Soledad | cases

Soledad, age 59

Soledad is a 59-year-old woman diagnosed with T2DM 9 years ago. She is seeing you in follow up after a hospitalization that included 2 coronary artery stents

She feels a little tired today

She is adherent with her current medications

She checks her FPG most days and reports a range of 150-220 mg/dL

primed

Soledad | cases

Soledad, age 59

Vitals:

Temp 98.7 F	**Ht** 65 inches
HR 64 bpm	**Wt** 200 lbs
RR 18	**BMI** 33.3 kg/m²
BP 120/74 mmHg	**WC** 39 inches

primed

Soleded | cases

Soledad, age 59

Medical history:

T2DM × 9 years
HTN
Hyperlipidemia
Obesity
Hypothyroidism

Surgical History:

C/S x 2
Laparoscopic cholecystectomy

Social History:

Denies tobacco
Denies ETOH

primed

Soleded | cases

Soledad, age 59

Medications:

Metformin 1000 mg BID	Atorvastatin 40 mg QD
Glimepiride 8 mg QD	Aspirin 81 mg QD
Lisinopril 20 mg QD	Levothyroxine 125 mcg QD
Metoprolol 50 mg BID	

Allergies: Penicillin

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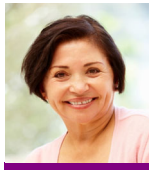
Relevant Labs (fasting)

cases



Soledad, age 59

HbA1c	8.3%
Fasting Plasma Glucose	172 mg/dL
LDL	95 mg/dL
HDL	45 mg/dL
TGs	290 mg/dL
BUN	20 mg/dL
Creatinine	0.8 mg/dL
eGFR	78 mL/min/1.73m²
TSH	1.2 mU/L

primed

Soledad

cases

Soledad, age 59

After ACS, what complication is Soledad at most risk of developing?

HbA1c 8.3%
eGFR 78 mL/min/1.73m²

Metformin 1000 mg BID
Glimepiride 8 mg QD
Lisinopril 20 mg QD
Metoprolol 50 mg BID

Atorvastatin 40 mg QD
Aspirin 81 mg QD
Levothyroxine 125 mcg QD

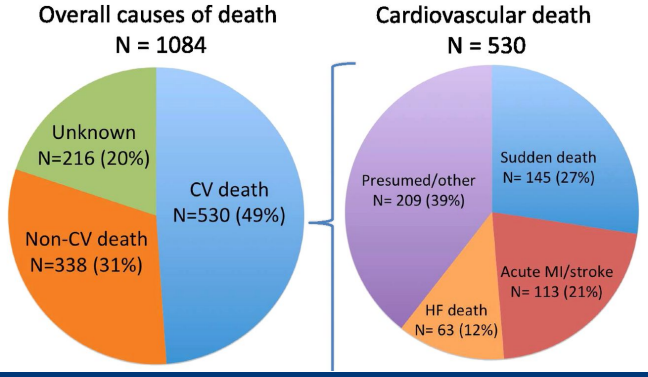
primed

T2DM and CV Risk

- Heart disease rates among adults with diabetes are **2 to 4** times higher than rates for adults without diabetes
- The rate of cardiovascular death is increased by **50%** in those with diabetes
- Diabetes **increases** the risk of **stroke**, with RR ranging from 1.8 - 6 fold increased risk
- **The event rate for CHF is higher than any other complications after ACS in patients with diabetes**
- Diabetic men and women ≥50 years of age live an average of 7.5 and 8.2 years less than their nondiabetic equivalents. The differences in life expectancy free of CVD are 7.8 and 8.4 years, respectively.

1. Go AS, Mozaffarian D, Roger VL, et al.; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2014;129:e28–e292. 2. Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W. Arch Intern Med. 2007;167:1145–1151; 3. Malmberg K et al. *Circulation*. 2000;102:1014-1019.

Causes of Death in Patients with T2DM and CV Disease

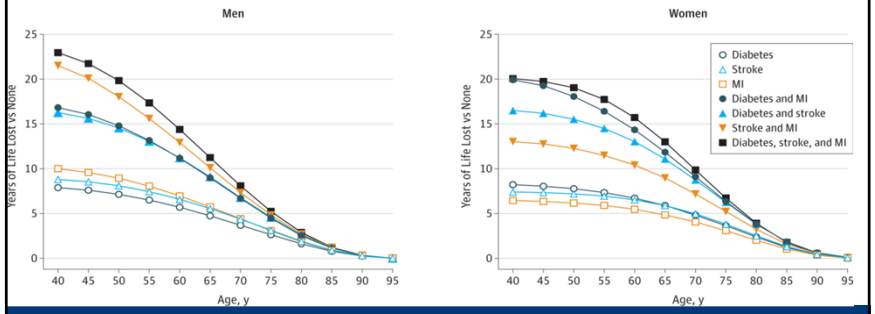


Sharma A, et al. Diabetes Care. 2017;4-(12):1763-1770.

