Stanford MEDICINE | Division of Primary Care and Population Health
Department of Medicine

Updates in Cardiovascular Risk Reduction

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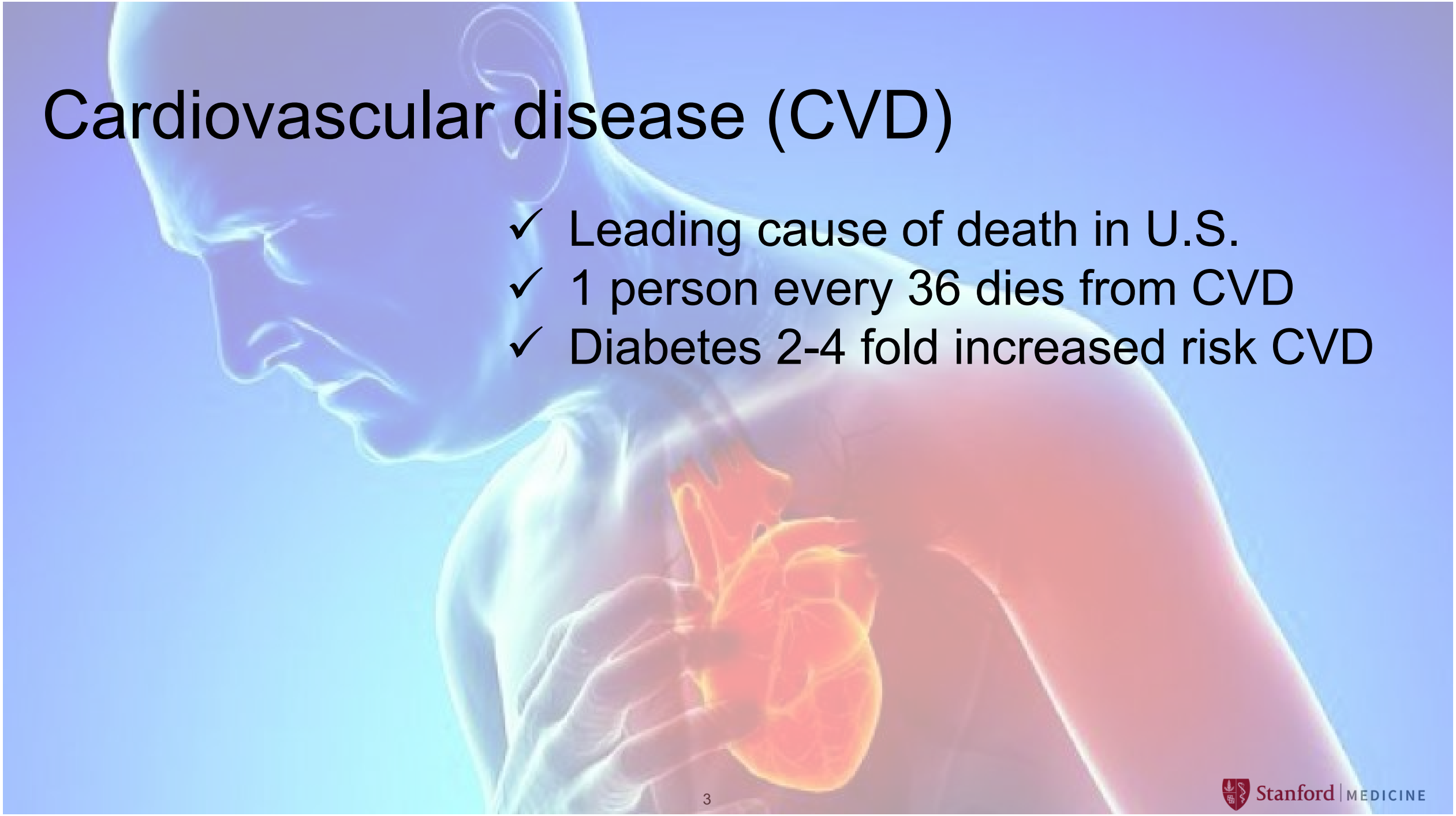
Department of Medicine

No financial disclosures

Cardiovascular disease (CVD)



- ✓ Leading cause of death in U.S.
- ✓ 1 person every 36 dies from CVD
- ✓ Diabetes 2-4 fold increased risk CVD

Mr. JB is 52 year old South Asian male...

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MI 3 years ago

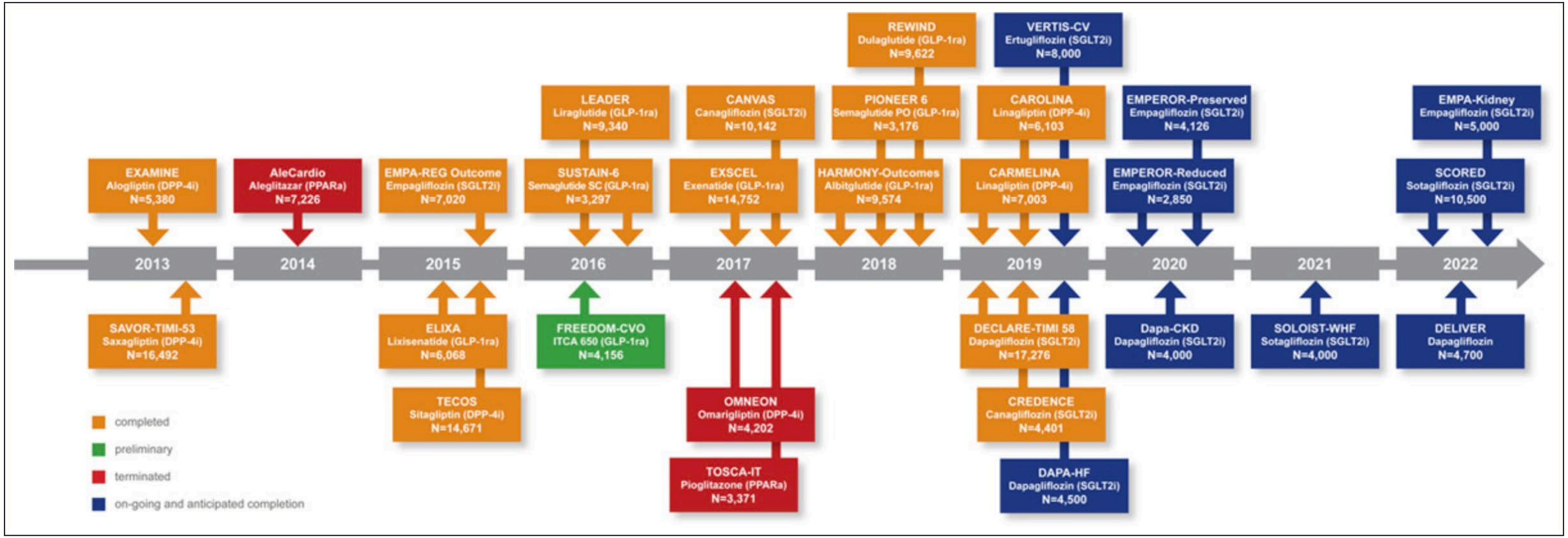
Triglycerides	300 mg/dL	(statin + ezetimibe)
LDL-C	130 mg/dL	(statin + ezetimibe)
Diabetes HbA1c	7.5%	(metformin)

“How can I prevent another heart attack?”

(because I don't feel I can change my lifestyle further)

Lots of CVD studies!

