

Strategies for CV risk reductions in Diabetes

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Introduction

- The burden of Type 2 diabetes (T2D) is increasing exponentially in the world with an alarming rise in developing countries.

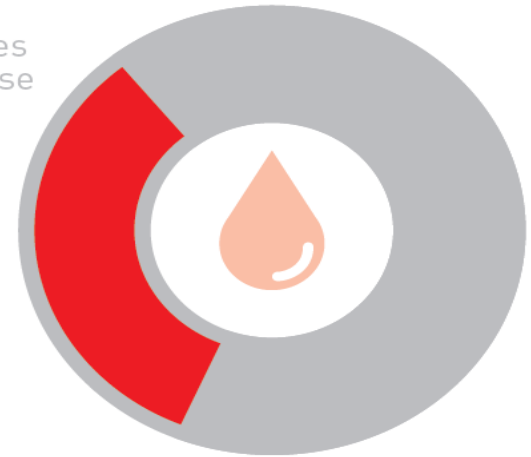
DIABETES IS
ON THE RISE



422 MILLION
adults have diabetes

3.7 MILLION
deaths due to diabetes
and high blood glucose

1.5 MILLION
deaths caused
by diabetes

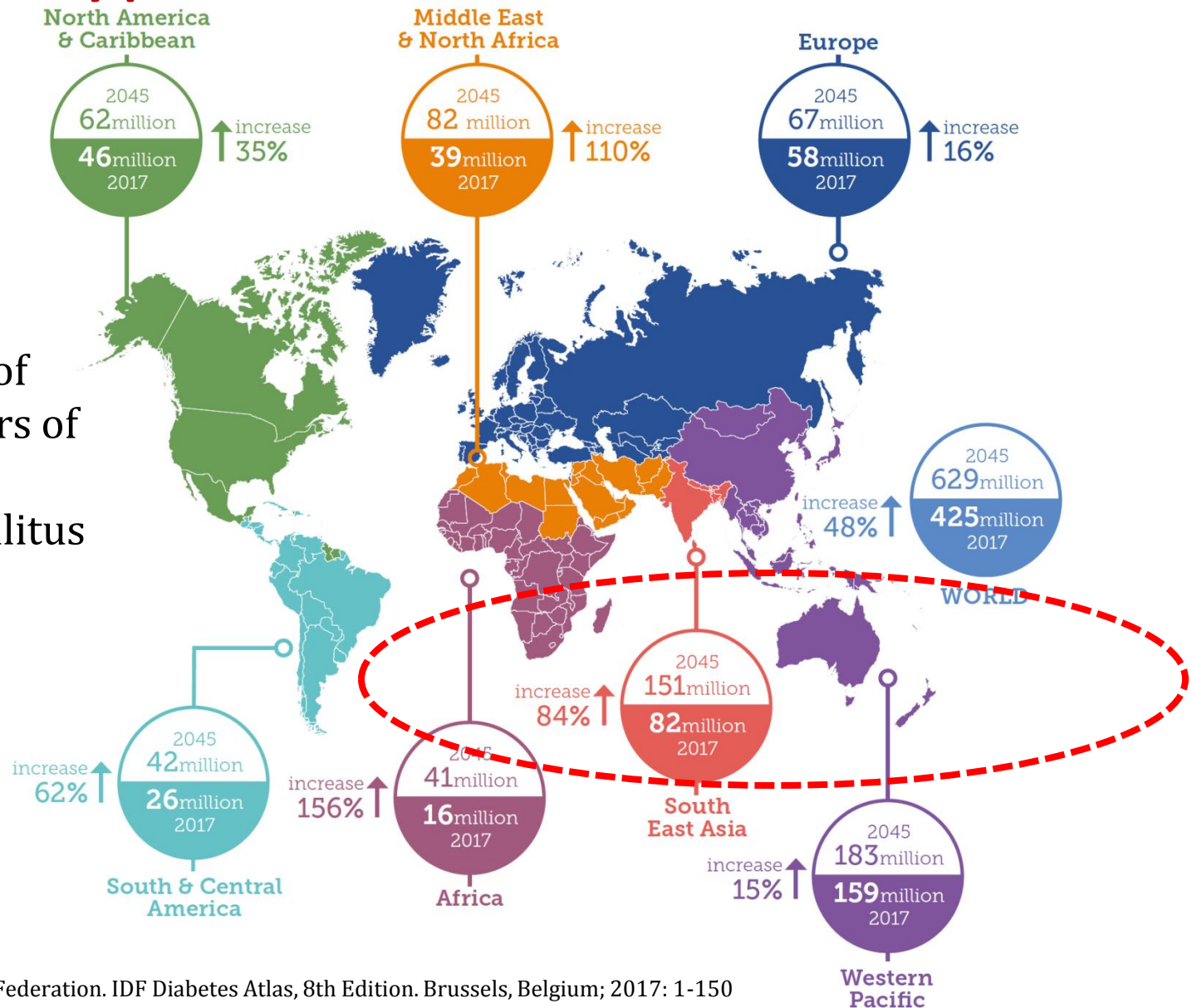


THAT'S **1** PERSON IN **11**



Type II Diabetes Mellitus

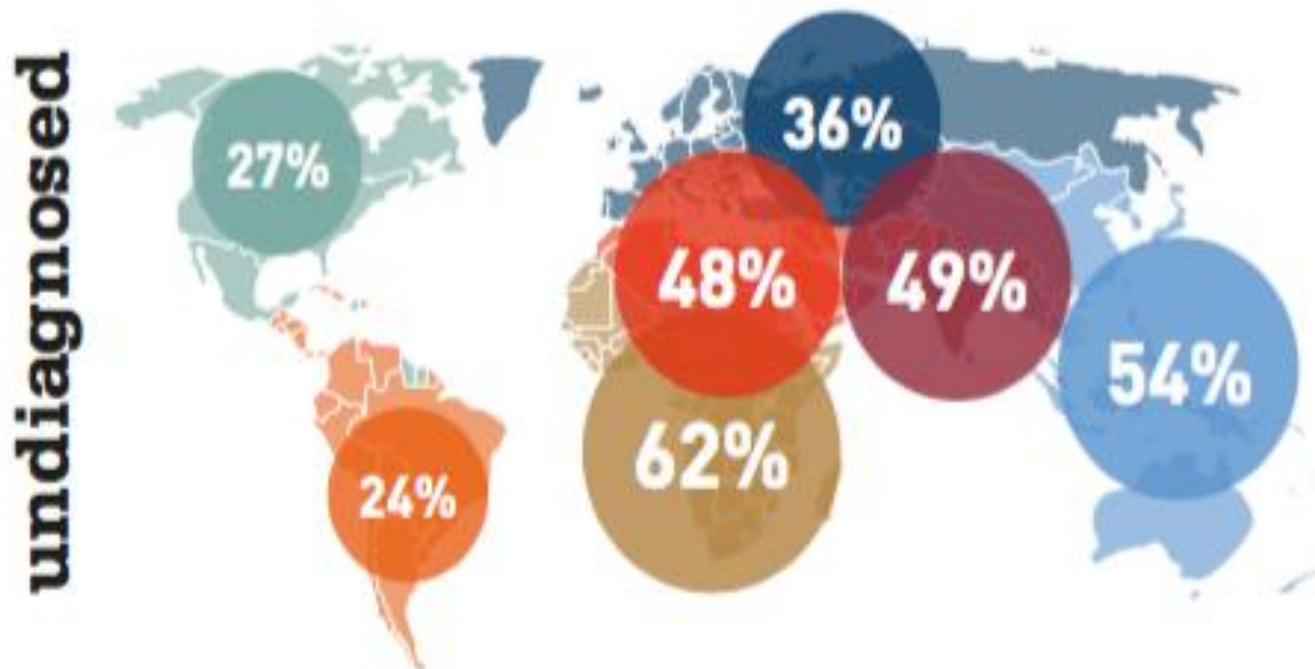
- India is one of the epicenters of the global diabetes mellitus pandemic.



Managing Diabetes

The human and economic costs of diabetes could be significantly reduced by investing in prevention, particularly early detection, in order to avoid the onset of diabetic complications

At least 50% of all people with diabetes are unaware of their condition



GOALS FOR GLYCEMIC CONTROL

INDIVIDUALIZE GOALS

$A1C \leq 6.5\%$

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

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

Entry A1C ≥ 7.5%

Entry A1C > 9.0%

MONOTHERAPY*

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

If not at goal in 3 months
proceed to Dual Therapy

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

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

PROGRESSION OF DISEASE

PROFILE 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 m ²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m ² 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 ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
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

