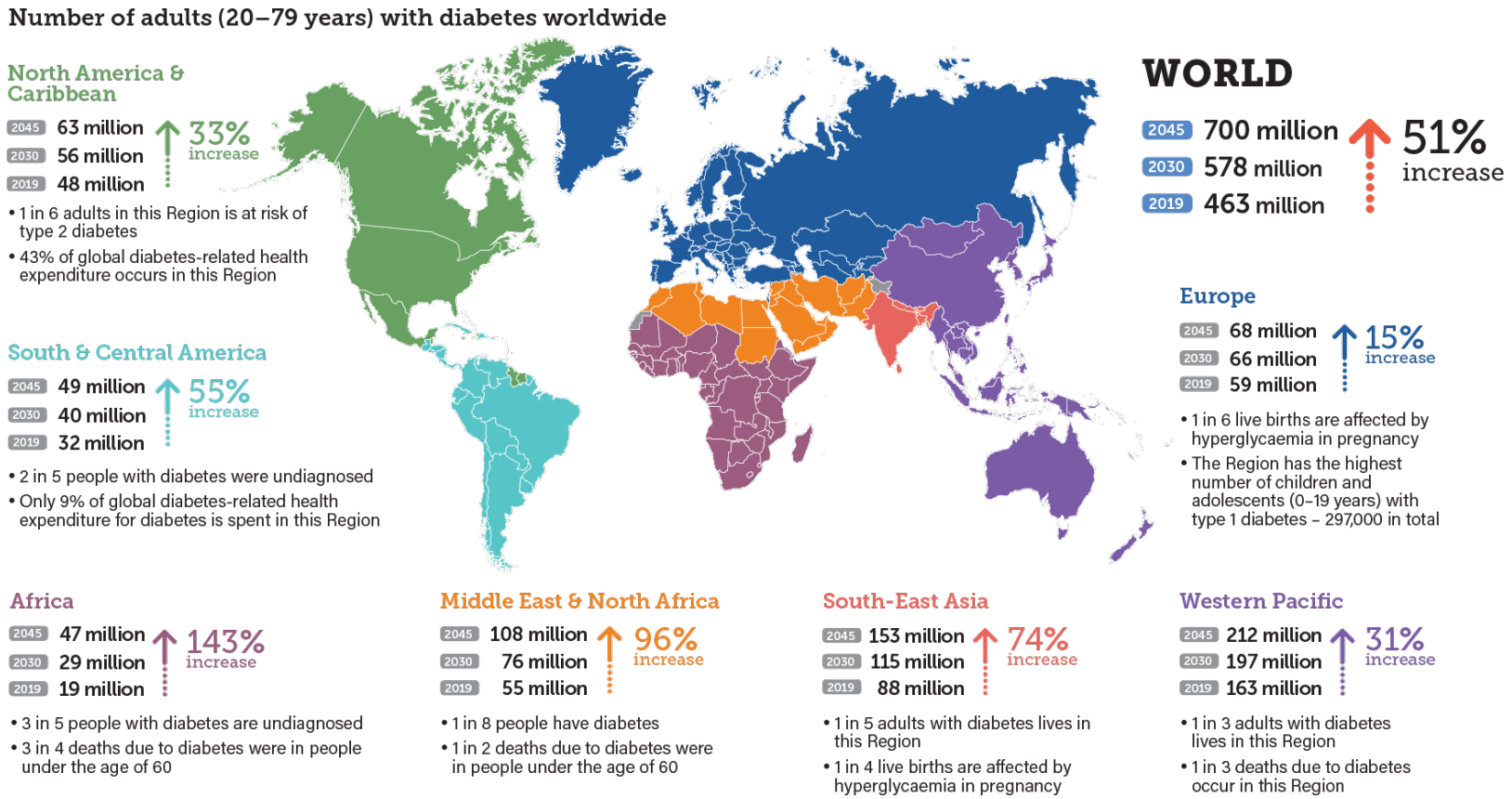
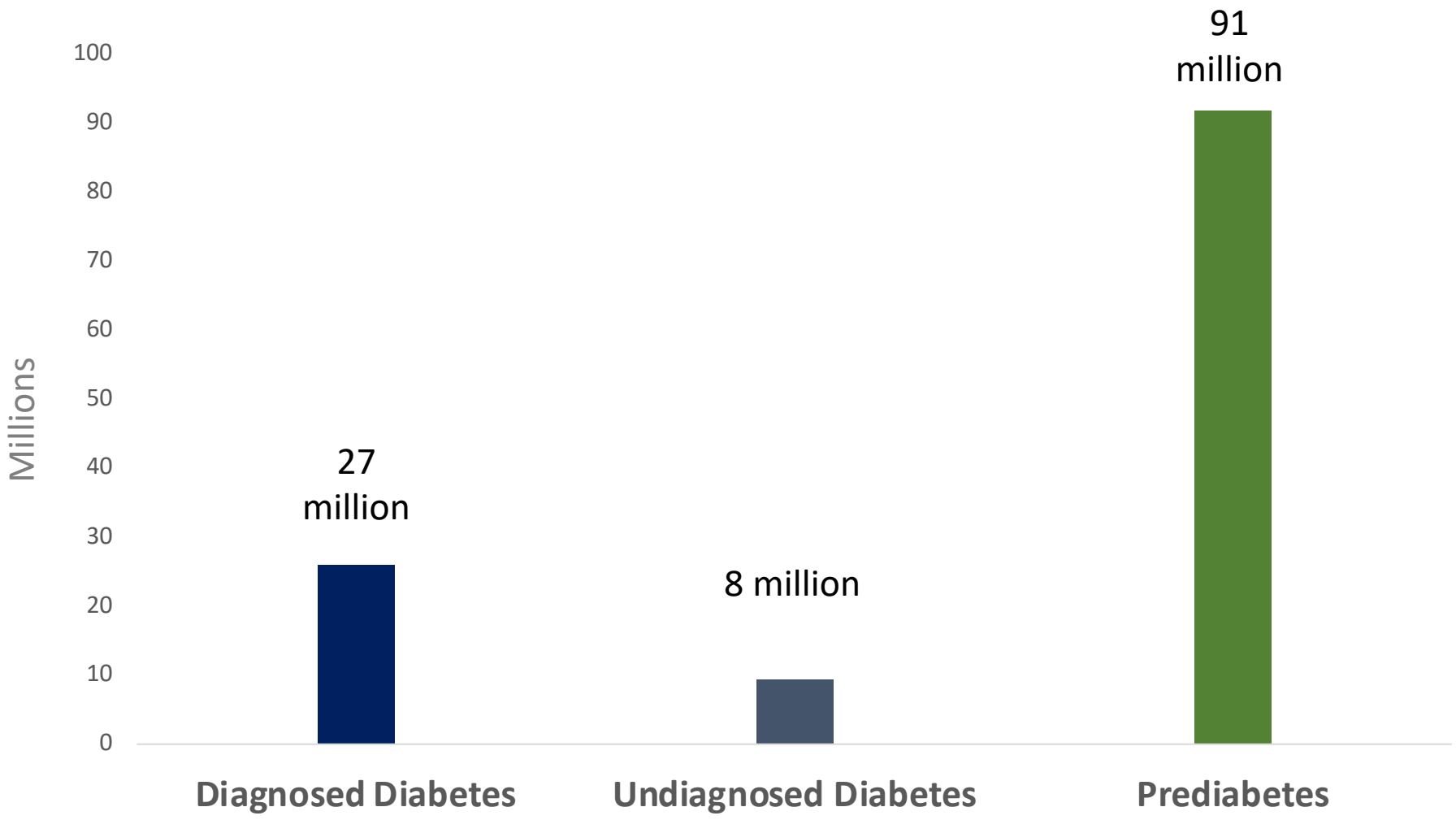
1. Describe the epidemiology of diabetes on global, national, and statewide level
2. Describe how diabetes increases the risk of cardiovascular disease
3. Identify the therapies approved to treat diabetes and lower cardiovascular risk
4. Identify when to use GLP1 agonists vs SGLT2 inhibitors
5. Describe a brief, evidence-based approach to smoking cessation among smokers with type 2 diabetes

Diabetes

- Prevalence of diabetes is increasing – currently half billion ppl worldwide which will increase 25% by 2030
- People with diabetes and PAD are at much higher risk for amputation and critical limb ischemia than those without diabetes.
- Top 3 countries per prevalence of DM: 1) China 2) US 3) India