Cardiovascular Outcome Trials (CVOT) in type 2 diabetes



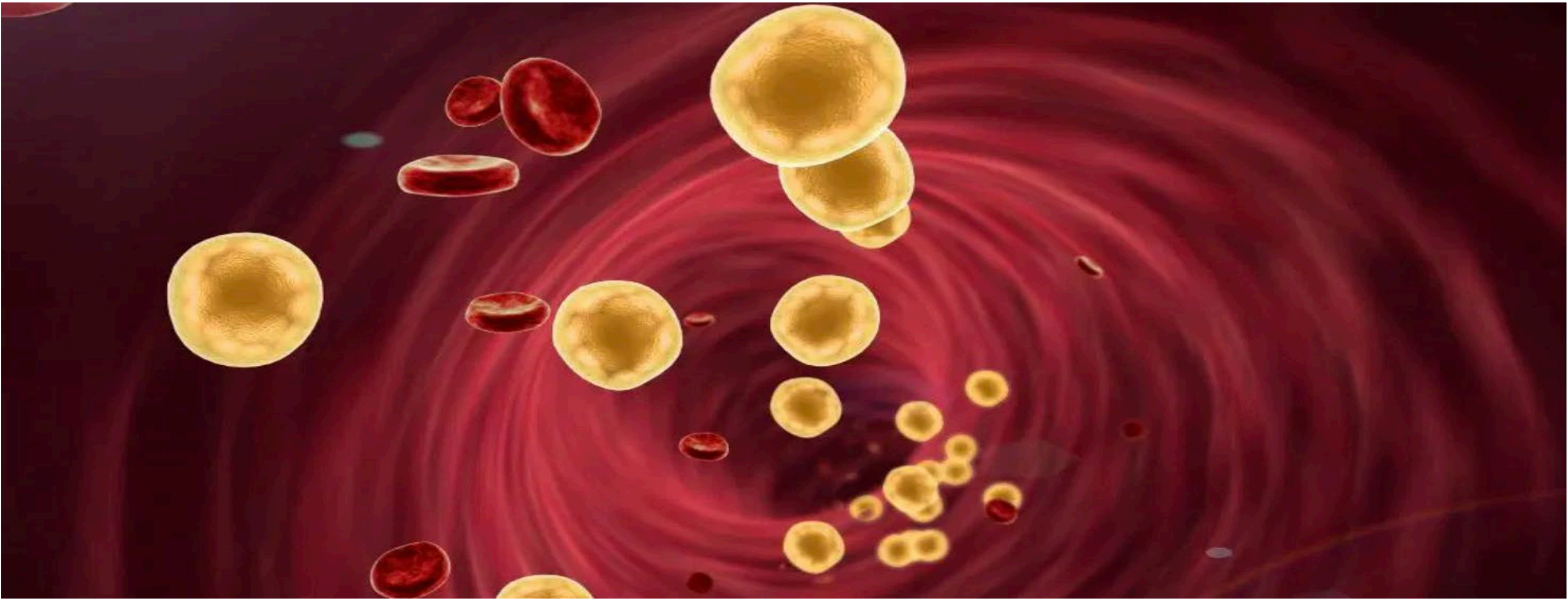
Sharma et al. Impact of Regulatory Guidance on Evaluating Cardiovascular Risk of New Glucose-Lowering Therapies to Treat Type 2 Diabetes. Circulation March 2020

Key updates for Mr. JB

- LDL-C reduction
- Triglyceride reduction
- Type 2 diabetes CVD risk reduction

- Impact on CVD and diabetes guidelines

Lipid management – high LDL cholesterol



Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

2015

2015

Indications

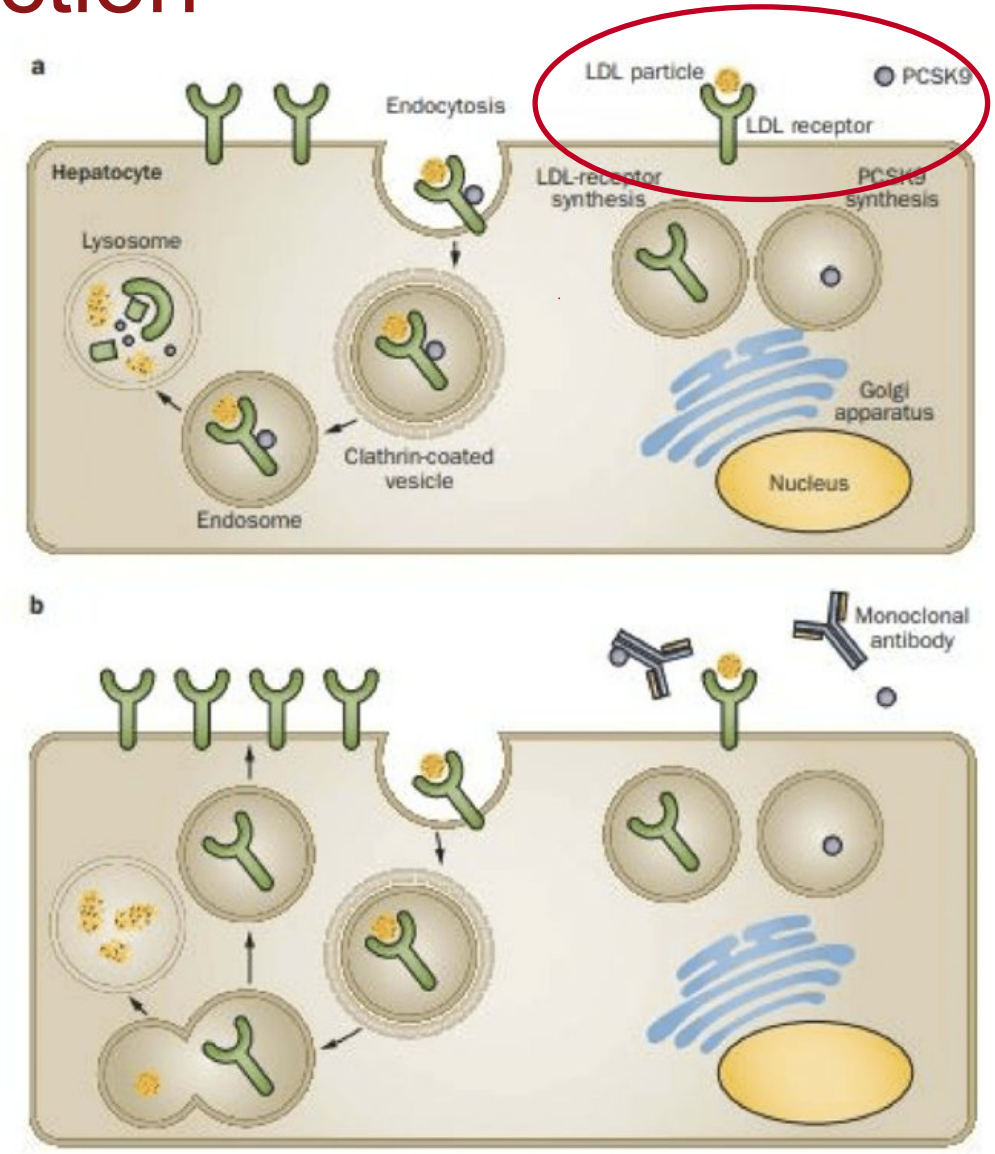
1. HoFH and HeFH
2. Established ASCVD
3. Very high risk patients