■ Likelihood of adverse effects

■ Use with caution

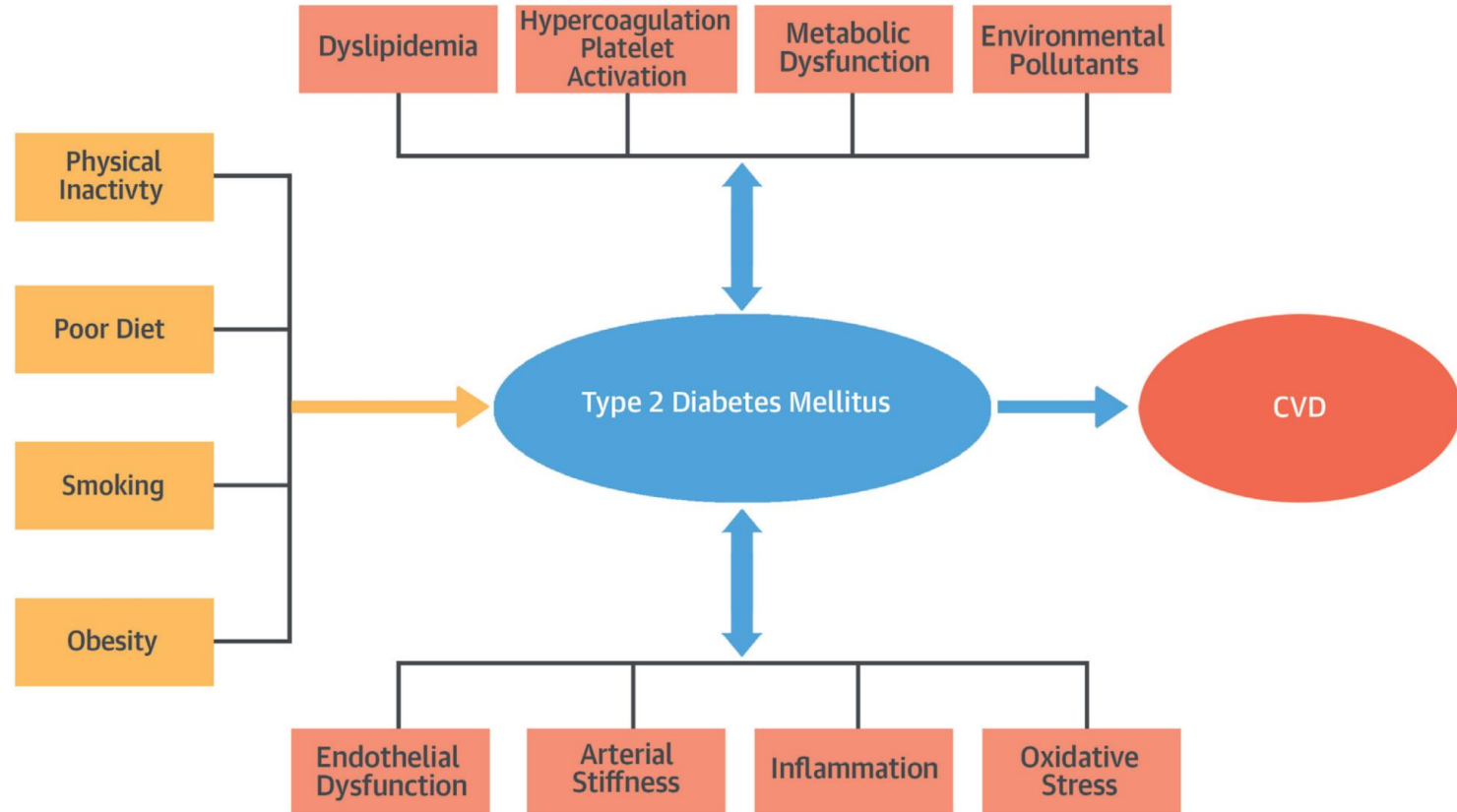
1. Liraglutide—FDA approved for prevention of MACE events.

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.

Cardiovascular disease and Diabetes

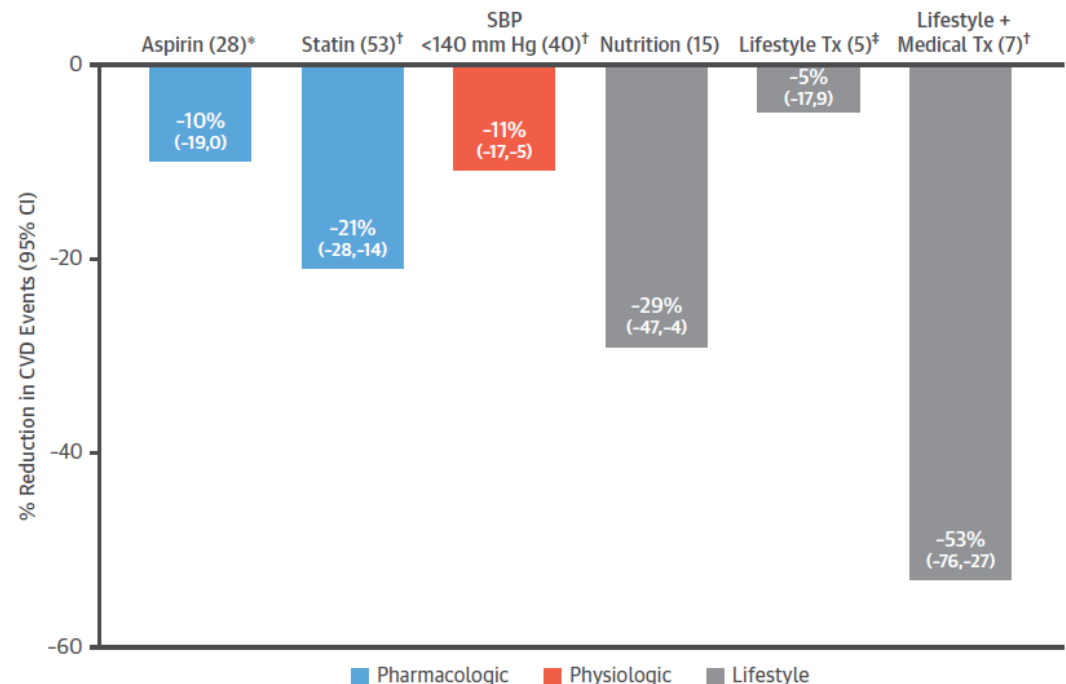
- Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in diabetes
- Managing risk factors for CVD in patients with diabetes reduces both.