Persons in the US at High Risk for Heart Disease



Heart Disease and Stroke Statistics, 2020

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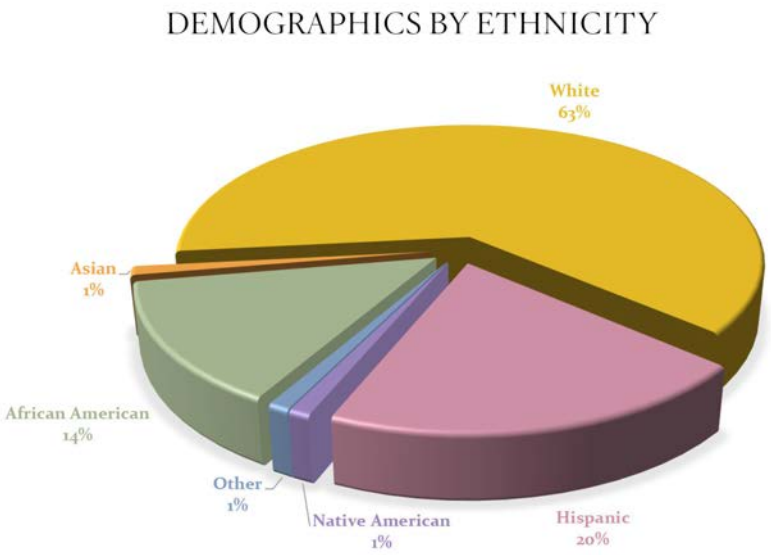
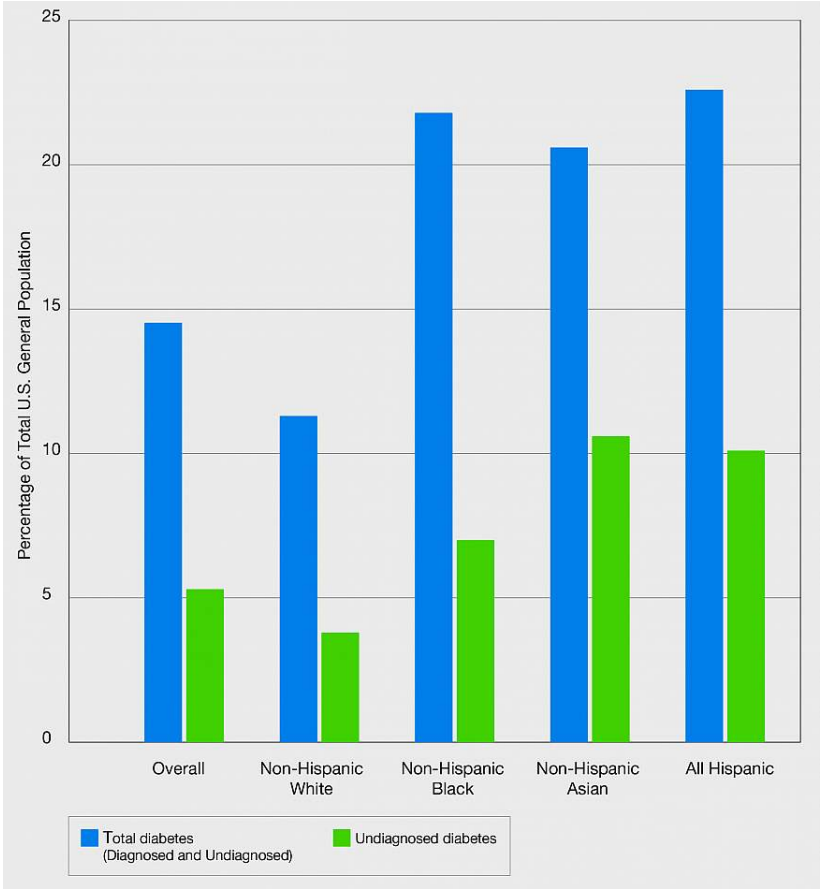
General Diabetes





~10% of all Ohioans have diabetes

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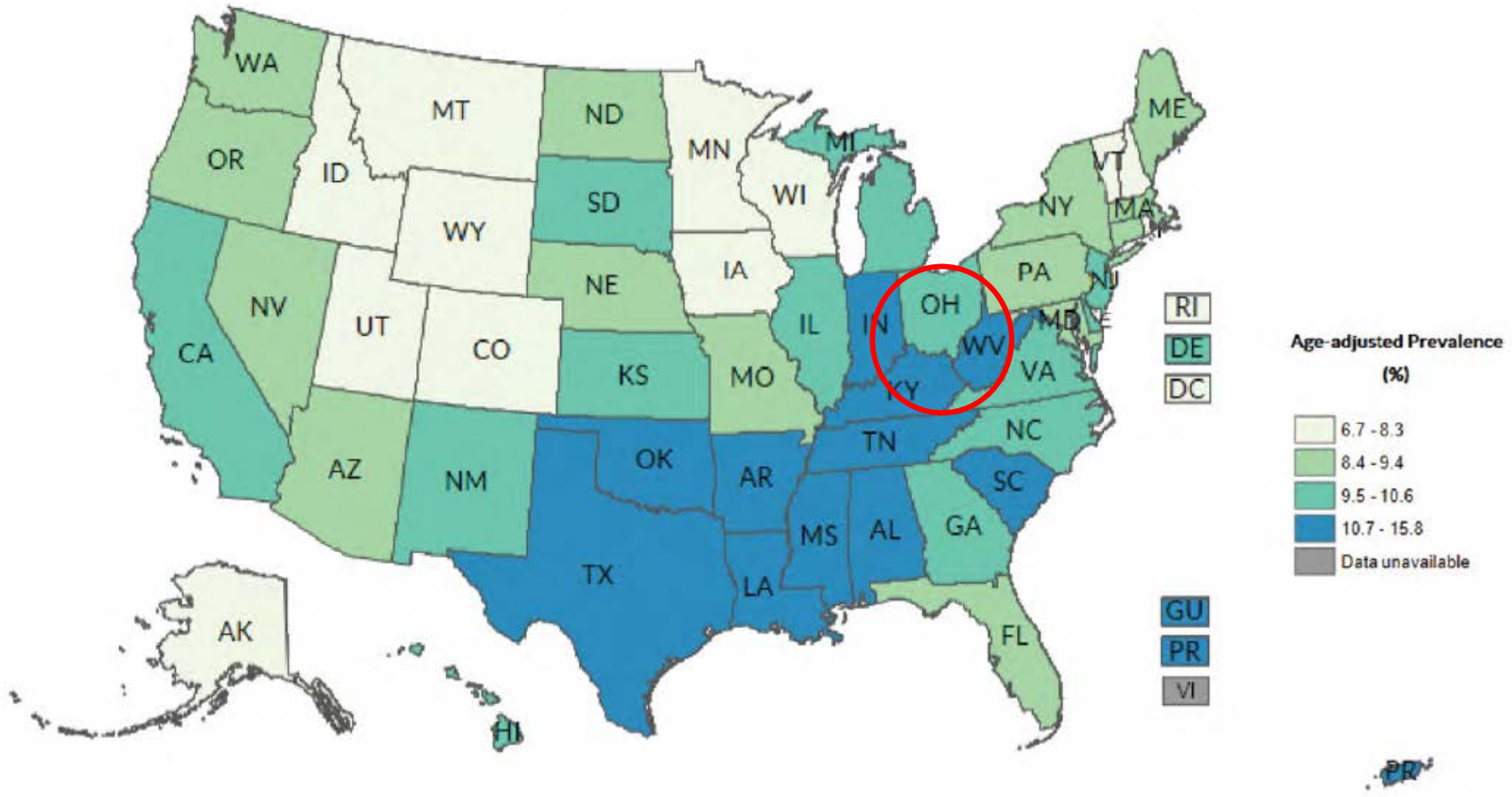
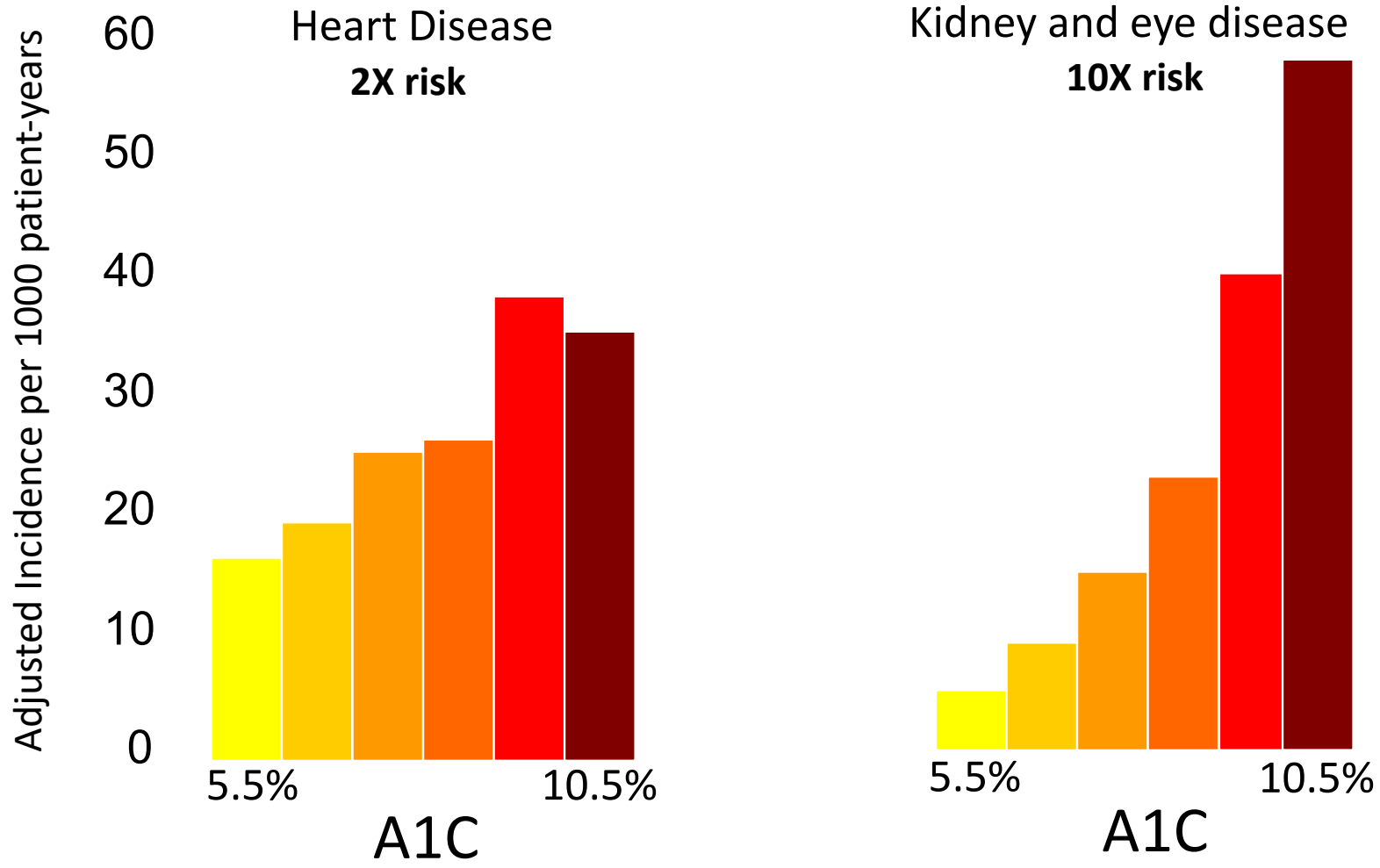