Lowers LDL 60-70%

Cost $466/mo

Mechanism of action

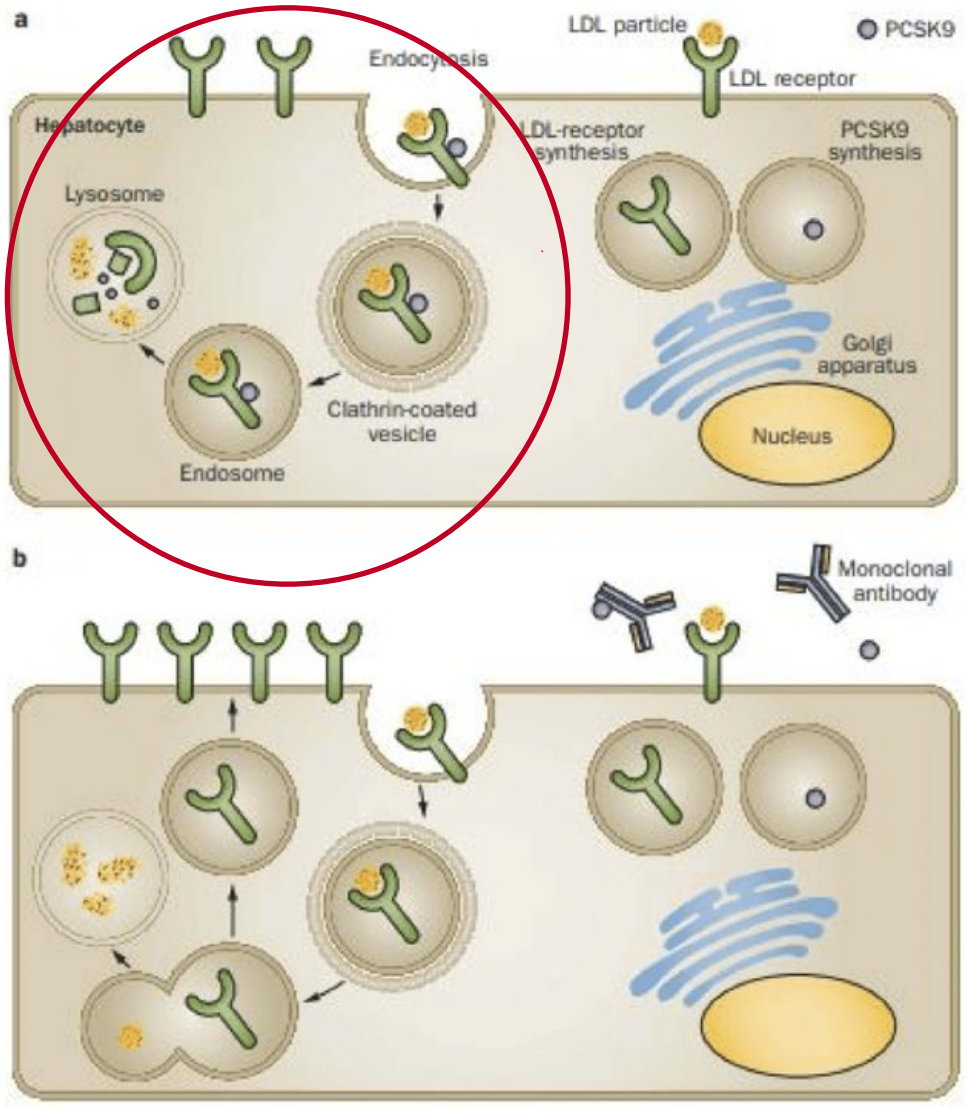
Monoclonal antibody to PCSK9 enzyme



Mayo Clinic Nov 2015

Mechanism of action

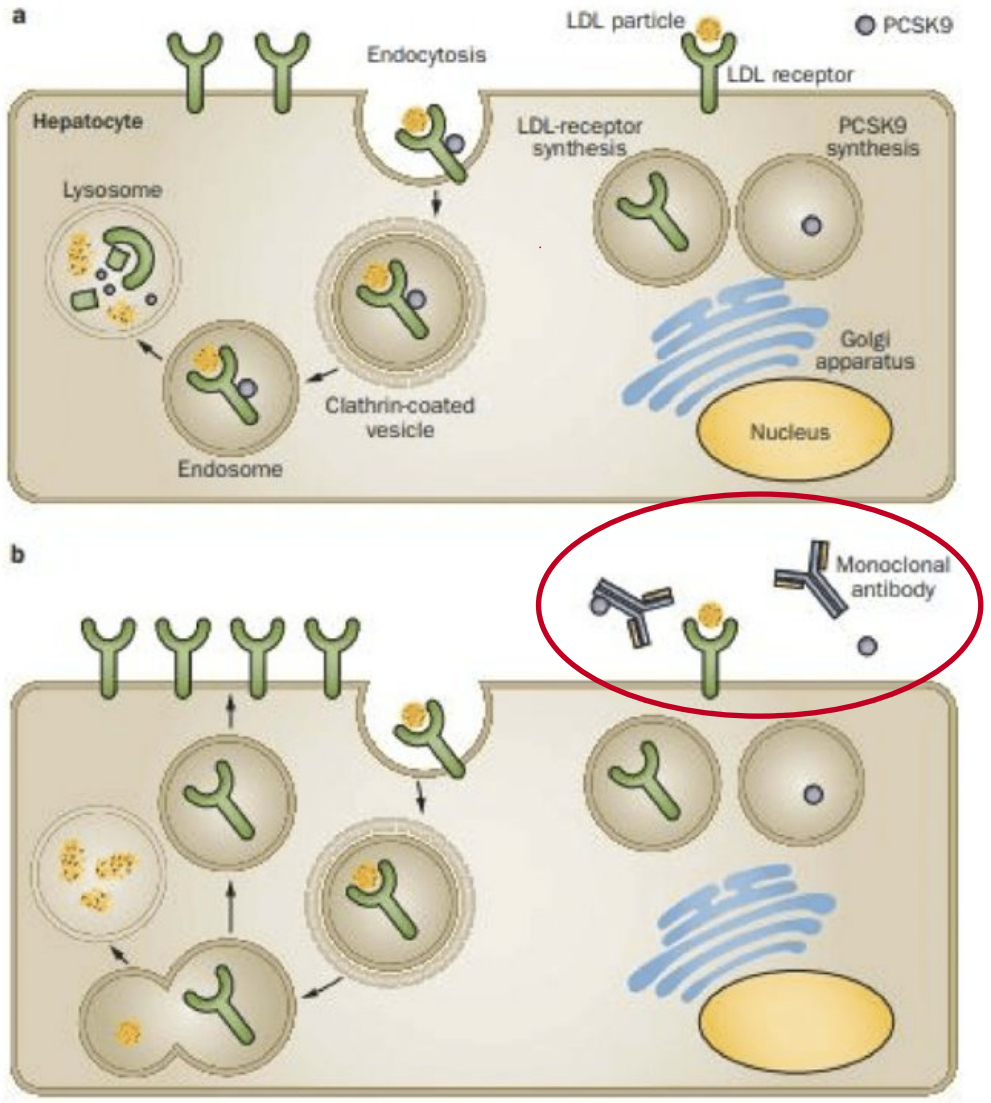
Monoclonal antibody to PCSK9 enzyme



Mayo Clinic Nov 2015

Mechanism of action

Monoclonal antibody to PCSK9 enzyme



Mayo Clinic Nov 2015

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Mechanism of action

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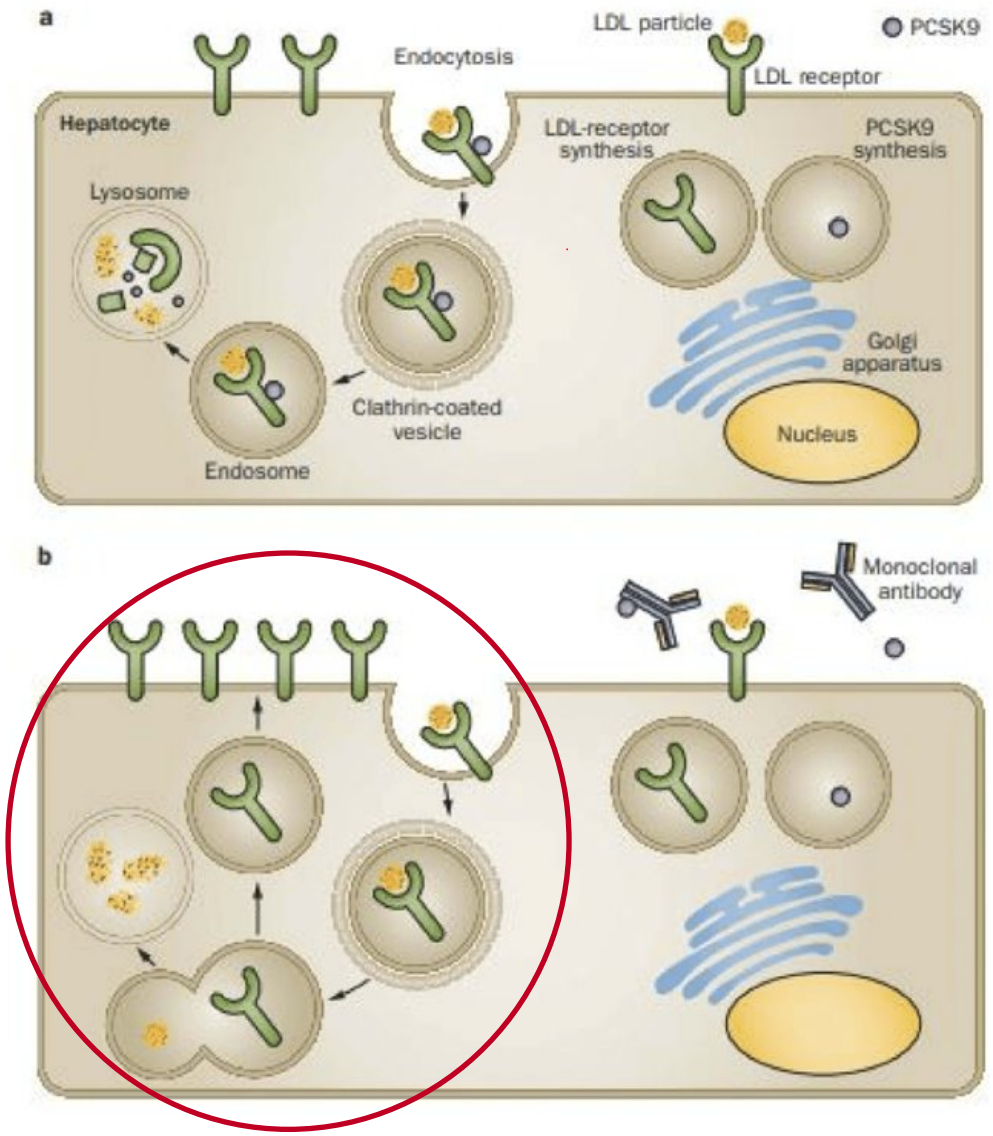