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

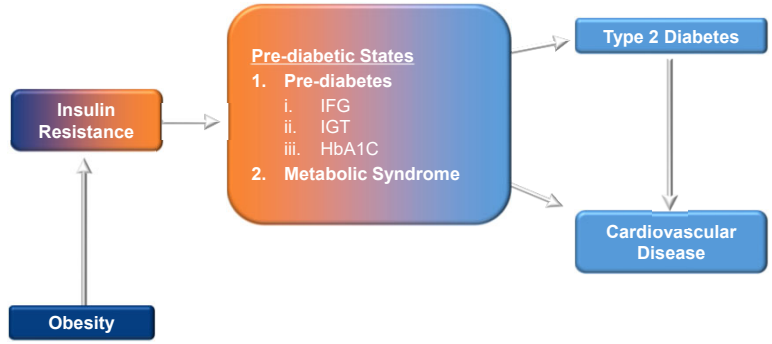
Multimorbidity and T2DM

By age 60, a history of any 2 of these conditions was associated with 12 years of reduced life expectantly; a history of all 3 conditions was associated with 15 years of reduced life expectancy



The Emerging Risk Factors Collaboration. Association of Cardiometabolic Multimorbodity with Mortality. JAMA. 2015;314(1):52-60.

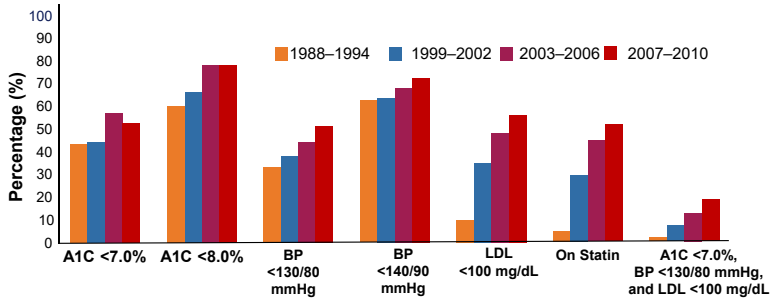
The Spectrum of Cardiometabolic Disease



IFG = impaired fasting glucose; IGT = impaired glucose tolerance; HbA1C = glycosylated hemoglobin.
Courtesy of WT Garvey, 2011.

CV Risk is Not Well-Managed Despite Improvements
NHANES Study

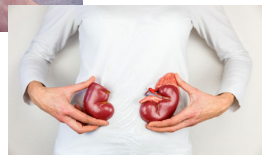
Percentage % meeting ABC goals among adults aged ≥20 years with diagnosed diabetes, 1988–2010



Stark Casagrande S, et al. Diabetes Care. 2013;36;2271–2279.

We Will Discuss:

- ▶ Considering CV risk when choosing diabetes therapy
- ▶ Lipid management
- ▶ Blood pressure
- ▶ Antiplatelet agents
- ▶ Heart failure
- ▶ Chronic kidney disease association with CV disease



Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

Soledad | cases

HbA1c 8.3%
eGFR 78 mL/min/1.73m²

Despite maximum doses of metformin and glimepiride, Soledad has a HbA1c of 8.3%. What do you think about the following treatment options?

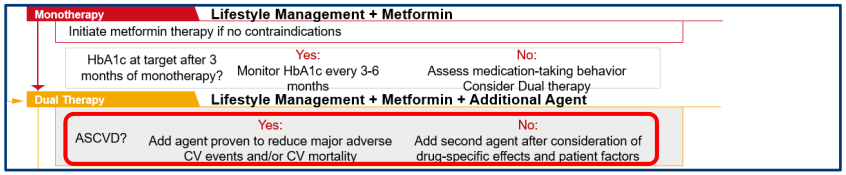
Metformin 1000 mg BID
Glimepiride 8 mg QD
Lisinopril 20 mg QD
Metoprolol 50 mg BID

Atorvastatin 40 mg QD
Aspirin 81 mg QD
Levothyroxine 125 mcg QD

primed

CV Disease and Diabetes Treatment Guidelines

2018 ADA Standards of Medical Care in Diabetes placed ASCVD at the center of its treatment algorithm



ASCVD = atherosclerotic cardiovascular disease

Adapted from ADA. *Diabetes Care*. 2018; 41(1):S73-85.

ADA/EASD Guidance on Management of T2DM
October 5, 2018

The treatment approach to T2DM should **begin with an assessment of CV risk**, other comorbidities, and patient preferences

For patients with **cardiovascular disease**, an SGLT2 inhibitor or a GLP-1 RA with proven cardiovascular benefit is recommended

For patients with **chronic kidney disease (CKD)** or **heart failure and ASCVD**, an SGLT2 inhibitor with proven benefit should be considered

EASD - European Association for the Study of Diabetes

https://diabetologia-journal.org/2018/10/05/new-easd-ada-consensus-guidelines-on-managing-hyperglycaemia-in-type-2-diabetes-launched-at-easd-meeting-new-recommendations-include-specific-drug-classes-for-some-patients-and-enhancing-medication-a/ Press release October 5, 2018

Soledad | cases

HbA1c 8.3%
eGFR 85 mL/min/1.73m²

You and Soledad discuss starting an additional antidiabetes medication that will also decrease CV risk. Which of the following can you recommend to her?