Heart Disease and Stroke Statistics, 2020

Uncontrolled diabetes = heart and kidney disease



Stratton IM, et al. *BMJ* 2000;321:405-412

Heart Disease #1 Cause of Death in Patients with Diabetes

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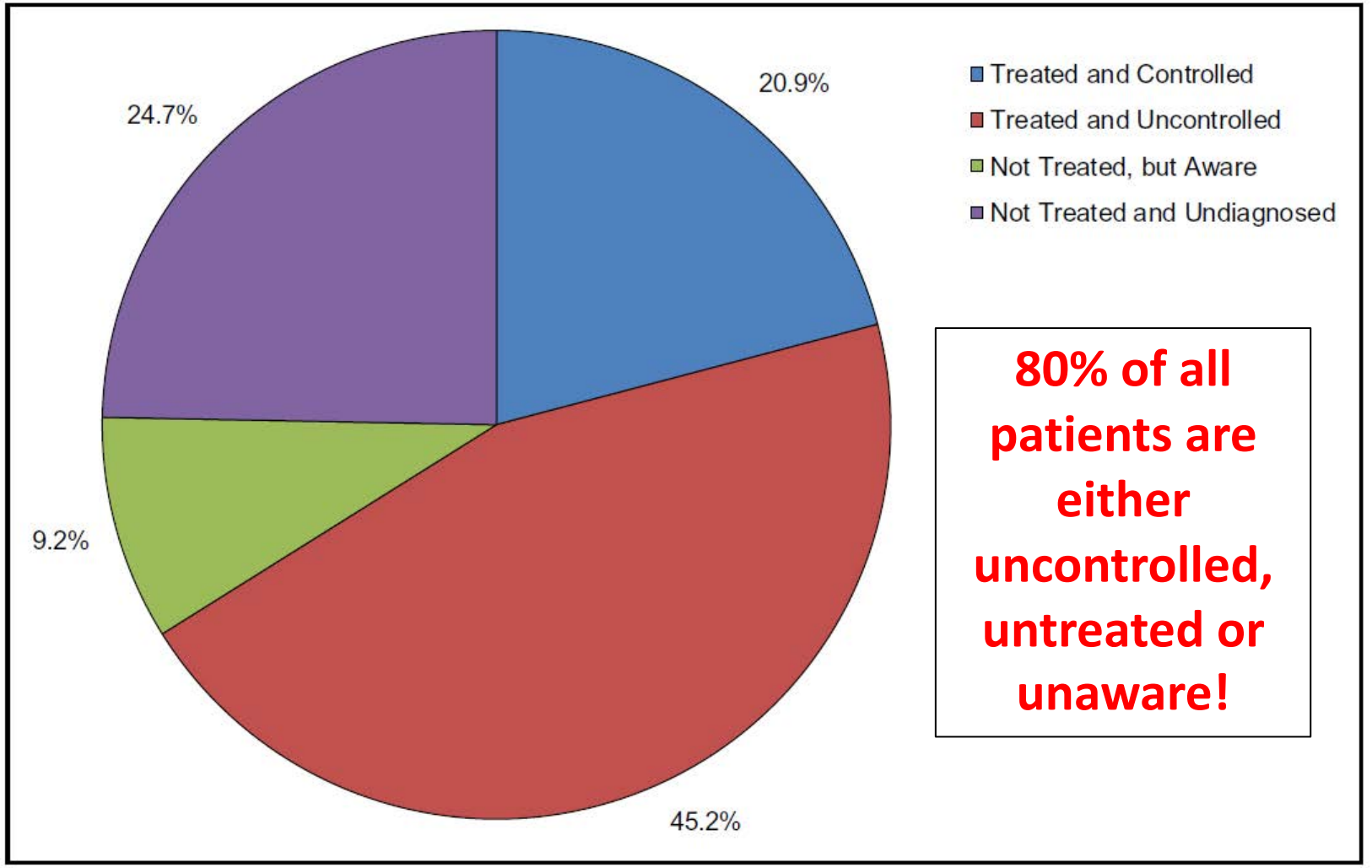
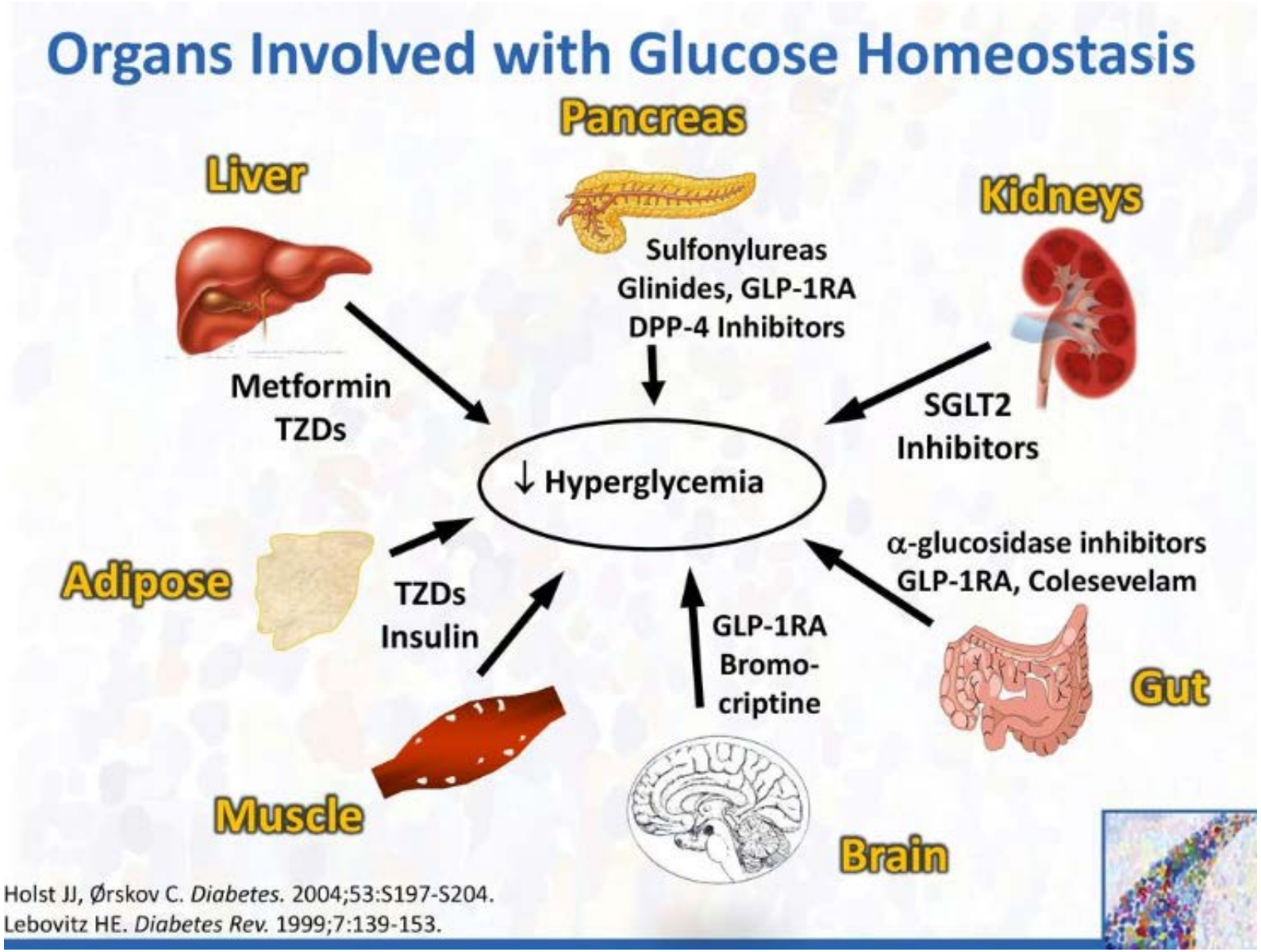
http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