Mayo Clinic Nov 2015

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

FOURIER

Patients with ASCVD

LDL ≥70 mg/dL statin ± ezetimibe

Median f/u 2 years

⬇ ASCVD 15% RRR

ODYSSEY

Patients with ACS

LDL ≥70 mg/dL statin ± ezetimibe

Median f/u 2.8 years

⬇ ASCVD 15% RRR

Side effects

- Well-tolerated
- No significant muscle aches
- No major adverse events in patients with very low LDL <30 mg/dL
- Rash

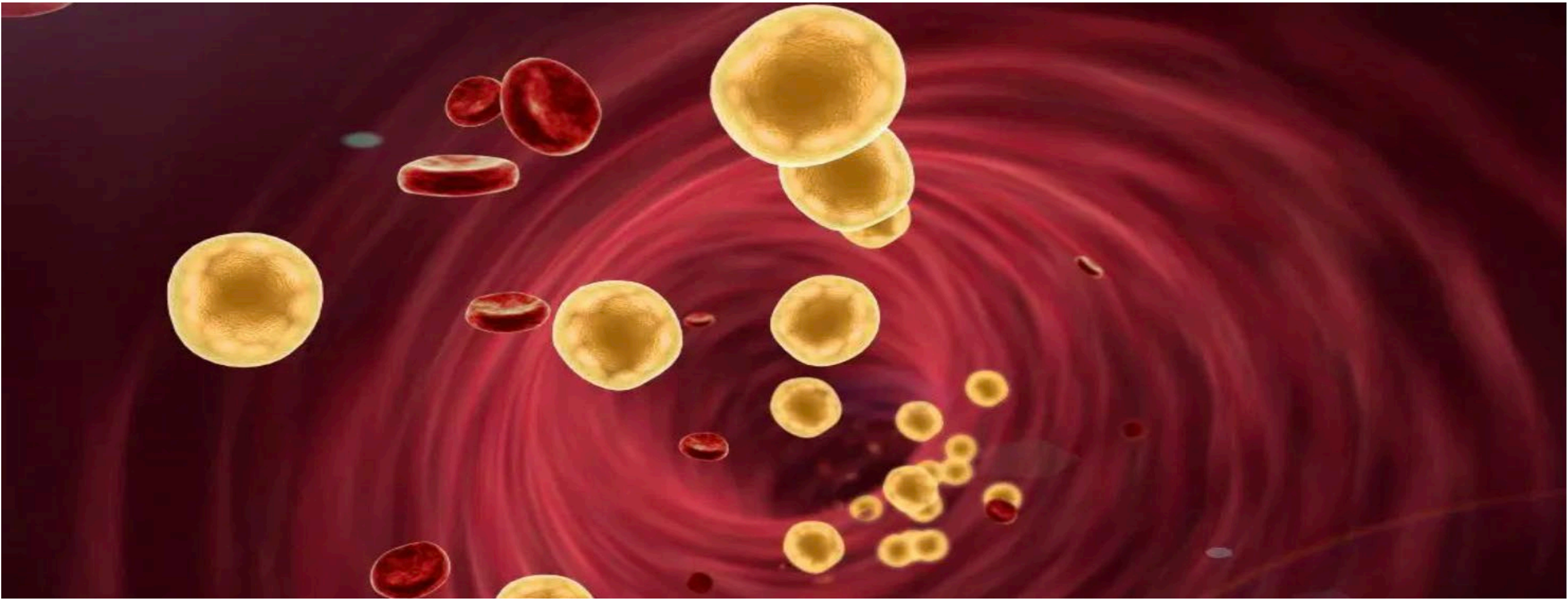
Mr. JB is 52 year old South Asian male....

MI 3 years ago

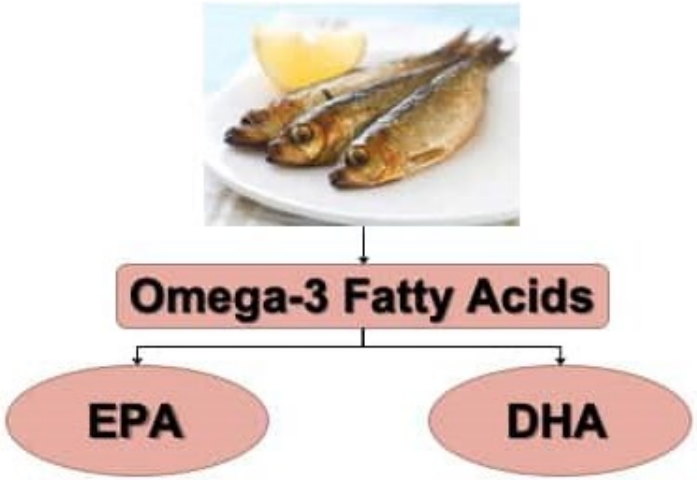
Triglycerides	300 mg/dL	(statin + ezetimibe)
LDL-C	130 mg/dL	(statin + ezetimibe)
Diabetes HbA1c	7.5%	(metformin)

Start PCSK9 inhibitor because LDL ≥70 mg/dL

Lipid management – high triglycerides



prescription fish oil: Icosapent ethyl



Ethyl eicosapentaenoic acid (E-EPA)