The multifaceted approach

- Studies suggest that multifactorial interventions targeting several important risk factors simultaneously result in greater CV risk factor control.

Primary Prevention of CVD Events in Patients With T2D



CVD events are defined as cardiovascular death, myocardial infarction, or stroke and: *all-cause mortality; †revascularization or amputation; ‡hospitalization for angina. CI = confidence interval; CVD = cardiovascular disease; SBP = systolic blood pressure; T2D = type 2 diabetes; TX = treatment.

How to estimate total cardiovascular risk?

- The SCORE (Systematic Coronary Risk Estimation) charts are used.
- SCORE, which estimates the 10 year risk of fatal CVD, is recommended for risk assessment
- Can assist in making logical management decisions and may help to avoid both under- and over treatment.

Recommendation for how to estimate cardiovascular risk

Recommendation	Class ^a	Level ^b	Ref ^c
Total CV risk estimation, using a risk estimation system such as SCORE, is recommended for adults >40 years of age, unless they are automatically categorised as being at <i>high-risk</i> or <i>very high-risk</i> based on documented CVD, DM (>40 years of age), kidney disease or highly elevated single risk factor (Table 5).	I	C	11, 25

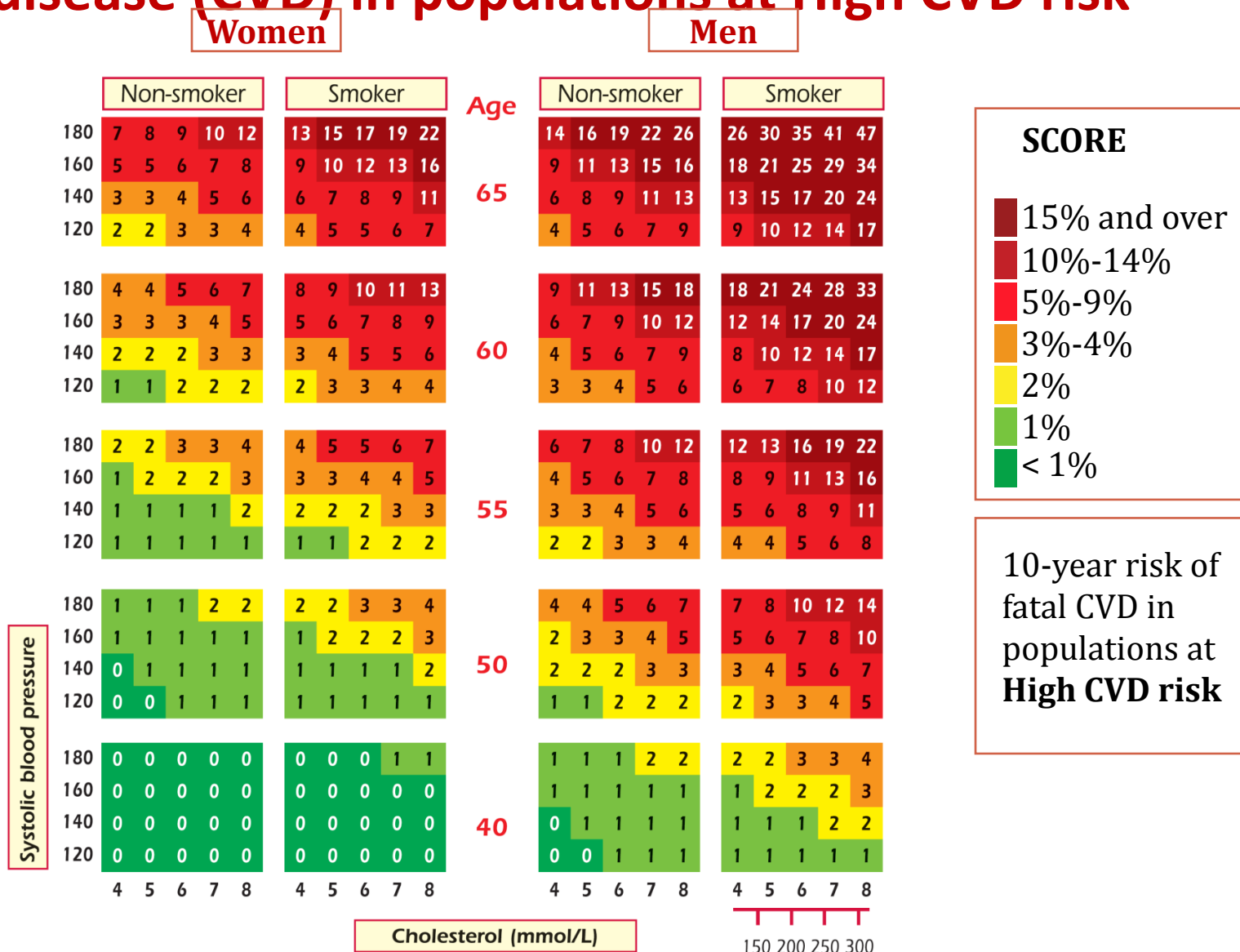
CV = cardiovascular; DM = diabetes mellitus; SCORE = Systematic Coronary Risk Estimation.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