Metformin 1000 mg BID
Glimepiride 8 mg QD
Lisinopril 20 mg QD
Metoprolol 50 mg BID

Atorvastatin 40 mg QD
Aspirin 81 mg QD
Levothyroxine 125 mcg QD

primed

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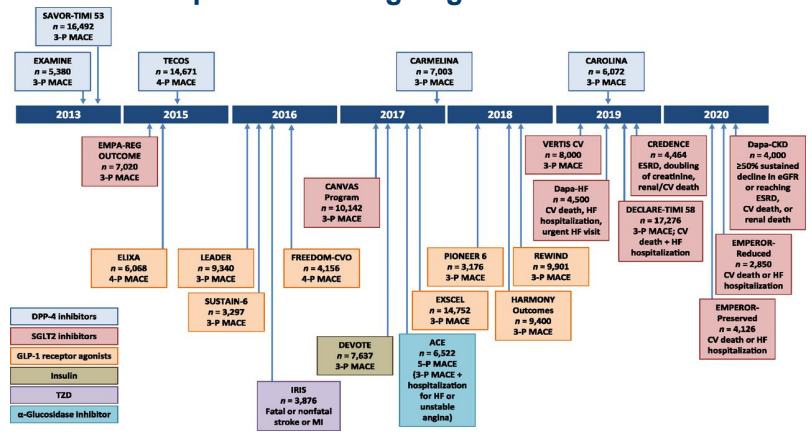
Antidiabetes Therapies and CV Risk

	Metformin	SUs	TZDs	DPP-4 Is	GLP-1 RAs	SGLT2 Is	Insulin
Body weight	↓	↑	↑	↔	↓	↓	↑
LDL	↔	NA	↑	↔	↓	↑	↓
HDL	↑ or ↔	↔	↑ or ↔	↔	↔	↑	↔ or ↑
TGs	↓ or ↔	↔	↓ or ↔	↔	↓		↓
Blood Pressure	↓ or ↔	↑ or ↔	↓	↔	↓	↓	
CRP	↓	↔	↓		↓		
ASCVD Risk	↓	↑	↓ Pioglitazone	↔	↓ Liraglutide Semaglutide	↓ Empagliflozin Canagliflozin	↔
CHF Risk	↔	↔	↑	Potential ↑ Saxagliptin Alogliptin	↔	↓ Empagliflozin Canagliflozin	↔

ADA *Diabetes Care*. 2018; 41(1):S73-85. Azimova K, San Juan Z, Mukherjee *D.Ochsner J*. 2014 Winter;14(4):616-32; Granberry MC, Fonseca VA. *Am J Cardiovasc Drugs*. 2005;5:201–209; Cefalu W, et al. *Diabetes Care*. 2018;41(1):14-31; Sun F, et al. *Clin Ther*. 2015;37(1):225-241. Chaudhuri A, Dandona P. *Diabetes Obes Metab*. 2011;13(10):869-879; Zhang X, Zhao Q. *J Hypertens*. 2016;34(2):167-175.

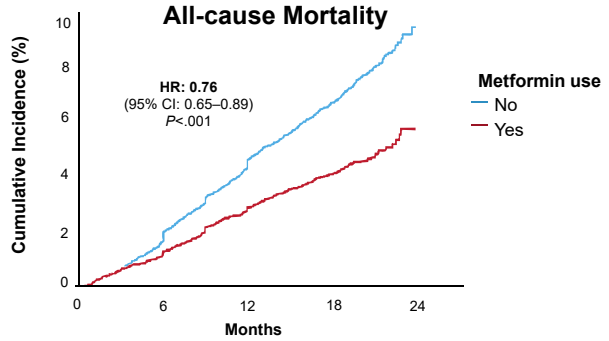
Completed and Ongoing CVOTs for Diabetes



Cefalu W, et al. Diabetes Care. 2018;41(1):14-31.

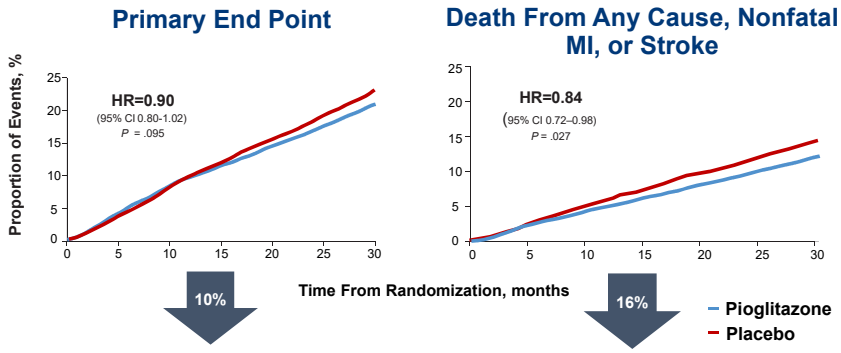
Metformin: *Patients with T2DM and Atherothrombosis*

Associated with a 24% reduction in all-cause mortality after 2-years of follow-up



Roussel R, et al. *Arch Intern Med*. 2010;170:1892-1899.

Pioglitazone: *PROactive Trial*



Primary endpoint: all-cause mortality, nonfatal MI, ACS, cardiac intervention, stroke, major amputation, bypass surgery, revascularization of leg

Dormandy JA et al. *Lancet*. 2005;366:1279-1289.