Indications

1. TG ≥500 mg/dL (2012)
2. TG 150-499 mg/dL despite statin to reduce CV events (2019)

Reduces TG up to 33%

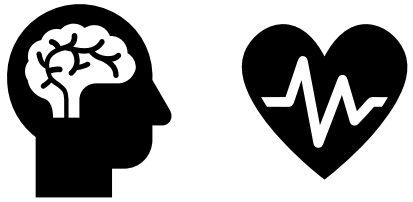
Cost $241/mo

31% RRR CV events

>8000 people
statin therapy
11 countries
473 sites

45+ yo ASCVD
50+ yo DM with 1+ RF
TG ≥150-<500
LDL-C >40-≤100
on statin ≥4 weeks

reduce-it™

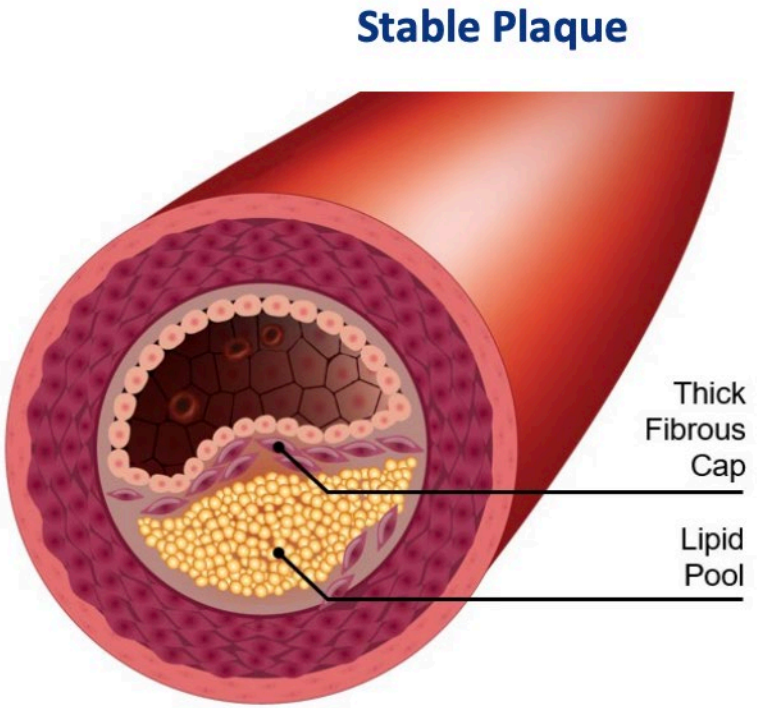


CV endpoint
-MI/stroke, CV death, revascularization/unstable angina

Icosapent ethyl 2 g BID
Or
Placebo

Bhatt et al. N Engl J Med. 2019 Jan 3;380(1):11-22

Mechanism of cardiovascular benefit

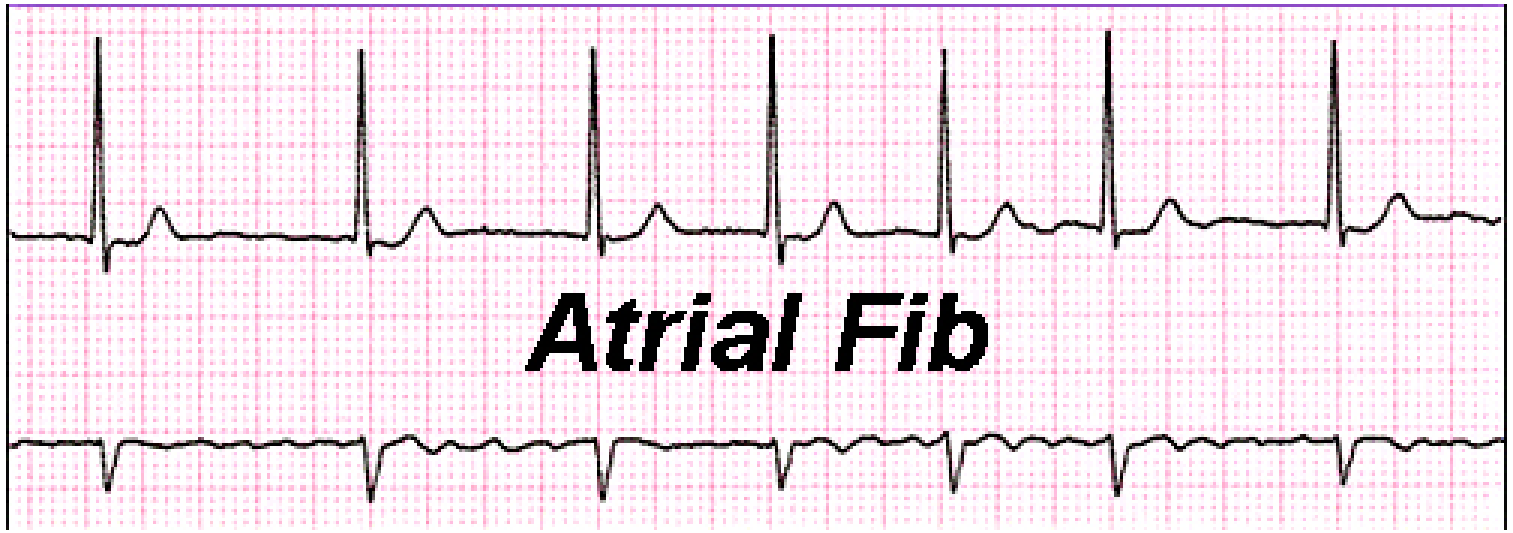


Multiple atherogenic processes

- TG-rich lipoproteins
- Plaque
- Endothelium
- Anti-inflammatory
- apoB

Side effects

- Bleeding
- Atrial fib/flutter

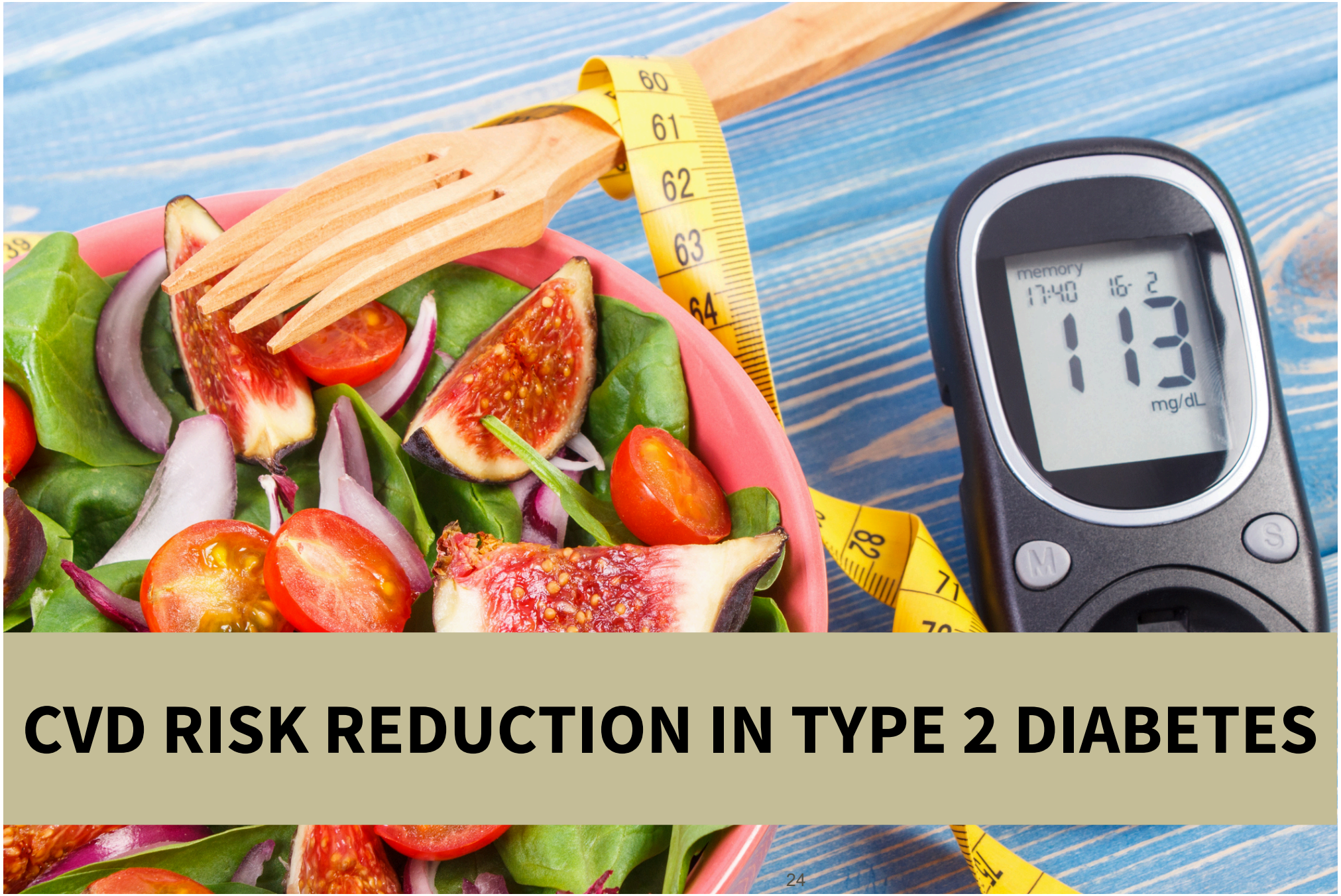


Mr. JB is 52 year old South Asian male....

MI 3 years ago

Triglycerides	300 mg/dL	(statin + ezetimibe)
LDL-C	130 mg/dL	(statin + ezetimibe)
Diabetes HbA1c	7.5%	(metformin)

Start Icosapent Ethyl at 2 grams BID if LDL controlled and TG remain high



CVD RISK REDUCTION IN TYPE 2 DIABETES

Sodium glucose cotransporter2 (SGLT2) inhibitors

Steglatro® (ertugliflozin)