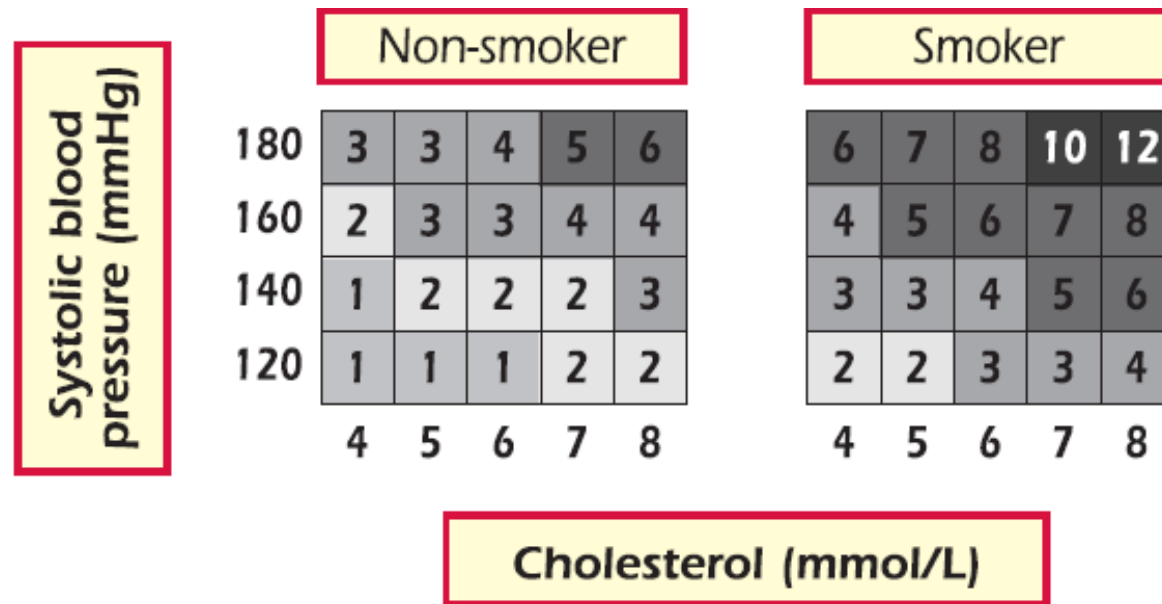
SCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at High CVD risk



Relative risk chart

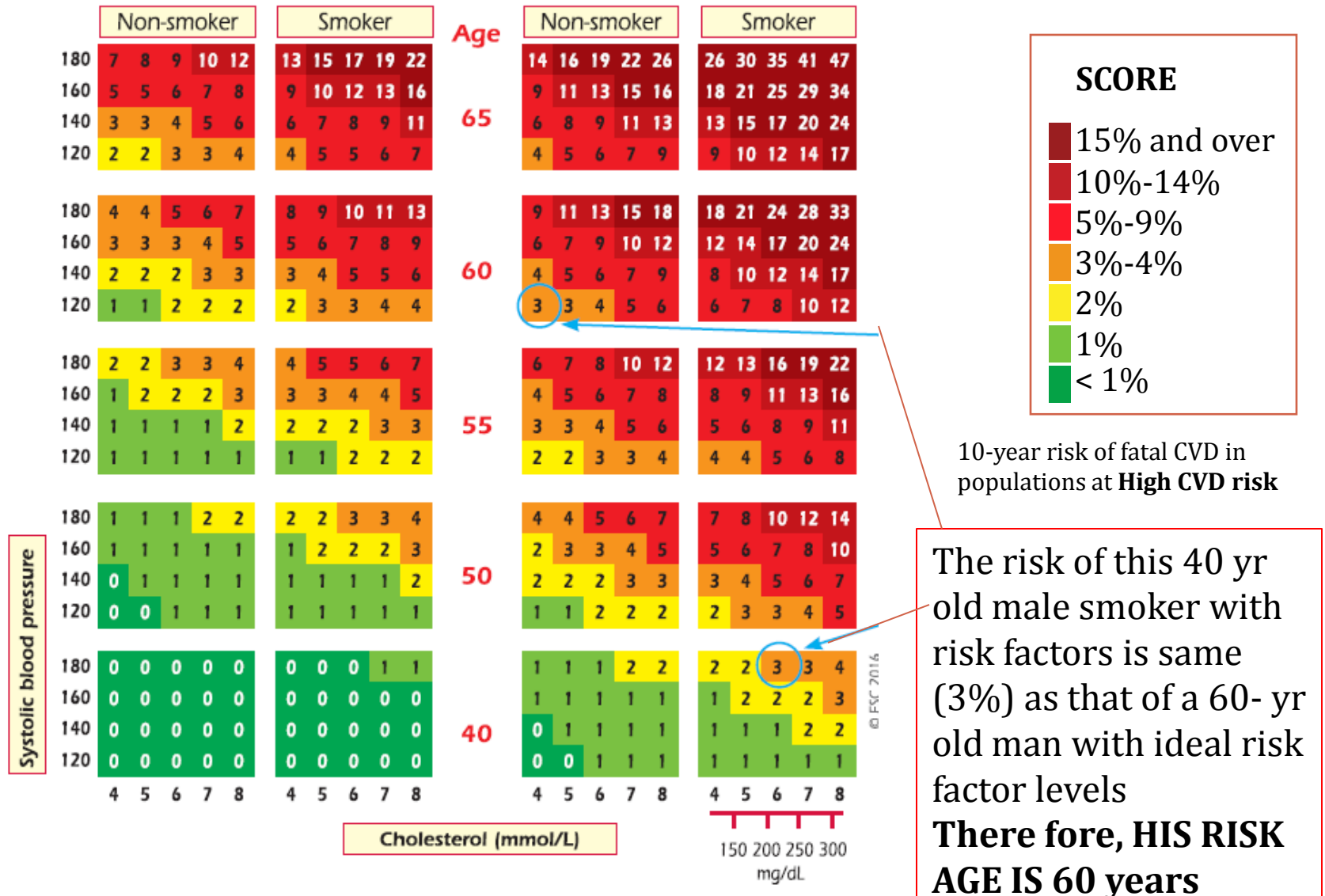
Chart may be used to show younger people at low absolute risk that, relative to others in their age group, their risk may be many times higher than necessary.