Awareness, treatment, and control of diabetes in US adults



80% of all patients are either uncontrolled, untreated or unaware!

Heart Disease and Stroke Statistics, 2020



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2 Classes of Therapies

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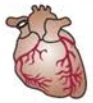
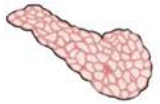
	GLP-1 receptor agonist		SGLT2 inhibitor	Combination therapy
Appetite	↓		↑ (?)	↓
Bodyweight	↓		↓	↓↓
Ischaemic cardiovascular events	↓		↓	↓↓
Heart failure events	↔		↓	↓
Insulin secretion	↑		↓	↑
Glucagon secretion	↓		↑	↔
Hepatic glucose output	↓		↑	↔
Ketone body production	↓ (?)		↑	↔
Glucose uptake (insulin-mediated)	↑ (?)		↑	↑↑
Diuresis, natiruresis	↑ (acutely)		↑	↑
Urinary glucose excretion	↔		↑	↑
Renoprotection	↔		↑	↑

Mechanism

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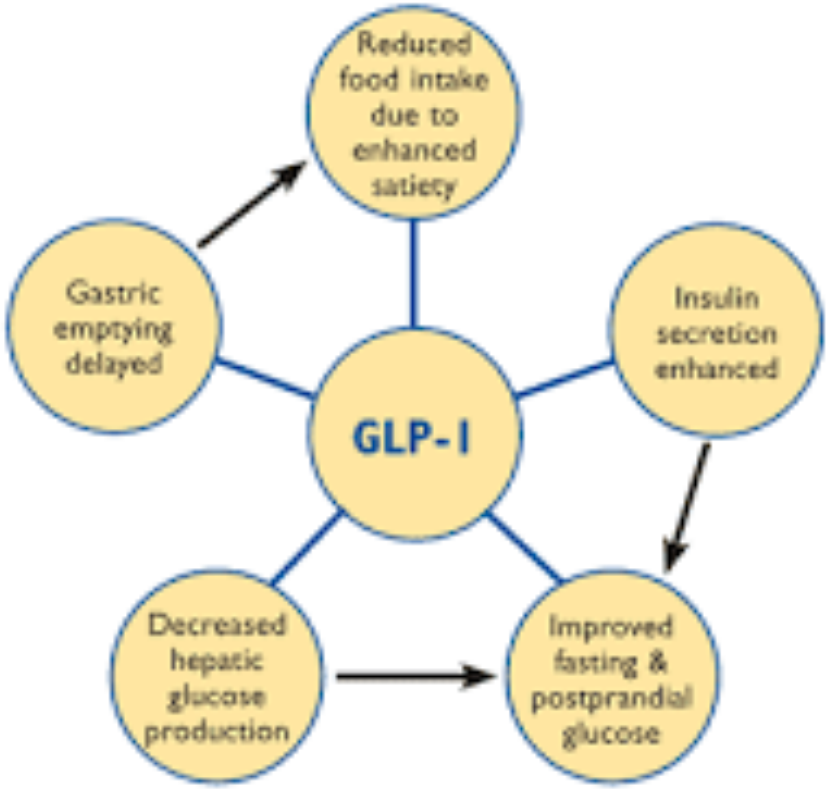
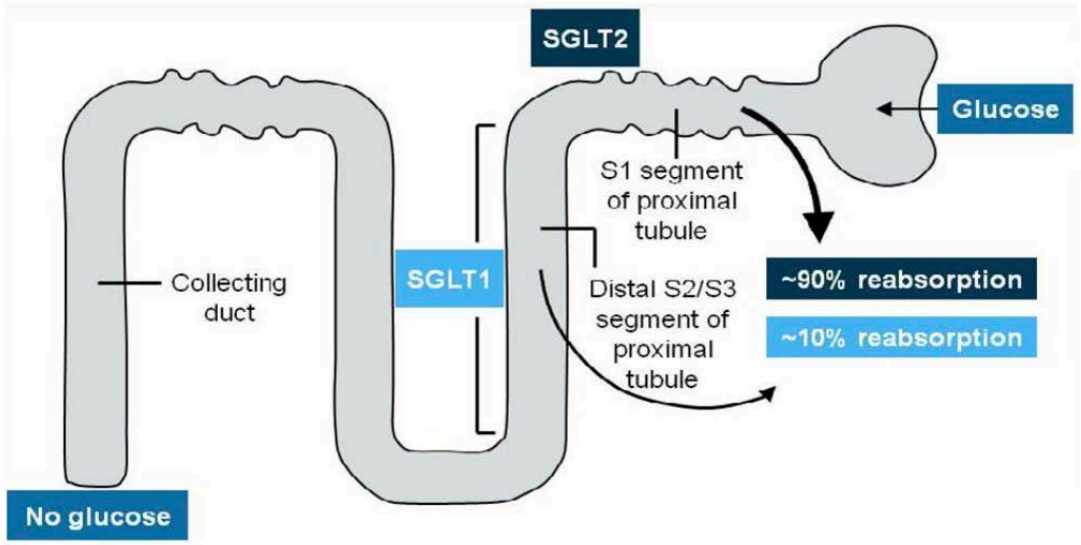
Figure 3. Mechanism of Action of GLP-1



GLP-1: glucagon-like peptide-1. Source: Reference 32.



Trials with Diabetic patients

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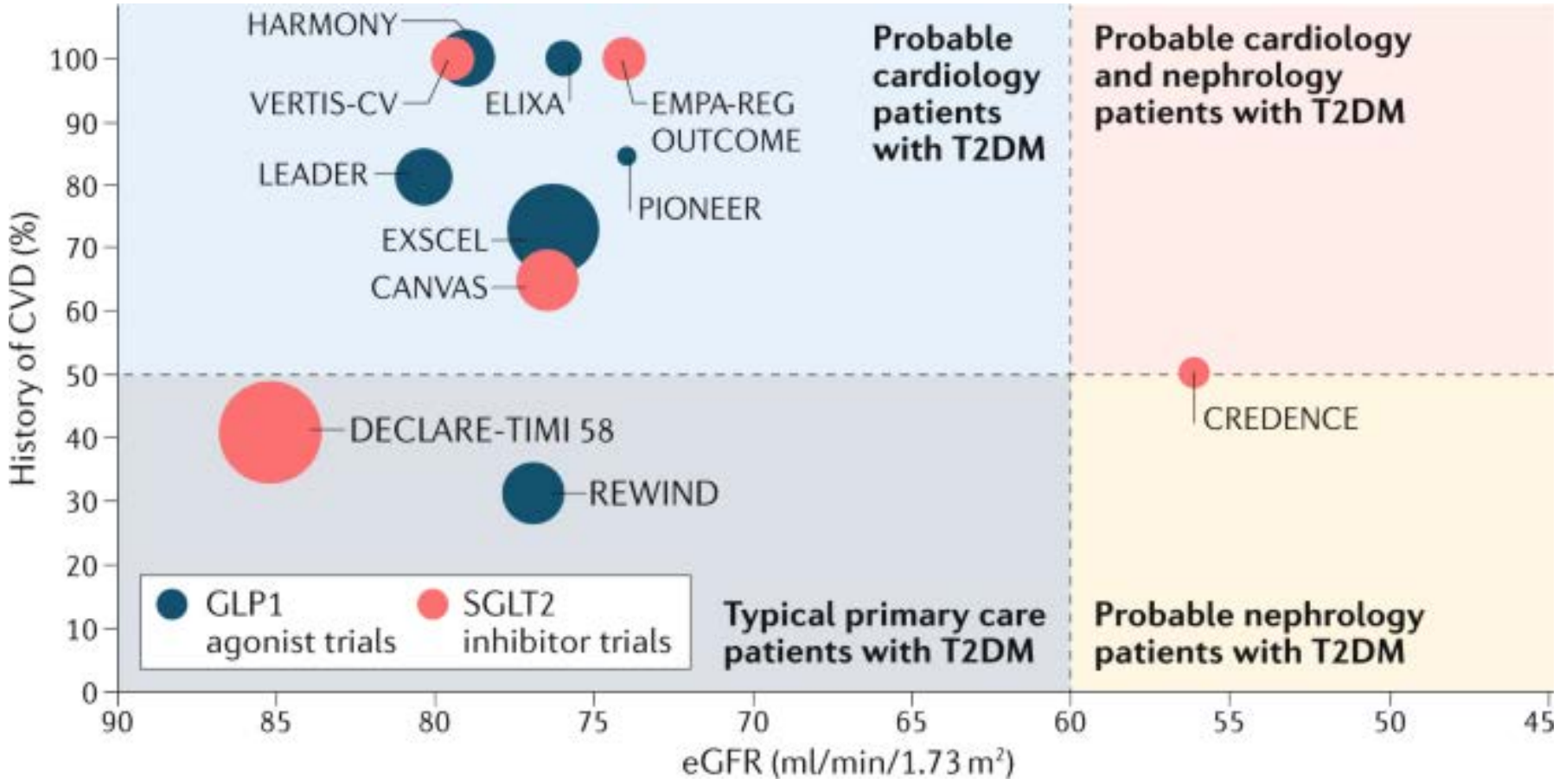