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

Results of CVOT for Newer Diabetes Therapies

	DPP-4 Is			GLP-1 RAs						SGLT2-Is	
	Saxa	Alo	Sita	Lixi	Lira	Exena QW	Sema	Dula	Alba	Empa	Cana
*MACE	Neutral	Neutral	Neutral	Neutral	↓ (13%)	Neutral	↓ (26%)	↓	↓ (22%)	↓ (14%)	↓ (14%)
CV Death					↓ (22%)					↓ (38%)	↓ (13%)
Death (Any Cause)					↓ (15%)	Neutral					
Non-Fatal Stroke							↓ (39%)				
Hosp for HF	↑	NS ↑				Neutral				↓ (35%)	↓ (33%)

*MACE = Death From CV Causes, Nonfatal MI, or Nonfatal Stroke (+/- hospitalization for unstable angina) **NS = non-statistically significant**

Cefalu W, et al. Diabetes Care. 2018;41(1):14-31; Hernandez AF, et al. Lancet. 2018;392(10157):1519-1529; https://www.healio.com/endocrinology/diabetes/news/online/%7B6a15d82b-f25b-4e5f-b14b-857ddc955fd8%7D/rewind-dulaglutide-reduces-cv-risk-in-type-2-diabetes-without-cvd

CV Considerations and GLP-1 RAs

Pleiotropic effects of GLP-1 RAs include improvements in:

- **Systolic blood pressure**
- **Overweight/obesity**
- **Dyslipidemia**
- **Renoprotection**
- **CV risk**

Wang B, et al. Diabetes Obes Metab. 2013;15(8):737-749; Herzlinger S, Horton ES. *Diabetes Res Clin Pract.* 2013;100(1):1-10; Marso SP. *N Engl J Med.* 2016 Sep 16; 375:311-322.

CV Considerations and SGLT2 Inhibitors

Effects of SGLT2 inhibitors include improvements in:

- **Body weight**
- **Blood pressure**
- **Renoprotection**
- **CV risk**

FDA-Approval to Decrease CV Risk

Liraglutide: FDA-approved for reducing the risk of myocardial infarction, stroke, and CV death

Empagliflozin: FDA-approved for reducing the risk of cardiovascular death*

Canagliflozin: FDA-approved for reducing the risk of major CV events, stroke, and CV death*

*** In adults with T2DM who have established cardiovascular disease**

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Soledad

cases

After discussing the risks and benefits, you and Soledad agree to start empagliflozin to improve glycemia and decrease her CV risk

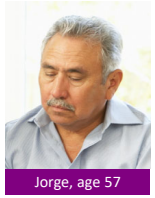
HbA1c 8.3%
eGFR 78 mL/min/1.73m²

Metformin 1000 mg BID
Glimepiride 8 mg QD
Empagliflozin 10mg QD
Lisinopril 20 mg QD
Atorvastatin 40 mg QD
Aspirin 81 mg QD
Metoprolol 50 mg BID
Levothyroxine 125 mcg QD

primed

Jorge

cases



Soledad expresses concern about her 57-year-old brother who also has diabetes. She wonders if his CV risk can be assessed

(She also tells her brother what a great doc you are and he becomes your patient, too)

HbA1c 7.5%
TGs 300 mg/dL
LDL 100 mg/dL
eGFR 74 mL/min/1.73m²

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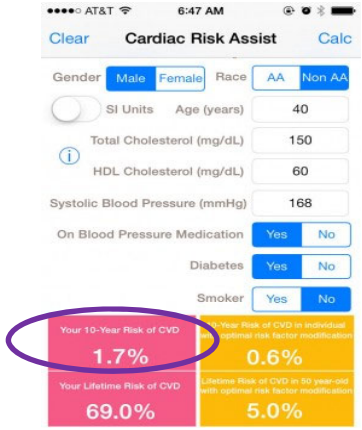
ASCVD Risk Calculator

ACC-AHA Pooled Cohort Equation

Estimates 10-year risk for a first ASCVD event



google: "ASCVD risk calculator"

http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx?example. Accessed Sept 7, 2018; ADA. *Diabetes Care*. 2018: 41(1):S86-104.

ADA Recommendations for CV Risk Assessment

Cardiovascular risk factors should be systematically assessed at least annually in all patients with diabetes:

- **Dyslipidemia**
- **Hypertension**
- **Smoking**
- **Family history of premature coronary disease**
- **Chronic kidney disease**
- **Presence of albuminuria**

Modifiable abnormal risk factors should be treated

ADA. *Diabetes Care*. 2018: 41(1):S86-104.

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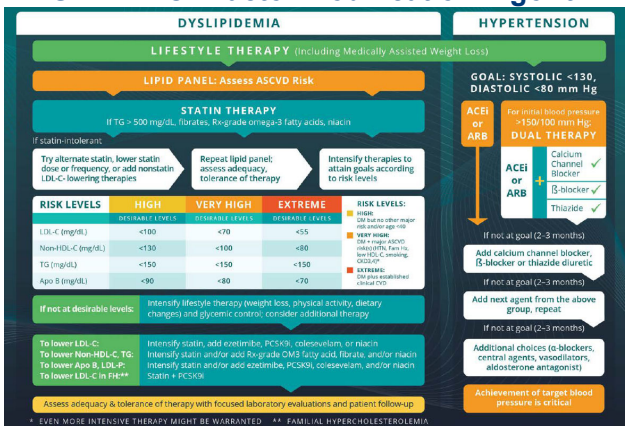
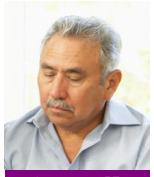
AACE/ACE ASCVD Risk Factor Modification Algorithm



Garber AJ, et al. Endocr Pract. 2018;24(1):91-120.