Help to motivate decisions about avoidance of smoking, healthy nutrition and exercise, as well as flagging those who may become candidates for medication



Please note that this chart shows RELATIVE not absolute risk. Risks are RELATIVE to 1 in the bottom left. Thus a person in the top right hand box has a risk that is 12 times higher than a person in the bottom left.

Illustration of the risk age concept.





Hypertension Management

New blood pressure targets and treatment recommendations

- For years, hypertension was classified as blood pressure (BP) reading of 140/90 mm Hg or higher.
- But the updated guideline classifies hypertension as a BP reading of **130/80 mm Hg or higher**.
- The updated guideline also provides new treatment recommendations, which include lifestyle changes as well as BP-lowering medications

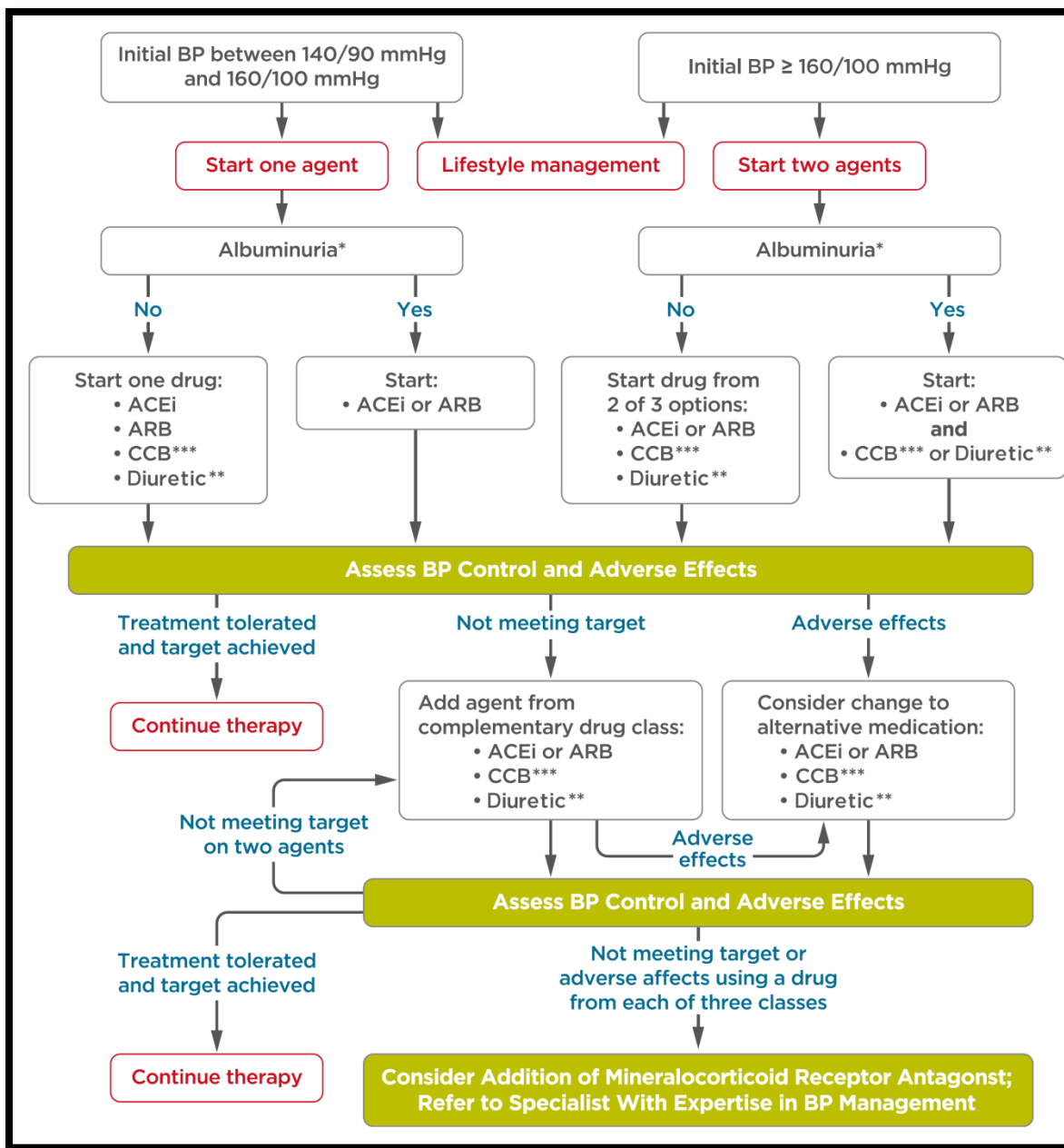
2017 ACC/ AHA Hypertension Guidelines

BP Category	Systolic BP		Diastolic BP	Treatment or Follow-up
Normal	<120 mm Hg	and	<80 mm Hg	Evaluate yearly; encourage healthy lifestyle changes to maintain normal BP
Elevated	120-129 mm Hg	and	<80 mm Hg	Recommend healthy lifestyle changes and reassess in 3-6 months
Hypertension: stage 1	130-139 mm Hg	or	80-89 mm Hg	Assess the 10-year risk for heart disease and stroke using the atherosclerotic cardiovascular disease (ASCVD) risk calculator • If risk is less than 10%, start with healthy lifestyle recommendations and reassess in 3-6 months • If risk is greater than 10% or the patient has known clinical cardiovascular disease (CVD), diabetes mellitus, or chronic kidney disease, recommend lifestyle changes and BP-lowering medication (1 medication); reassess in 1 month for effectiveness of medication therapy – If goal is met after 1 month, reassess in 3-6 months – If goal is not met after 1 month, consider different medication or titration – Continue monthly follow-up until control is achieved
Hypertension: stage 2	≥140 mm Hg	or	≥90 mm Hg	Recommend healthy lifestyle changes and BP-lowering medication (2 medications of different classes); reassess in 1 month for effectiveness • If goal is met after 1 month, reassess in 3-6 months • If goal is not met after 1 month, consider different medications or titration • Continue monthly follow-up until control is achieved

Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ADVANCE BP (17)	11,140 participants with T2D aged 55 years and older with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) systolic/diastolic: 136/73 mmHg	Control: placebo Achieved (mean) systolic/diastolic: 141.6/75.2 mmHg	- Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (142)
HOT (143)	18,790 participants, including 1,501 with diabetes	Diastolic blood pressure target: ≤ 80 mmHg	Diastolic blood pressure target: ≤ 90 mmHg	- In the overall trial, there was no cardiovascular benefit with more intensive targets - In the subpopulation with diabetes, an intensive diastolic target was associated with a significantly reduced risk (51%) of CVD events
SPRINT (144)	9,361 participants without diabetes	Systolic blood pressure target: < 120 mmHg Achieved (mean): 121.4 mmHg	Systolic blood pressure target: < 140 mmHg Achieved (mean): 136.2 mmHg	- Intensive systolic blood pressure target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) - Intensive target reduced risk of death 27% - Intensive therapy increased risks of electrolyte abnormalities and AKI

Recommendations for the treatment of confirmed Hypertension in patients with Diabetes



Lipid Management

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.

Intervention strategies as a function of total CV risk and LDL-C level

Total CV risk (SCORE) %	LDL-C levels				
	< 70 mg/dL	70 to < 100 mg/dL	100 to < 155 mg/dL	155 to < 190 mg/dL	> 190 mg/dL
< 1	No lipid intervention	No lipid intervention	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
Class/Level	I/C	I/C	I/C	I/C	IIa/A
≥ 1 to < 5	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class/Level	I/C	I/C	IIa/A	IIa/A	I/A
> 5 to < 10, or high risk	No lipid intervention	Lifestyle intervention consider drug*	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class/Level	IIa/A				
≥ 10 or very high risk	Lifestyle intervention consider drug*	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class/Level	IIa/A	IIa/A	I/A	I/A	I/A