GLP-1 RA

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	Glucagon-like peptide-1 receptor agonists (brand name)			
	Exenatide (Byetta), exenatide LAR (Bydureon)	**Liraglutide (Victoza)**	**Albiglutide (Tanzeum)**	**Dulaglutide (Trulicity)**
Dosing	**Byetta**: 5 mcg twice daily; may increase to 10 mcg twice daily, if needed; administer 1 h before morning and evening meals **Bydureon**: 2 mg weekly	0.6 mg daily for 1 week only, then increase to 1.2 mg daily; may increase to 1.8 mg daily, if needed	30 mg once weekly; may increase to 50 mg once weekly, if needed	0.75 mg once weekly; may increase to 1.5 mg once weekly, if needed
Adverse reactions	Nausea, hypoglycemia, vomiting, diarrhea, dizziness, headache, dyspepsia, constipation	Headache, nausea, diarrhea, anti-liraglutide antibody formation	URTI, diarrhea, nausea, injection site reaction, cough, back pain, arthralgia, sinusitis, influenza	Nausea, diarrhea, vomiting, abdominal pain, decreased appetite
Precautions	Pancreatitis, hypoglycemia, renal impairment	Thyroid tumors, pancreatitis, hypoglycemia, renal impairment	Thyroid tumors, pancreatitis, hypoglycemia, renal impairment	Thyroid tumors, pancreatitis, hypoglycemia, renal impairment
Contraindications	MTC, MEN2 (exenatide LAR **only**)	MTC, MEN2	MTC, MEN2	MTC, MEN2
Renal dosing	Avoid in patients with CrCl ≤ 30 ml/min	Use caution in patients with renal dysfunction; no dose adjustments required	Use caution in patients with renal dysfunction; no dose adjustments required	Use caution in patients with renal dysfunction; no dose adjustments required
Comments	Exenatide LAR must be reconstituted before use	Recommend that patients restart at 0.6 mg dose if more than 3 doses are missed	Must be reconstituted before use; missed doses can be administered within 72 hours of missed dose and prior once-weekly dosing schedule can be resumed	Missed doses can be administered within 72 hours of missed dose and prior once-weekly dosing schedule can be resumed

SGLT2-INHIBITORS

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TABLE 1

FDA-approved SGLT2 inhibitors[2]

Generic agent (brand)	Canagliflozin (Invokana)	Dapagliflozin (Farxiga)	Empagliflozin (Jardiance)
Initial dose (maximum dose)	100 mg/d if eGFR is 45 to <60 and 300 mg/d if eGFR ≥60	5 mg/d (10 mg/d)	10 mg/d (25 mg/d)
Renal dosage adjustments	Discontinue if eGFR is persistently <45 (Contraindicated if eGFR <30)	Do not administer/discontinue with eGFR <60	Do not initiate/discontinue with eGFR persistently <45 (Contraindicated if eGFR <30)
Hepatic dosage adjustments	No adjustment for mild to moderate impairment; not recommended in severe impairment (has not been studied)		None to note
Drug interactions	If receiving concurrent UGT enzyme inducers and eGFR is 45 to <60, consider alternative antihyperglycemic therapy	None to note	
Administration	Administer prior to first meal	Administer in the morning without regard to food	
Common adverse effects	Genital mycotic infections, urinary tract infections, volume-related effects such as dizziness and hypotension		
Available combination products, generic (brand)	canagliflozin + metformin (Invokamet)	dapagliflozin + metformin ER (Xigduo)	empagliflozin + metformin (Synjardy) empagliflozin + linagliptan (Glyxambi)

eGFR, estimated glomerular filtration rate (reported in mL/minute/1.73 m²); UGT, uridine 5′-diphospho-glucuronosyltransferase enzyme inducers (eg, rifampin, phenytoin, phenobarbital, ritonavir).

J Fam Pract. 2016 September;65(9):587-593

BENEFITS AS SEEN IN TRIALS

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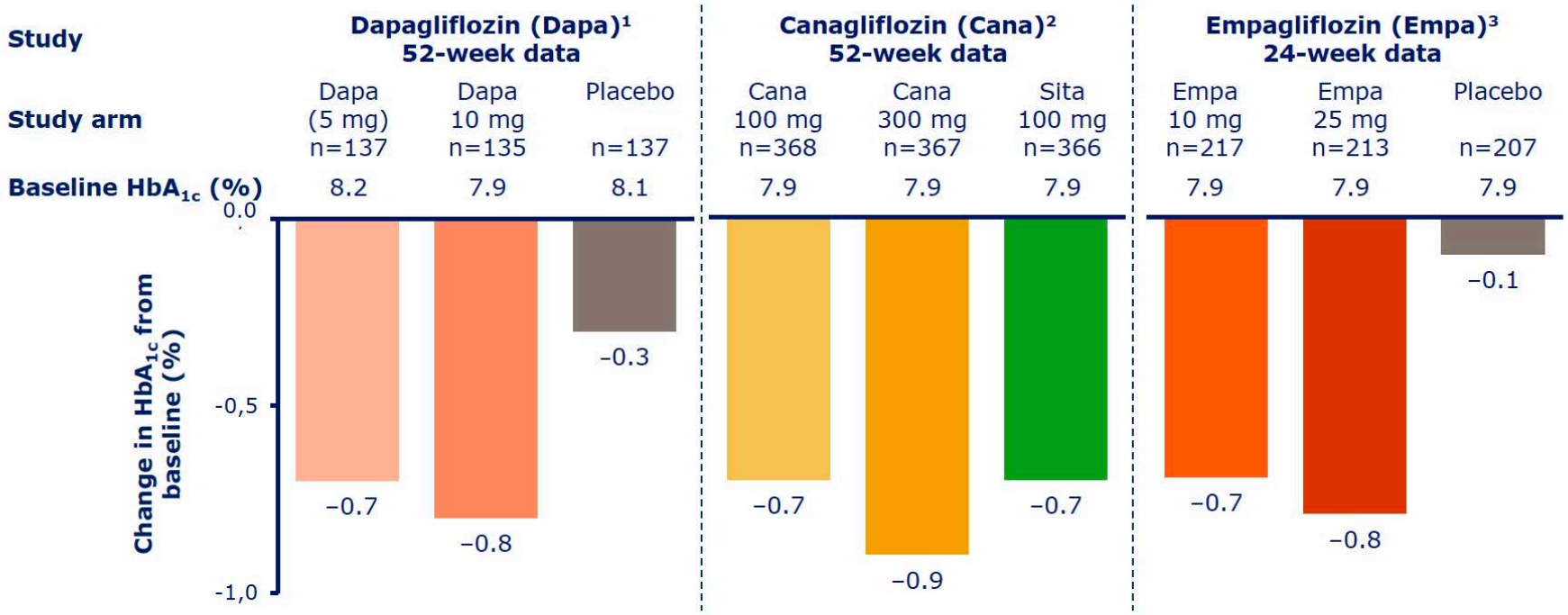
Comparison of SGLT-2 inhibitors: HbA_{1c}