Lipids

Jorge | cases



Jorge, age 57

HbA1c 7.5%
TGs 300 mg/dL
LDL 100 mg/dL
HDL 55 mg/dL
eGFR 84 mL/min/1.73m²

Metformin 1000 mg BID
Simvastatin 20 mg QD

Jorge has T2DM and Hyperlipidemia but no known ASCVD

According to the 2018 ADA guidelines, what recommendations should you make Jorge for lipid control?

primed

ADA Recommendations for Dyslipidemia in Patients with Diabetes

- **All patients**
  - **Lifestyle interventions**
- **TG ≥ 150 mg/dL and/or HDL < 40 mg/dL (men)/ or < 50 mg/dL (women)**
  - **intensify lifestyle changes, optimize glycemic control**
- **High-intensity statin for all patients with ASCVD**
  - **If LDL ≥ 70 mg/dL on maximally-tolerated statin, consider adding ezetimibe or PCSK9 inhibitor**
  - **Statins contraindicated in pregnancy**
- **<40 years with additional risk factors for ASCVD**
  - **Consider moderate-intensity statin**
- **≥ 40 yrs w/o ASCVD**
  - **Moderate-intensity statin**

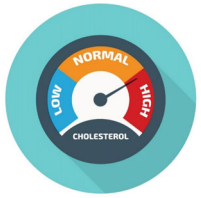
ADA. *Diabetes Care*. 2018: 41(1):S86-104.

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

AHA/ACC: Statin Benefit

Diabetes (primary prevention)

- Age 40-75 yrs and LDL-C 70-189 mg/dL: STATIN!
  - moderate-intensity statin if 10 year ASCVD risk < 7.5%
  - High intensity statin If 10 year ASCD risk ≥ 7.5%
- If <40 or >75 years, individualize statin use based on
  - ASCVD risk, Potential for adverse events, Drug-drug interactions
  - Patient preference



ACSVD (secondary prevention)

- STATIN!
  - Age ≤ 75 yrs and no safety concerns: high-intensity statin
  - Age ≥ 75 yrs or safety concerns: moderate-intensity statin

Stone NJ, et al. J Am Coll Cardiol. 2014;63(25 Pt B):2889-2934.

Intensity of Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C on average, by approximately ≥50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%	Daily dose lowers LDL-C on average, by <30%
Atorvastatin (40†)-80 mg **Rosuvasatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20-40 mg‡** **Pravstatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* **Pravastatin 10-20 mg** **Lovastatin 20 mg** *Fluvastatin 20-40 mg* *Pitavastatin 1 mg*

Stone NJ et al. *Circulation*. 2014;129:S1-45.

Ezetimibe

IMPROVE-IT Trial

Adding ezetimibe to a statin improved outcomes patients with DM

24% relative reduction MI

39% relative reduction in ischemic stroke

Giugliano R, et al. Circulation. 2017;137:1571-1582.

PCSK9 Inhibitors –CV Outcomes Trials

Evolocumab - FOURIER trial

- 15% RRR in primary outcome
- 20% RRR in stroke/CV death

Alirocumab – ODYSSEY trial

- 15% RRR in primary outcome
- 15% RRR in all cause mortality

PCSK9 = Proprotein convertase subtilisin/kexin type 9 RRR = relative risk reduction

Sabatine MS et al. N Engl J Med 2017; 376:1713-1722; ACC Scientific Sessions 2018.

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

Blood Pressure

Maria | cases

Maria, age 78

HbA1c 7.2%
LDL 70 mg/dL
eGFR 48 mL/min/1.73m²

Metformin 850 mg BID
Aspirin 81 mg QD
Donepezil 10 mg QD

Soledad has now recruited her 78-year-old mother, Maria, to you practice

Maria also had T2DM as well as mild dementia.

She has no history of HTN but her repeat BP reading in your office are all in the range of 162/100 mmHg.

primed

BP Goals for Patients With Diabetes

ADA

- Measure BP at every visit
- Goal <140/<90 mm Hg
- Lower goal (130/80 mm Hg) recommended for certain patients, such as those at high risk of CVD

ACC/AHA

- Goal <130/80 mm Hg in most individuals (including those with diabetes)
- Goal not endorsed by ACP or AFP*

AACE/ACE

- Goal <130/<80 mm Hg for most patients
- Individualize based on risk

ADA. Diabetes Care. 2018; 41(S1):S86-S104; Whelton PK, et al. Hypertension. 2017;71(6):1269-1324; Garber AJ, et al. Endocr Pract. 2018;24(1):91-120

ADA Recommendations for Treating Confirmed HTN in People with Diabetes

≥140/90 mmHg: titration of pharmacologic therapy to reduce BP

≥ 160/100 mmHg: initiate dual therapy with antihypertensives demonstrated to reduce CV events

Renal protection: ACE or ARB 1st line

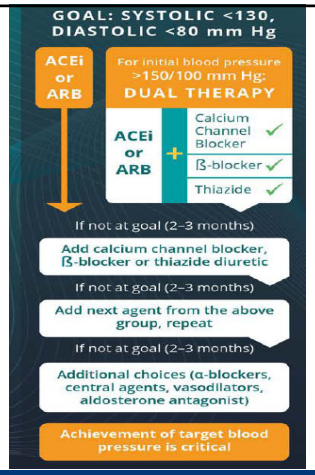
If not at goal with 3 med classes (including a diuretic) consider mineralocorticoid receptor agonist therapy

ADA. Diabetes Care. 2018; 41(S1):S86-S104.