Invokana™ canagliflozin tablets

Indications

1. Type 2 diabetes
   a. Reduce CVD risk when established CVD
   b. Reduce HF
   c. Reduce DKD

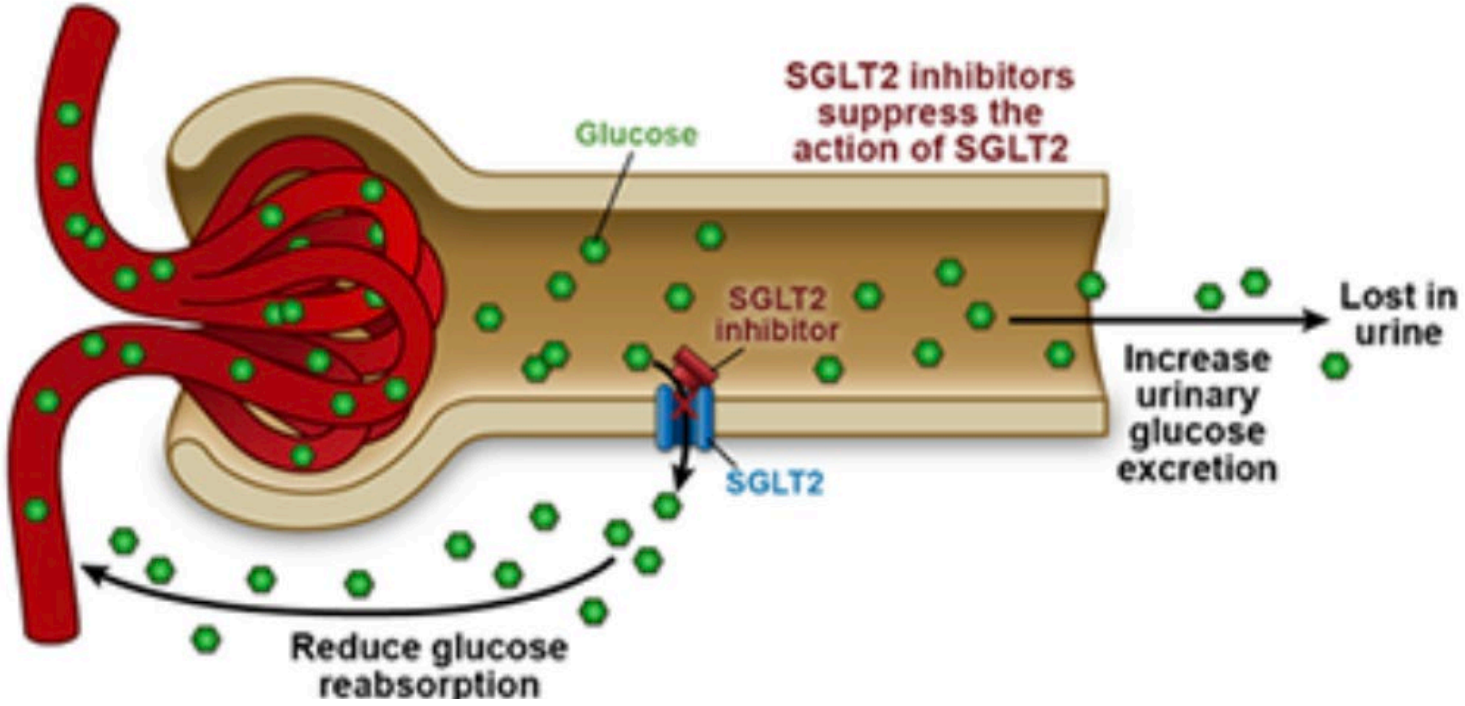
2. HFrEF reduce HF

Reduces A1c by 0.4-1.1%

Cost: $500/month

Jabbour SA. Postgrad Med. 2014;126:111-117.

Sodium glucose cotransporter2 (SGLT2) inhibitors



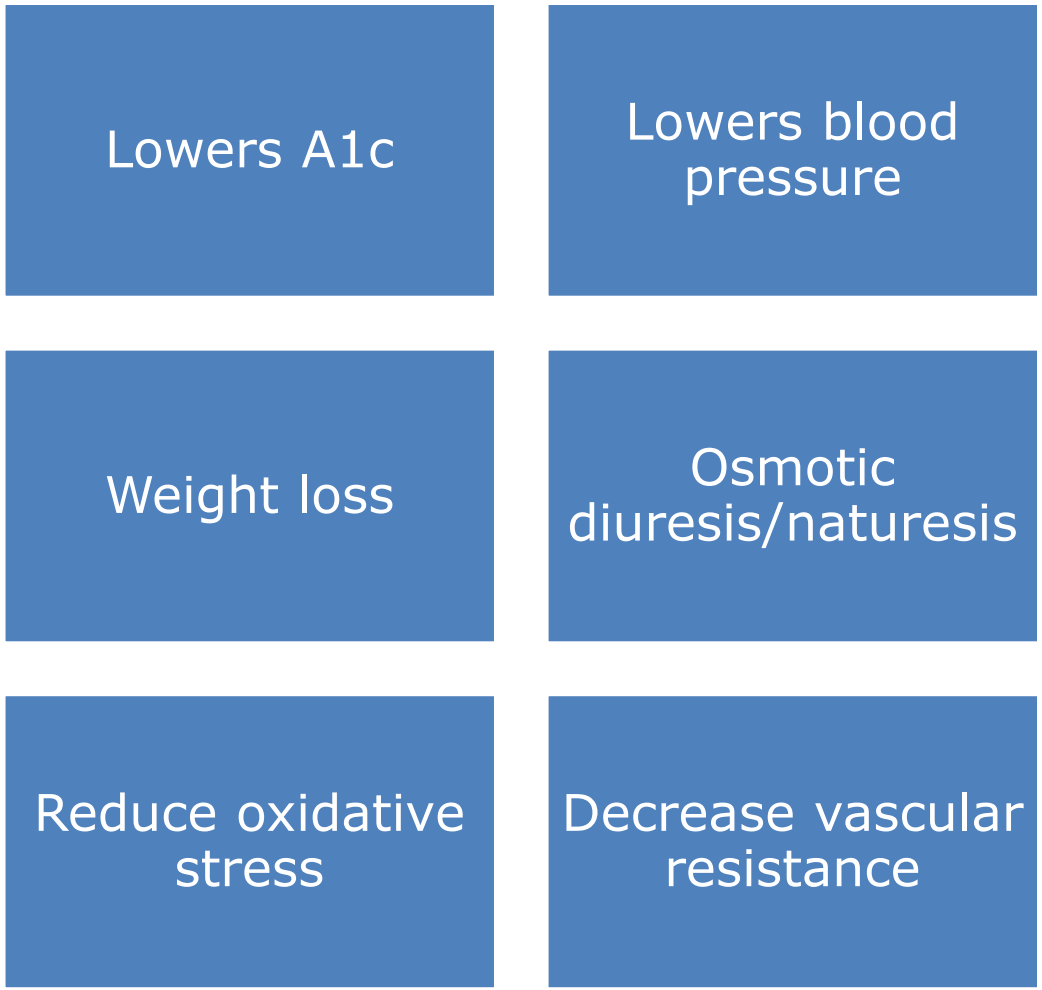
Jabbour SA. Postgrad Med. 2014;126:111-117.

CVOTs for SGLT2 inhibitors

	CVOT	MACE	HF benefit	Renal benefit
Empagliflozin	EMPA-REG	14% RR CVD	✓	✓
Canagliflozin	CANVAS	14% RR CVD	✓	✓
Dapagliflozin	DECLARE-TIMI		✓	✓
Ertugliflozin	VERTIS-CV		✓	✓

Lo et al., Cardiorenal Medicine. Jan 2020.

Mechanism of cardiovascular benefit



Garg V et al. Progress in Cardiovascular Diseases. Aug 2019

Side effects

- Urogenital infections
- Diabetic ketoacidosis
- Acute kidney injury
- Canagliflozin – amputation

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MI 3 years ago

Triglycerides	300 mg/dL	(statin + ezetimibe)
LDL-C	130 mg/dL	(statin + ezetimibe)
Diabetes HbA1c	7.5%	(metformin)

Start SGLT2i to improve A1c and reduce CV event risk

Glucagon-like peptide 1 receptor agonist (GLP1RA)