1. Bailey CJ et al. *Lancet* 2010;375:2223–2233; 2. Lavalle Gonzalez FJ et al. *Diabetologica* 2013;56:2582–2592; 3. Häring HU et al. *Diabetes Care* 2014;37: 1650–1659

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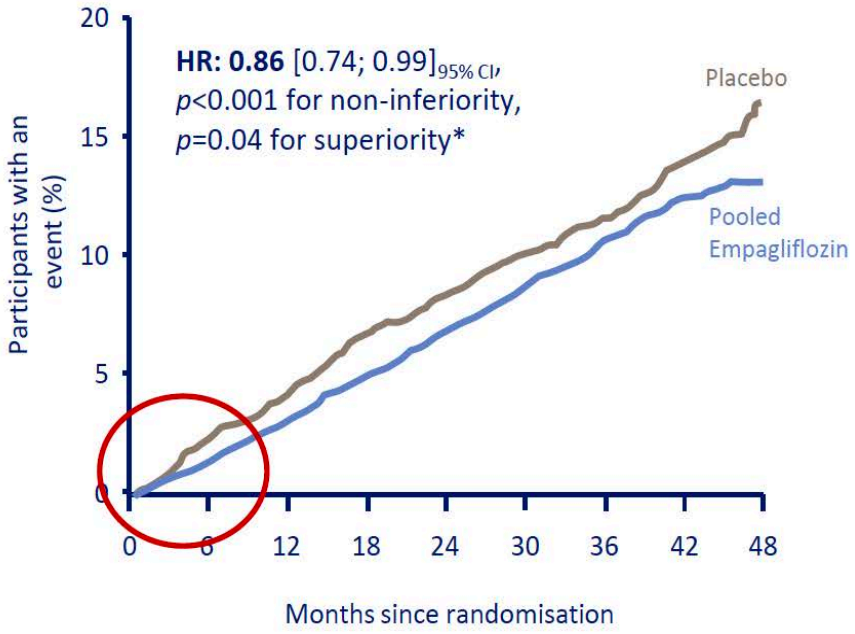
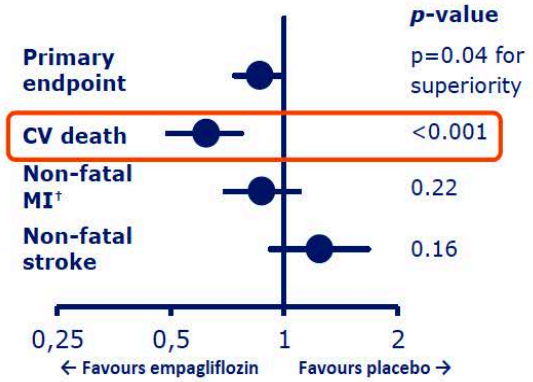
Empagliflozin: EMPA-REG results





Heart failure

As compared with placebo, empagliflozin resulted in a significantly lower risk of **hospitalisation for heart failure**
HR: 0.65
[0.50; 0.85]95% CI, *p*=0.002

The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke,
1. Zinman et al. *N Engl J Med* 2015;373:2117–28.

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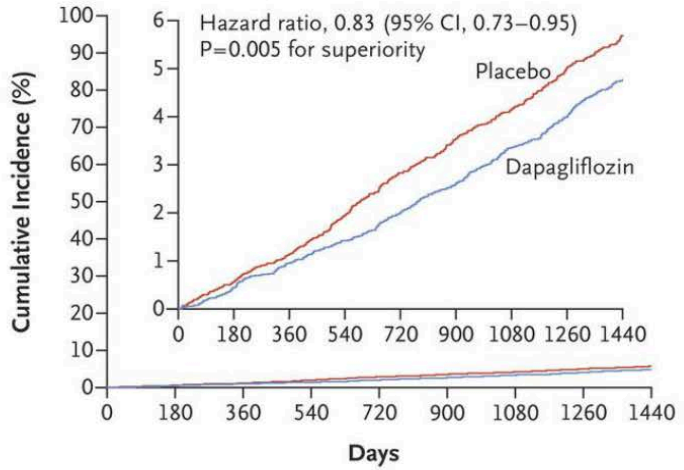
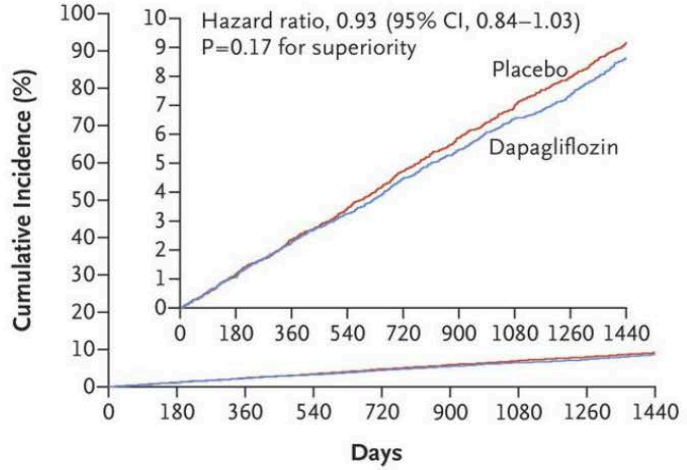
Dapagliflozin: DECLARE-TIMI 58 Results

Cardiovascular Death or Hospitalization for Heart Failure



No. at Risk									
Placebo	8578	8485	8387	8259	8127	8003	7880	7367	5362
Dapagliflozin	8582	8517	8415	8322	8224	8110	7970	7497	5445

MACE



No. at Risk									
Placebo	8578	8433	8281	8129	7969	7805	7649	7137	5158
Dapagliflozin	8582	8466	8303	8166	8017	7873	7708	7237	5225

SD Wiviott et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1812389

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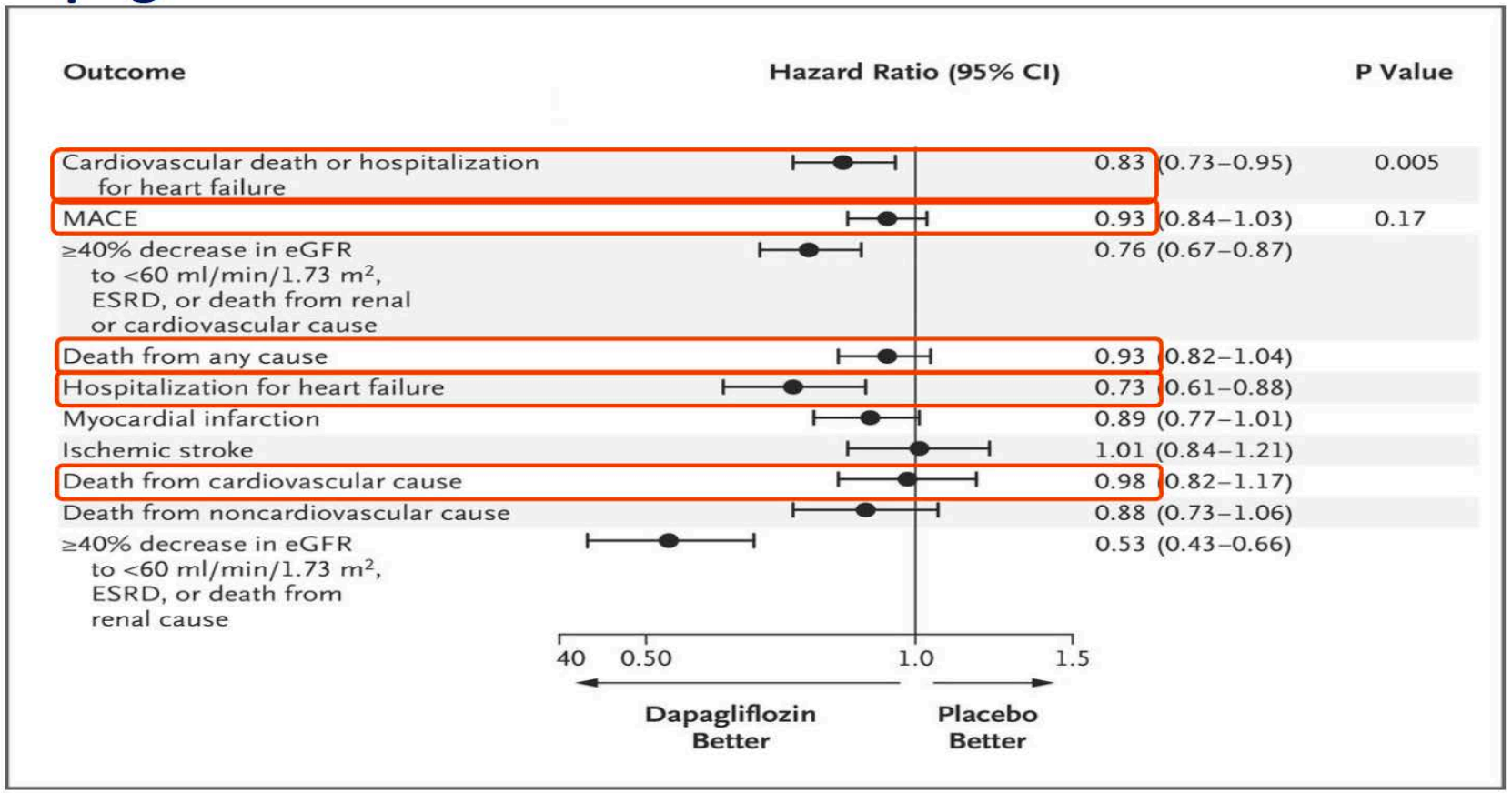
Dapagliflozin: DECLARE-TIMI 58 Results