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

AACE/ACE Algorithm for Treating HTN in Patients with Diabetes and ASCVD

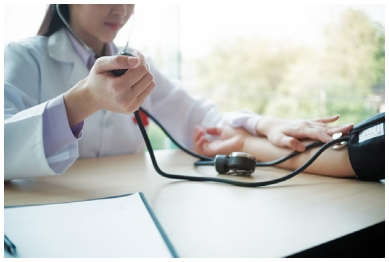
Always incorporate lifestyle therapy



Garber AJ, et al. Endocr Pract. 2018;24(1):91-120.

Special Considerations with Hypertension

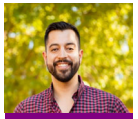
Selection of an antihypertensive regimen must take into account special circumstances, including CVD, heart failure, albuminuria, race/ethnicity



Garber AJ, et al. Endocr Pract. 2018;24(1):91-120.

Other Considerations in CV Risk

Joe | cases



Joe, age 41

Soledad's youngest brother, Joe, is 41 years old. He was just diagnosed with T2DM. He has no other risk factors for ASCVD. After Joe joins your practice, he asks about cardiovascular prevention.

According to the ADA, what recommendation should you give Joe about antiplatelet therapy ?

HbA1c 7.2%
LDL 84 mg/dL
HDL 47 mg/dL
TGs 146 mg/dL
eGFR 90 mL/min/1.73m²

Diet and exercise
Starting atorvastatin 20mg QD

primed

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

Aspirin for Primary Prevention in T2DM

- ASCEND study - August 2018
- 7.4 years
- For people with diabetes and no evident cardiovascular disease at trial entry, aspirin prevented serious vascular events BUT it caused major bleeding events (mostly GI and other extracranial bleeds)
- The absolute benefits were largely counterbalanced by the bleeding hazard

The ASCEND Study Collaborative Group. NEJM. August 26, 2018.DOI: 10.1056/NEJMoa1804988.

ADA: Antithrombotic Agents in Patients with Diabetes

- **Primary prevention: Aspirin in patients with**
  - Age ≥ 50 years
  - At least one additional major risk factor for ASCVD
  - Not at increased risk of bleeding
- **Secondary prevention Aspirin with all patients with ASCVD**
  - **Clopidogrel** if aspirin allergy
  - Dual antiplatelet therapy for 1 year after an acute coronary syndrome
  - **Rivaroxaban** combined with aspirin was recently FDA approved to reduce the risk of major CV events in patients with CAD or PAD
    - Reduced risk of major CV events by 24% (combined with aspirin) in patients with CAD and PAD compared with aspirin alone – COMPASS trial

Aspirin Dose 75-162 mg/day

ADA. Diabetes Care. 2018; 41(S1):S86-S104; Eikelboom JW, et al. NEJM. 2017;377:1319-1330; https://vascularnews.com/rivaroxaban-fda-approval-cad-pad/

Heart Failure and Diabetes

Up to 50% of patients with T2DM may develop HF[1]

T2DM is often unrecognized in HF patents and vice-versa[2]

The coexistence of T2DM and HF is associated with a higher risk of[2]

- HF hospitalization
- All-cause mortality
- CV mortality

Seferovic PM, et al. *Eur J Heart Fail.* 2018;20(5):853-872.

Treating Heart Failure in Patients with Diabetes

- **TZDs** have a strong relationship with increased risk of HF[1]
- **SUs** and **Insulin** have equivocal safety in HF[2]
- The **DPP4 Inhibitor** saxagliptin was associated with an increased risk of heart failure hospitalization[3]
- **Saxagliptin and alogliptin**: FDA warning about heart failure risk
- **SGLT2 inhibitors** (empagliflozin and canagliflozin) associated with reduction in HF hospitalizations in clinical trials[4,5]

1. ADA. Diabetes Care. 2018; 41(S1):S86-S104; 2. Seferovic PM, et al. *Eur J Heart Fail.* 2018;20(5):853-872 3. SAVOR-TIMI 53: Scirica, BM, et al. *New Eng J Med.* 2013;369(14):1317-1326; 4. Zinman, B et al. N Engl J Med. 2015;373:2117-2128, 5. Neal B, et al. N Engl J Med.2017;377:644-657

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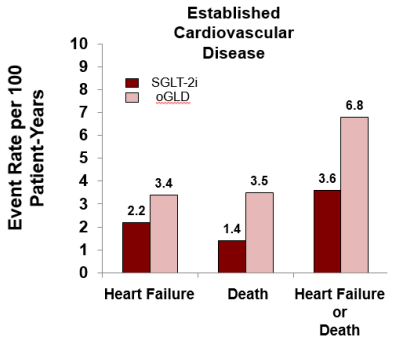
CVDReal: *Absolute Rates of HF and Death in Patients Treated with SGLT-2 Inhibitors*



Initiation of an SGLT2 inhibitor was associated with a significantly lower risk of hospitalization for heart failure and all-cause death than any other glucose-lowering drug

oGLD – other glucose lowering drugs
p<0.001 for all comparisons

Cavender M at al.. Presented at ADA Scientific Sessions; June 9 – May 13, 2017; San Diego, CA; Kosiborod M et al. Circulation. 2017;136(3):249-259.