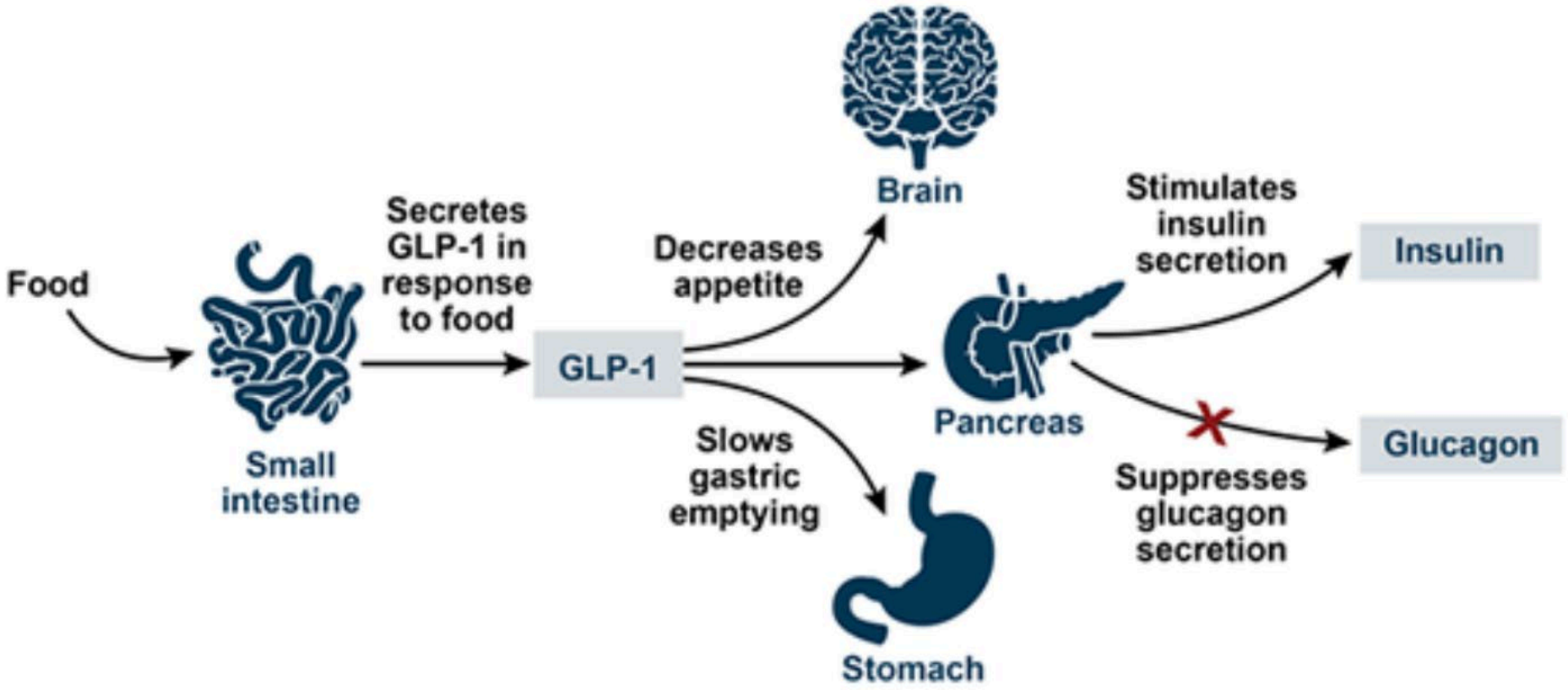
Semaglutide
Rybelsus and Ozempic

Indications
1. Type 2 diabetes
2. Reduce CVD risk-established CVD
3. Saxenda – obesity tx

Reduces A1c by 0.55-1.2%

Cost: $800-900/month

Glucagon-like peptide 1 receptor agonist (GLP1RA)



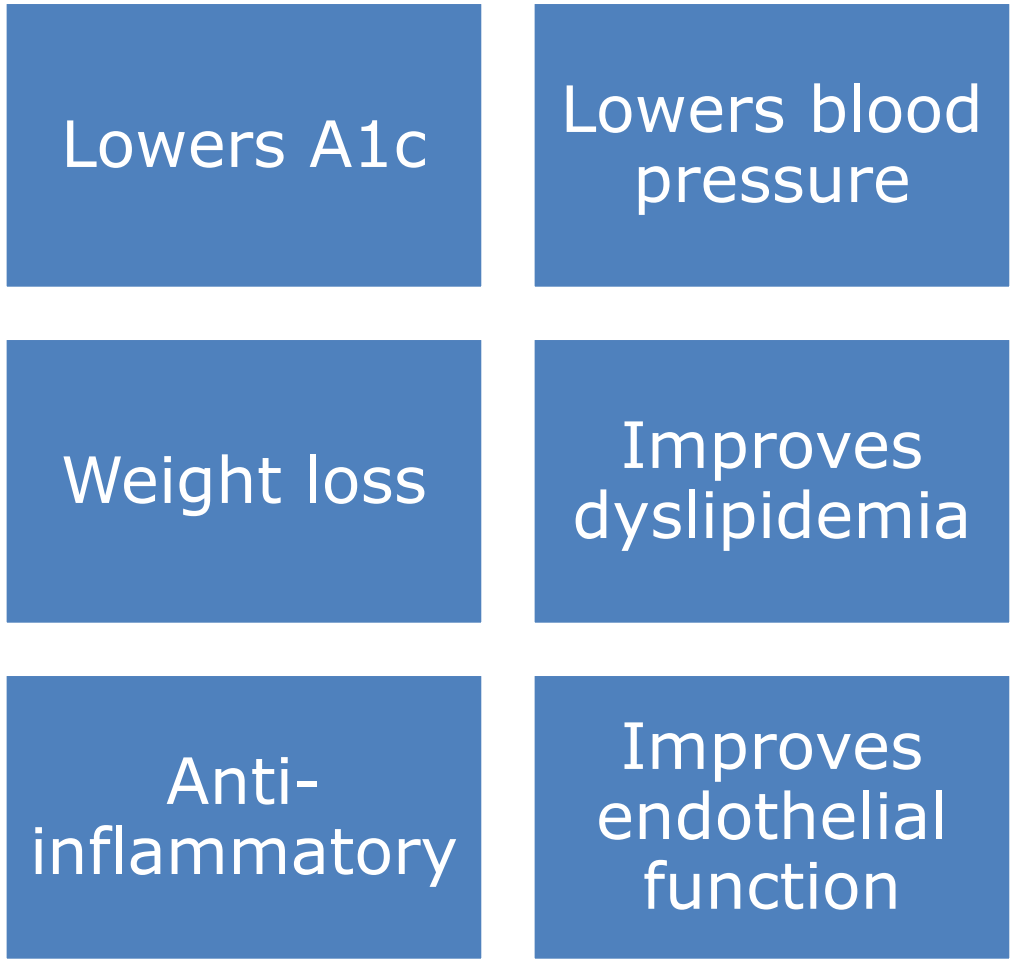
Meier JJ. *Nat Rev Endocrinol*. 2012;8:728-742.

CVOTs for GLP1RA

	CVOT	MACE
Liraglutide	LEADER	13% RR CVD
Semaglutide (inj only)	SUSTAIN-6	24% RR CVD
Dulaglutide	REWIND	12% RR CVD
Exenetide	EXSCEL	safe
lixisenatide	ELIXA	safe

Lo et al., Cardiorenal Medicine. Jan 2020.

Mechanism of cardiovascular benefit



Sposito et al. Cardiovasc Diabetol Dec 2018

Side effects

- GI symptoms
- Pancreatitis
- Diabetic retinopathy – injectable semaglutide

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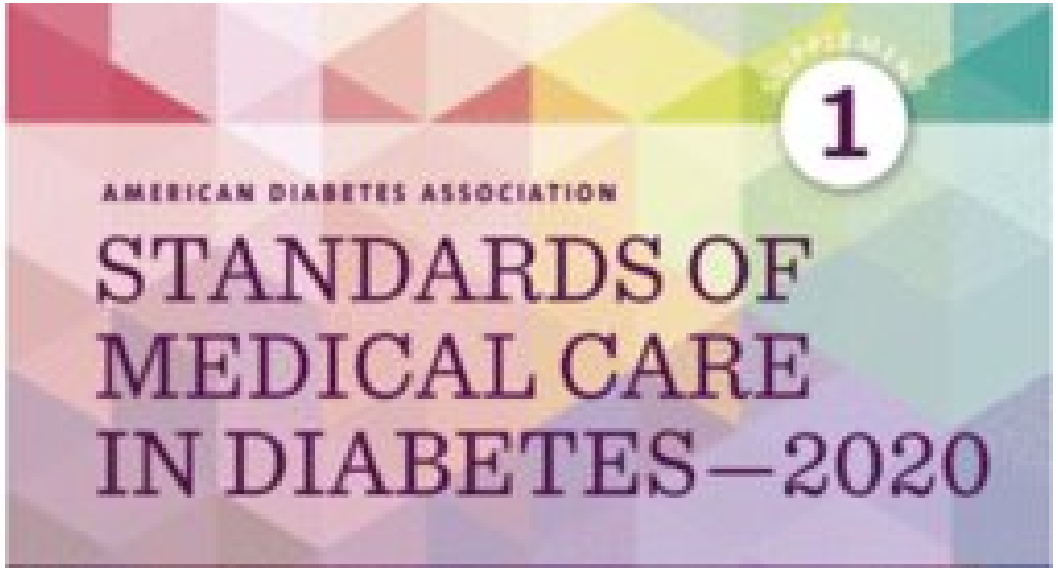
Start GLP1RA to improve A1c and reduce CV event risk



GUIDELINES HAVE RESPONDED

Summary

- PCSK9i recommended add on statin and ezetimibe in secondary prevention [1-3]
- Very high risk patients: LDL ≥70 mg/dL as threshold for non-statin addition to statin [1]
- Very high risk patients, Icosapent ethyl can be considered when TG 135-499 mg/dL despite statin therapy [2-4]
- SGLT2i and GLP1RA for diabetes and ASCVD to reduce CV events, HF, and progression of kidney disease independent of A1c [4-5]