SD Wiviott et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1812389

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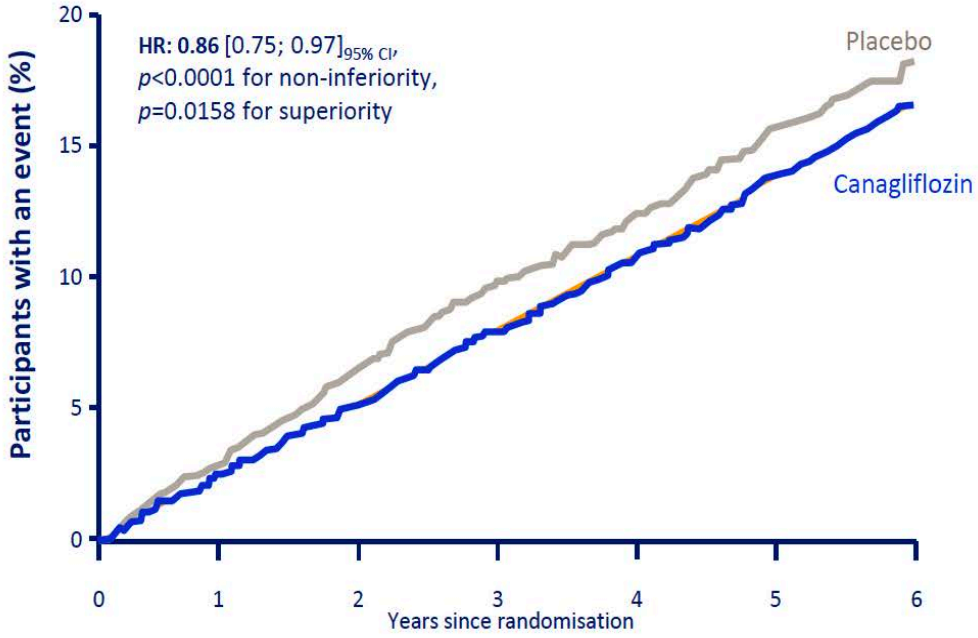
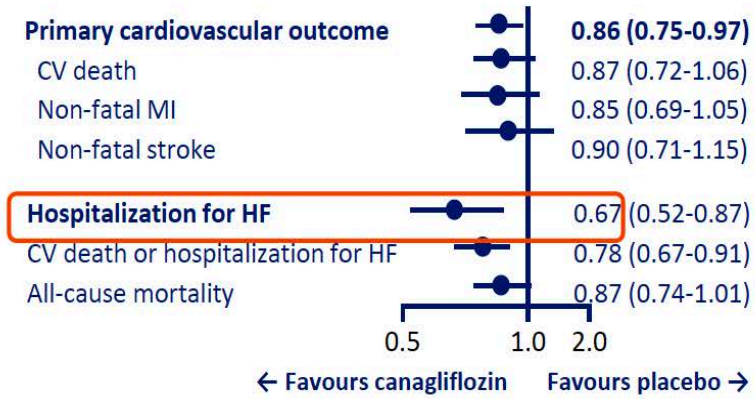
Canagliflozin: CANVAS results





The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke,
Neal *et al*. *N Eng J Med* 2017; DOI: 10.1056/NEJMoa1611925.

BENEFITS AS SEEN IN TRIALS

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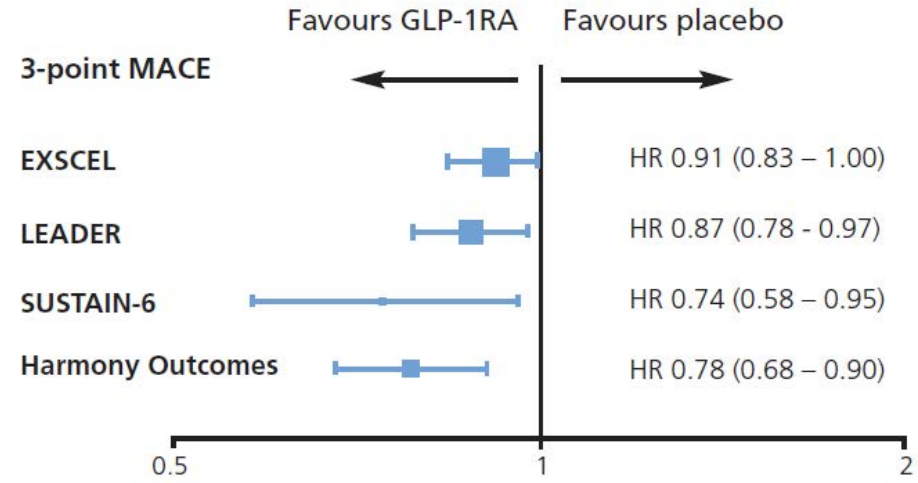
Figure 1. Comparison between the results of the four cardiovascular outcome studies with long acting GLP-1 receptor agonists. The agents studied were exenatide QW (EXSCEL), liraglutide (LEADER), semaglutide (SUSTAIN-6) and albiglutide (HARMONY Outcomes)



MACE, major adverse cardiovascular event. HR, hazard ratio.
Adapted from EASD Virtual Meeting (5).

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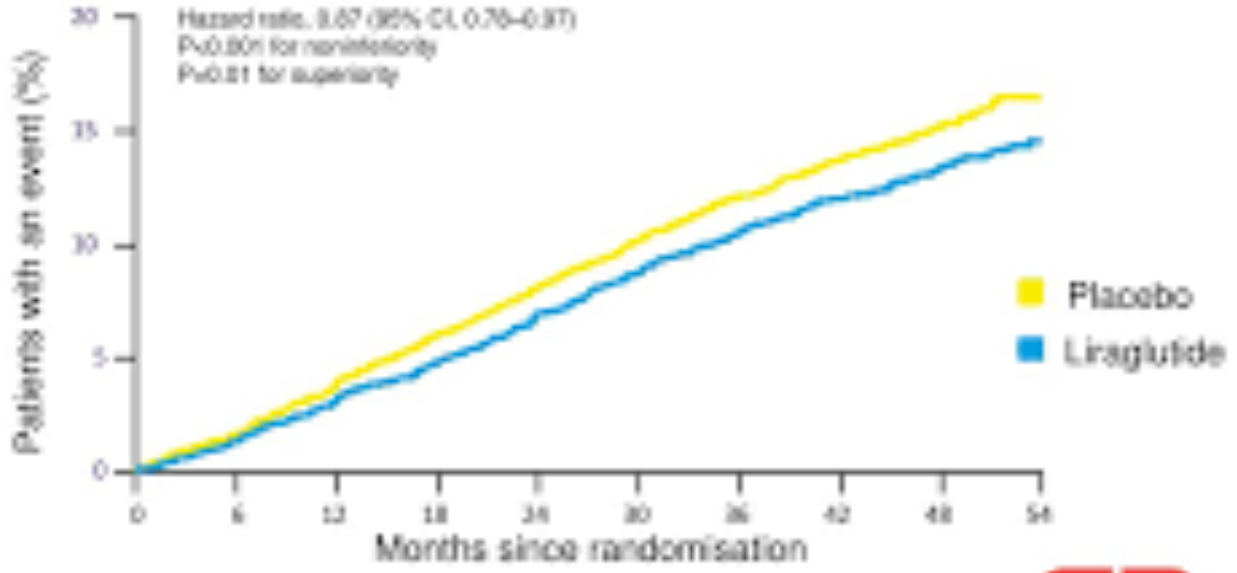
LEADER trial: Primary Outcome

First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis in patients with type 2 diabetes and high CV risk.



Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial

Adapted from Marso SP et al. NEJM 2016

Relative cost

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Table 1 Costs of Diabetes Medications, by Class

Drug/drug class	Cost of 30-day supply, range, $
Metformin	5-9
Insulin	145-650
Sulfonylureas	9-15
Pioglitazone	12-17
DPP-4 inhibitors	173-397
SGLT-2 inhibitors	432-443
GLP-1 receptor agonists	492-684

DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2.

Source: Cost obtained from GoodRx based on 30-day supply.