Diabetes and CKD

- CKD attributed to diabetes occurs in 20–40% of patients with diabetes
- May be present at diagnosis of T2DM
- Presence of CKD markedly increases cardiovascular risk in patients with diabetes
- Intensive glycemic control delays the onset and progression of albuminuria and reduced eGFR in patients with T2DM

ADA. Diabetes Care. 2018; 41(S1):S105-118.

Intensive Vs Normal Glycemic Control and Albuminuria Outcomes

Study	Intensified Treatment versus Normal Treatment HbA1c goals	Albuminuria Outcomes
ADVANCE	6.5% vs 7.3%	9%↓ in new ACR 30% ↓ in ACR progression
ACCORD	6.3% vs 7.6%	21% ↓ in new ACR 32% ↓ in ACR progression
VADT	6.9% vs 8.4%	32% ↓ in in new ACR 37% ↓ in ACR progression

ACR = albumin to creatinine ratio, **new ACR** = 3-30 mg/mmol, **ACR progression** = >30mg/mmol

ADVANCE: Patel A, et al. N Engl J Med 2008;358(24):2560–2572; ACCORD: Ismail-Beigi F, et al. Lancet 2010;376(9739):419–430; VADT: Duckworth W, et al. N Engl J Med 2009;360(2):129–139.

Association between Cardiac and Renal dysfunction

Microalbuminuria is a strong risk factor of cardiovascular mortality and CVD events

- Independent of traditional risk factors

Microalbuminuria can be used for risk stratification of cardiovascular disease

- Once present, aggressive cardiovascular risk factor reduction should be implemented

Cardiorenal syndrome can be:

- Bidirectional
- Acute or chronic

Weir MR. Clin J Am Soc Nephrol. 2007;2(3):581-590; Stehouwer CD, J Am Soc Nephrol. 2006;17(8):2106-2111.

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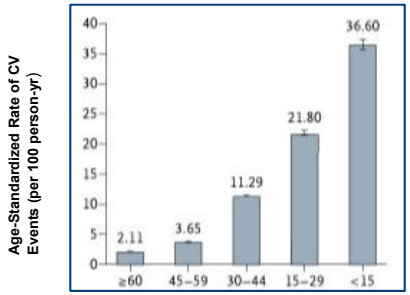
Even Early-Stage CKD is Associated with Risk of CV Events

The risk of CV disease began to rise once the GFR drops below 60 mL/min/1.73 M^2 of body surface area



Estimated GFR (mL/min/1.73 M²)

No. of Events	73,108	34,690	18,580	8809	3824

GO AS, et al. N Engl J Med. 2004;351:1296-1305.

Preventing Diabetic Nephropathy in Normotensive Patients

National Kidney Foundation:

- **Treatments that produce a lasting decrease in urinary albumin excretion may slow the progression of DKD even in the absence of hypertension**
- **Suggest using an ACE I or an ARB in normotensive patients with diabetes and albuminuria levels >30 mg/d who are at high risk of DKD or its progression**

DKD = diabetic kidney disease

National Kidney Foundation KDOQI Clinical Practice Guideline got Diabetes and CKD.: 2012 Update. Am J Kidney Dis. 2012;60(5):850-886.

Renal Effects of Antidiabetes Medications

Maria | cases

Maria, age 78

HbA1c 7.2%
LDL 70 mg/dL
eGFR 48 mL/min/1.73m²

Metformin 850 mg BID
Lisinopril 20mg QD
Metoprolol XL 50mg QD
Aspirin 81 mg QD
Donepezil 10 mg QD

Maria has T2DM and stage 3 kidney disease. Her blood pressure is 128/80 mmHg on her new medications

Soledad asks if there is another medication(besides lisinopril) that can help her Mother's kidneys

primed

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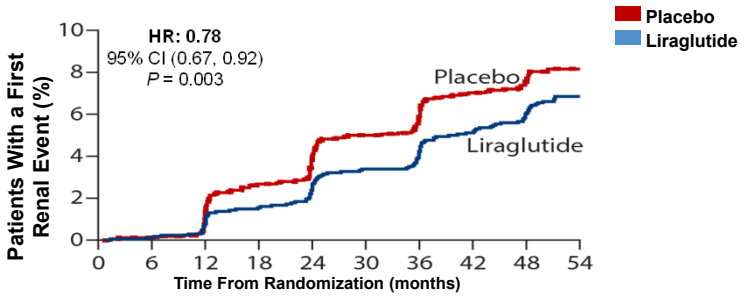
Liraglutide: *Renal Outcomes*

Composite Renal Outcome: Microalbuminuria, doubling of SCr, ESRD, renal death



ESRD = end-stage renal disease; SCr = serum creatinine.