1. ACC/AHA, American College of Cardiology, American Heart Association 2018 Guideline on the management of blood cholesterol
2. ESC/EAC, European Society of Cardiology, European Atherosclerosis Society Guidelines on management of dyslipidemias 2019
3. NLA Scientific Statement on the Use of Icosapent Ethyl in Statin-treated Patients with Elevated Triglycerides and High or Very High ASCVD Risk.
4. ADA, American Diabetes Associatio, Standards of Medical Care in Diabetes –2020
5. ACC/AHA *2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes*

Thank you

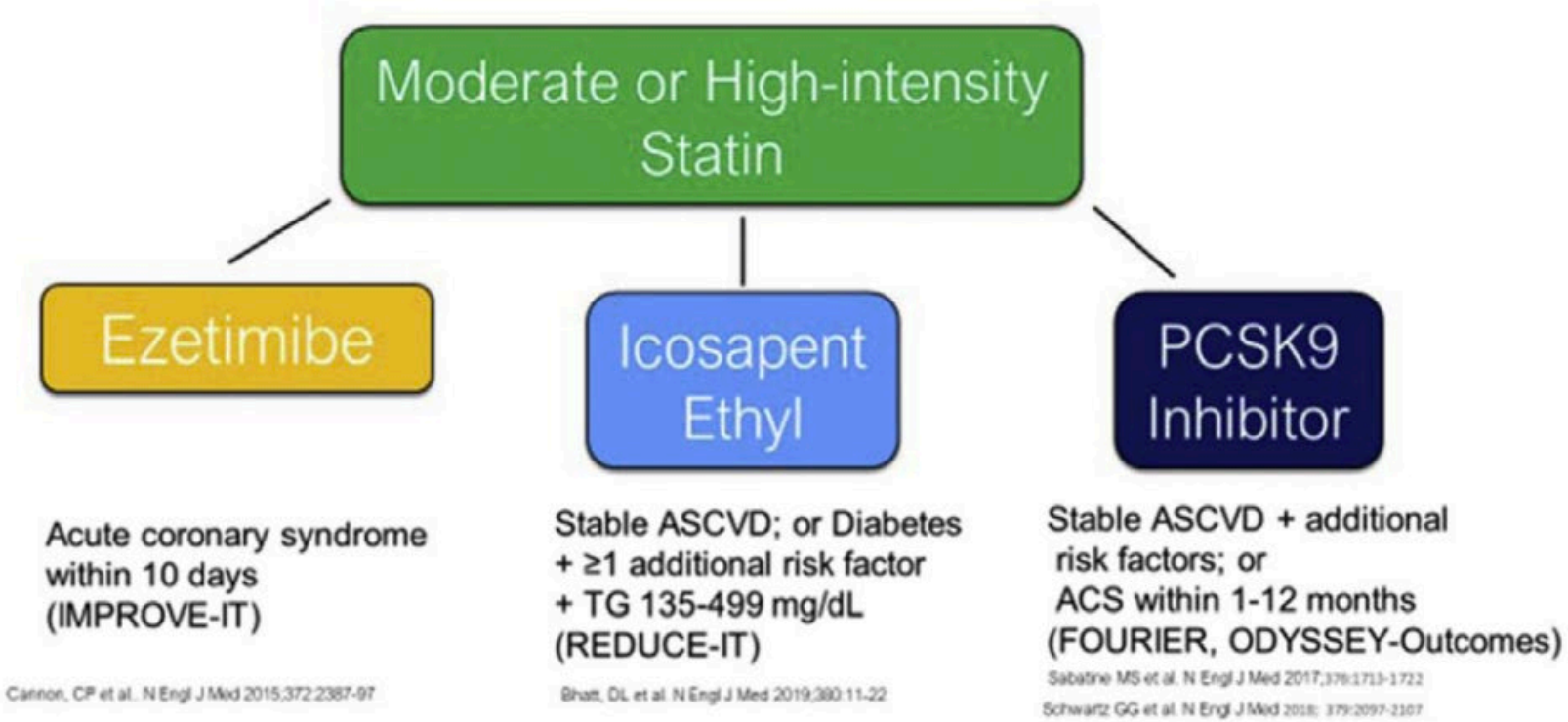
reduce-it™

Medial follow up: 4.9 years

	Primary CV Endpoint	TG	hsCRP	Hosp Afib/flutter	Serious bleeding
	**17.2%**	**-18%**	**-13.9%**	**3.1%**	**2.7%**
	**22%**	**+2.2%**	**+32.2%**	**2.1%**	**2.1%**
	(HR 0.75, p<0.001)			(p=0.004)	(p=0.06)

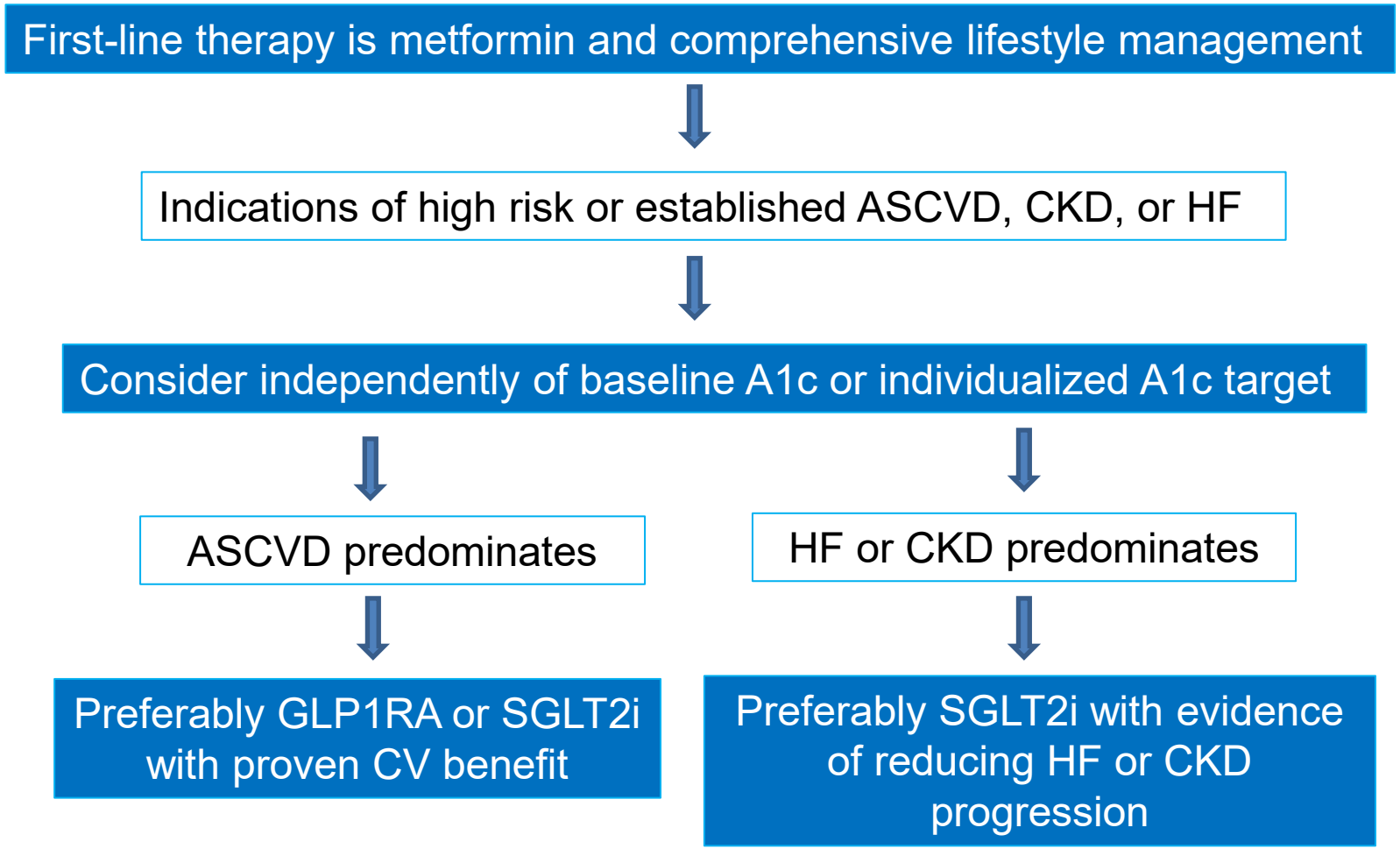
Bhatt et al. N Engl J Med. 2019 Jan 3;380(1):11-22

Adjunctive Therapies for ASCVD Risk Reduction in High- or Very-high-risk Statin-treated Patients Supported by RCT Evidence



Orringer et al. J Clin Lipidology Dec 2019

SGLT2i and GLP1RA for patients with diabetes and ASCVD/HF/CKD



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