Renal function and medication selection

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eGFR	UACR <30 mg/g	UACR 30–299 mg/g	UACR ≥300 mg/g
>60 ml/min per 1.73 m^2	SGLT2i or GLP-1 RA[a]	SGLT2i is preferred. GLP-1 RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk[b]	SGLT2i should be initiated. GLP-1 RA as an add-on for uncontrolled metabolic risk[c]
30–60 ml/min per 1.73 m^2	SGLT2i is preferred. GLP-1 RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk[b]		SGLT2i should be initiated. GLP-1 RA as an add-on for uncontrolled metabolic risk[c]
15–29 ml/min per 1.73 m^2	GLP-1 RA (dulaglutide) is preferred. Initiation of SGLT2i is currently contraindicated[d]		

SGLT2i, sodium glucose co-transporter 2 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; UACR, urinary albumin-to-creatinine ratio.
[a]In patients with low kidney failure risk, SGLT2i and GLP1-RA are similar in preventing worsening albuminuria. Consider SGLT2i if patients have a high risk for heart failure hospitalization. Consider GLP-1 RA if patients have uncontrolled metabolic risks.
[b]In patients with moderate kidney failure risk and adequate eGFR >30 ml/min per 1.73 m^2, SGLT2i is preferred. Consider adding GLP-1 RA for uncontrolled metabolic risks.
[c]In patients with high kidney failure risk and adequate eGFR >30 ml/min per 1.73 m^2, SGLT2i is preferred. Consider adding GLP-1 RA for uncontrolled metabolic risks.
[d]In patients with high kidney failure risk but eGFR is <30 ml/min per 1.73 m^2, GLP-1 RA (dulaglutide) is recommended for safer glycemic control and potential kidney protection. Currently, the data to support the use of SGLT2i for kidney failure prevention in eGFR <30 ml/min per 1.73 m^2 is lacking.

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Evidence-based Approaches to Smoking Cessation

Teachable Moments

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- Health-related events such as a diabetes diagnosis, increasing disease severity, or hospitalization can[1]:
  - Increase patients' interest in smoking cessation
  - Trigger attempts to quit smoking
  - Improve rates of smoking cessation
- Fewer than 30% of patients use evidence-based methods to quit smoking[2]
  - 25% used only one method for quitting on most recent quit attempt
  - 15% tried cold turkey as their only method (~5% success rate)
  - 25% switched completely to e-cigarettes
  - 15% got assistance from a health professional

1. U.S. Department of Health and Human Services, 2020. Smoking Cessation. A Report of the Surgeon General.
2. Caraballo RS, et al. Quit Methods Used by US Adult Cigarette Smokers, 2014–2016. *Prev Chronic Dis* 2017; 14:160600.

Tobacco Cessation Guidelines

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- The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using, and provide behavioral interventions and FDA-approved medications for cessation.

- Grade: A
  - *The USPSTF recommends the service. There is high certainty that the net benefit is substantial.*

  - *Suggestions for Practice: Offer or provide this service.*

USPSTF Recommendations. *Ann Intern Med*. 2015;163:622-634. doi:10.7326/M15-2023

Evidence for Behavioral Methods

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- ***Evidence is strongest for physician and nurse advice*** (8-13% cessation rates), telephone quit lines, and tailored self-help materials[1]
- Brief in-person counseling (<10 min) by primary care providers increases the proportion of adults who quit smoking and remain abstinent for 1 year[2]
- Even minimal interventions (<3 min) have been found to increase cessation rates[2]

1. Stead LF, et al. *Cochrane Database Syst Rev*. 2013;5:CD000165.
2. USPSTF Recommendations. *Ann Intern Med*. 2015;163:622-634. doi:10.7326/M15-2023

Screening, Brief Intervention & Referral to Treatment (SBIRT)

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- Brief integrated approach to treatment for people with substance use disorders and those at-risk (5-10 minutes)
- Used across diverse populations for tobacco, alcohol, substance use, & abuse of prescription meds
- Associated with increased likelihood of smoking quit attempts & increased satisfaction with care[1]
- Even low-intensity SBIRT may prompt quit attempts and decrease cigarette use[2,3] (3-5 minutes)

1. *Bernstein S. et al. J Emerg Med 2010, 38(4), e35-e40.*
2. *Rahm AK, et al. Subst Abus 2015;36(3):281-8.*
3. *Cunningham et al. Acad Emerg Med 2010, 16(11), 1078-1088.*

‘Opening the Door’ (+ SBIRT & MI)

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Screening

- Step 1: After establishing rapport, **Ask about tobacco use**
  - Clinician: Mrs. Williams, do you currently smoke or use tobacco?
  - Mrs. Williams: Yes, I smoke.
  - Optional: Assess usage patterns and dependence (eg., CAGE for smoking, 4 C’s, Fagerstrom)

Brief Intervention

- Step 2: **Express Concern:** I’m concerned about your smoking.
- Step 3: **Medicalize the concern**
  - Clinician: Smoking makes it harder to control diabetes. It also increases your risk of developing serious health problems from diabetes.
- Step 4: **Solicit mutual concern**
  - Clinician: Does this concern you as well?
  - Mrs. Williams: Well, yes it does.
- Step 5: **Collaborate**
  - Clinician: Would it be okay if we discuss this for a few minutes today?
  - Mrs. Williams: Yes, that would be fine.
- Step 6: **Assess Importance**
  - Clinician: “On a scale from 0 to 10, how important would you say it is for you to quit smoking?”

Options

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Referral for Treatment

- If patient is willing to consider quitting or is ready to quit, refer to the Ohio Tobacco Quit Line, Smokefree.gov, or other resources

    - *Quitting tobacco is a process. Whether you are thinking about quitting, are not yet ready to quit, or have already quit, the Ohio Tobacco Quit Line can help you each step of the way.*
    -- https://ohio.quitlogix.org/en-US/

Ohio Tobacco Program
Quit Line: 1-800-QUIT-NOW

Options

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If not ready to consider quitting or make a quit attempt:

- Provide printed information about smoking risks & cessation methods
- Ask for permission to resume the discussion at a future visit

- During subsequent visits, provide brief motivational interviewing-based counseling to increase motivation and self-efficacy (eg. discuss health benefits, assess & build confidence, address concerns)

Reframing Quitting Cold Turkey

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- 25% used only one method for quitting on most recent quit attempt
- 15% tried cold turkey as their only method (~5% success rate)

- *When patients tell me they want to quit on their own, I try to build on their enthusiasm.*
- *What I say is, "It's great that you want to quit cold turkey. I want to give you a couple tools that will increase the likelihood that your effort to quit is successful."*
- *"I recommend that you talk with the Quit Line and also take nicotine lozenges to take the edge off when you're quitting cold turkey."*
- *I don't try to change their mind. I just try to reframe what cold turkey can be.*

Michael Fiore, MD, MPH, Director, Center for Tobacco Research and Intervention, University of Wisconsin School of Medicine and Public Health. In AMA Public Health, July 14, 2020. https://www.ama-assn.org/delivering-care/public-health/latest-smoking-cessation-8-things-physicians-should-know

Ohio Tobacco Quit Line (1-800-Quit-Now)

Ohio Tobacco Program
Quit Line: 1-800-QUIT-NOW

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- **Phone + Online**
  Coaching over the telephone, plus email, text, chat, web-based materials, and quit progress tracking via website

- **Phone Only**
  Coaching over the phone, plus materials, quit planning, and quit progress tracking

- **Online Only**
  Materials, quit planning, and quit progress tracking via website

- **Pharmacotherapy** options depend on patient's insurance plan or employer's program, NRT may be provided directly by the Quit Line

SmokeFree.gov

smokefree.gov

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- Sponsored by the National Cancer Institute
- Texting, smartphone apps, social media
  - Planning to quit, withdrawal, cravings, stress, mood
  - Relapse prevention
  - Tailored texting, apps, & social media content for:
    - women, teens, veterans, Spanish-speaking, over age 60
- NRT information for patients

Facilitating Referrals

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- EHRs can be programmed for electronic referral of patients to:
  - Ohio Tobacco Quit Line (1-800-QUIT-NOW)
    - Technical guidance for EHR integration is available
  - National Cancer Institute's smokefree.gov suite of cessation resources (including SmokefreeTXT)
  - Health system-based smoking cessation programs
  - Community smoking cessation programs
- Optimizing workflow: Care team members can implement the referral process via EHR, online, or via fax

Recap

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- Use the ‘Opening the Door’ technique plus SBIRT & MI
- Refer patients to the Ohio Tobacco Quit Line, Smokefree.gov, or community resources
  - Care team members can implement referrals via EHR, online, or by fax
- For patients who are not ready, request permission to resume the discussion at a future visit
  - Brief MI-based conversations over multiple visits
  - Support the patient in moving through the stages of change

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Thank you!

Questions/Discussion