Mann et al. *N Engl J Med.* 2017;377:839-48.

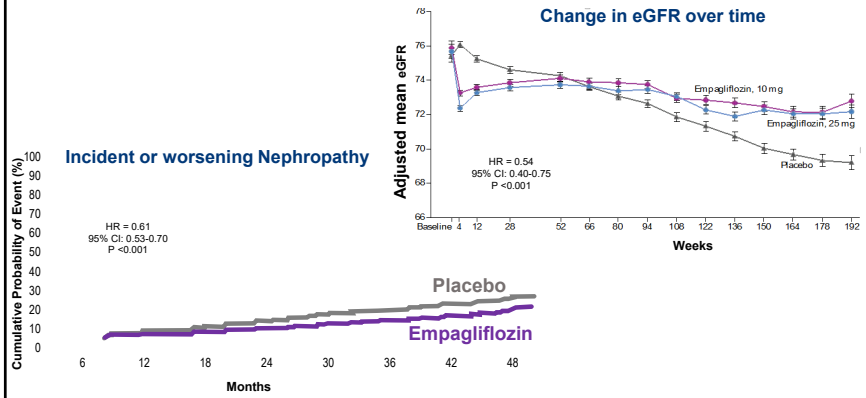
Semaglutide: *Renal Outcomes*

Post-hoc analysis of SUSTAIN 6 trial

- New or worsening nephropathy was lower with both semaglutide doses (1mg and 0.5 mg) compared to placebo
- Persistent macroalbuminuria was lower with both semaglutide doses compared to placebo
- UACR decreased with increasing renal impairment for semaglutide 1 mg

VILSBØLL T, et al. *Diabetes.* 2018;67(S1). 10.2337/db18-1084-P (post-hoc analysis of SUSTAIN 6).

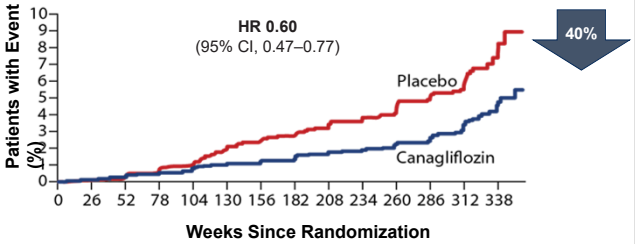
Empagliflozin: *Renal Outcomes*



Wanner C et al. *N Engl J Med.* 2016;375:323–334.

Canagliflozin: *Renal Outcomes*

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



CREDENCE: Terminated early based on the achievement of pre-specified efficacy criteria (primary composite endpoint of end-stage kidney disease (time to dialysis or kidney transplantation), doubling of serum creatinine, and renal or cardiovascular (CV) death)

Neal B, et al. *N Engl J Med.* 2017;377(7):644-657; https://www.mdmag.com/medical-news/janssen-ends-canagliflozin-credence-trial-early-after-hitting-t2d-ckd-endpoints. Accessed Sept 10, 2018.

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Reminder: SGLT2 Inhibitors: Dosing in Renal Disease

Medication	eGFR (mL/min) > 60	eGFR (mL/min) 45-60	eGFR (mL/min) < 45
Canagliflozin[1]	100 mg QD. Titrate to 300 mg QD	100 mg QD	**Do not initiate** ***Discontinue*** if eGFR falls into this range
Dapagliflozin[2]	5 mg QD. Titrate to 10 mg QD	**Do not initiate** ***Discontinue*** if eGFR falls into this range	
Empagliflozin[3]	10 mg QD. titrate to 25 mg QD	10 mg QD. Titrate to 25 mg QD	
Ertugliflozin[4]	5 mg QD. Titrate to 15 mg QD	► Do not use if eGFR < 30 mL/minute/1.73 m^2 ► Do not initiate if eGFR is 30 to 59 mL/minute/1.73 m^2 ► Do not continue if eGFR is persistently between 30 and 59 mL/min/1.73 m^2	

(1) Invokana™ (canagliflozin) PI. http://www.pdr.net/full-prescribing-information/invokana?druglabelid=3094. (2) Farxiga™ (dapagliflozin) PI. http://www.pdr.net/full-prescribing-information/farxiga?druglabelid=3427. (3) Jardiance (empagliflozin) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204629s008lbl.pdf (4) Steglatro™ (ertugliflozin) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209803s000lbl.pdf.

Summary

- Patients with T2DM are at **HIGH risk** for CV events
- The **2018 ADA treatment guidelines** recommend adding an agent proven to reduce CV events and CV mortality for dual therapy in patients with ASCVD
- **GLP-1 RAs**
  - Liraglutide and semaglutide showed significant decrease in CV risk in clinical trials
  - Liraglutide is FDA-approved to reduce the risk of CV death, MI and stroke in adults with T2DM and established CVD
- **SGLT2 inhibitors**
  - Empagliflozin and canagliflozin showed CV and renal benefit and decreased hospitalizations for HF
  - Empagliflozin is FDA-approved to reduce the risk of cardiovascular death in adults with T2DM and cardiovascular disease
  - Canagliflozin is FDA-approved to reduce the risk of major CV events, stroke, and CV death in adults with T2DM and cardiovascular disease

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