Dietary recommendations to lower LDL-C and improve overall lipoprotein profile

	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Cereals	Whole grains	Refined bread, rice and pasta, biscuits, corn flakes	Pastries, muffins, pies, croissants
Vegetables	Raw and cooked vegetables	Potatoes	Vegetables prepared in butter or cream
Legumes	Lentils, beans, fava beans, peas, chickpeas, soybean		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles, fruit juice	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, chocolate, candies	Cakes, ice creams, fructose, soft drinks
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork or veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	Skim milk and yogurt	Low-fat milk, low-fat cheese and other milk products, eggs	Regular cheese, cream, whole milk and yogurt
Cooking fat and dressings	Vinegar, mustard, fat-free dressings	Olive oil, non-tropical vegetable oils, soft margarines, salad dressing, mayonnaise, ketchup	Trans fats and hard margarines (better to avoid them), palm and coconut oils, butter, lard, bacon fat
Nuts/seeds		All, unsalted (except coconut)	Coconut
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

ANTIPLATELET AGENTS

ANTIPLATELET AGENTS

- Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention).
- The Antithrombotic Trialists' Collaboration published an individual patient-level meta-analysis of the six large trials of aspirin for primary prevention in the general population.
 - These trials collectively enrolled over 95,000 participants
 - Overall, they found that aspirin reduced the risk of serious vascular events by 12% (RR 0.88 [95% CI 0.82–0.94]).

ACC/AHA guideline focused update on DAPT

COR	LOE	RECOMMENDATIONS
I	B-R	In patients with ACS treated with DAPT after BMS or DES implantation, P2Y ₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months (16,50-55,72,96-98).
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended (56-60,75-78).
IIa	B-R	In patients with ACS treated with DAPT after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y ₁₂ inhibitor therapy (53,72).
IIa	B-R	In patients with ACS treated with DAPT after coronary stent implantation, who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y ₁₂ inhibitor therapy (54,55).
IIb	A ^{SR}	In patients with ACS treated with coronary stent implantation who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use) continuation of DAPT for longer than 12 months may be reasonable (16,22-26,28,30,40,41,43,53,54,72).
IIb	C-LD	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y ₁₂ therapy after 6 months may be reasonable (17-21,34,36,37).
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA (54).

CORONARY HEART DISEASE

Cardiac Testing

- Candidates for advanced or invasive cardiac testing include those with
 - 1) typical or atypical cardiac symptoms and
 - 2) an abnormal resting electrocardiogram (ECG).
- Exercise ECG testing without or with echocardiography may be used as the initial test.
- In adults with diabetes >40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment.

Cardiac Testing (contd..)

- Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities).
- In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging.
- In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging

CORONARY HEART DISEASE

Screening

- In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated.
- Consider investigations for coronary artery disease in the presence of any of the following:
 - atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort);
 - signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or
 - electrocardiogram abnormalities (e.g., Q waves).

CORONARY HEART DISEASE

Treatment

- In patients with known atherosclerotic cardiovascular disease, consider ACE inhibitor or ARB therapy to reduce the risk of CV events.
- In patients with prior myocardial infarction, b-blockers should be continued for at least 2 years after the event.
- In patients with type 2 diabetes with stable congestive heart failure(CHF), metformin may be used if eGFR rate remains >30 mL/min but should be avoided in unstable or hospitalized patients with CHF.

CORONARY HEART DISEASE

Treatment (contd..)

- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease,
 - antihyperglycemic therapy should begin with lifestyle management and metformin and
 - subsequently incorporate an agent proven to reduce major adverse CV events (currently empagliflozin and liraglutide), after considering drug-specific and patient factors
- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, after lifestyle management and metformin,
 - the antihyperglycemic agent canagliflozin may be considered to reduce major adverse CV events, based on drug-specific and patient factors

Guideline-Based Care for CVD Prevention for Patients With Diabetes

Risk Factor	Specific Recommendation	Level of Evidence
Physical activity	≥150 min/week moderate intensity (50%–70% MPHR) over ≥3 days/week with ≤2 consecutive days without exercise	ADA LOE: A
Nutrition	Diet improves glycemic control and CVD risk factors Consumption of fruits, vegetables, legumes, whole grains, and dairy in place of other carbohydrate sources Carbohydrate monitoring as an important strategy for glycemic control	ADA LOE: B
Weight management	Counsel overweight and obese patients that lifestyle changes can lead to a sustained 3%–5% rate of weight loss and clinically meaningful health benefits	ACC/AHA Class I, LOE: A
Cigarette Smoking	Advise all patients not to use cigarettes, other tobacco products, or e-cigarettes Include smoking cessation counseling and other forms of treatment as a routine component of care	ADA LOE: A
Glycemic control	Lower HbA1c ≤7% in most patients to reduce risk of microvascular disease Consider HbA1c <6.5% for patients with diabetes of short duration, long life expectancy, and no significant CVD if can be achieved safely HbA1c <8% or higher for patients with severe hypoglycemia, limited life expectancy, and/or comorbid conditions	ADA LOE: B ADA LOE: C

Risk Factor	Specific Recommendation	Level of Evidence
Blood pressure	Achieve a goal of <130/80 mm Hg for most diabetic patients Pharmacotherapy should include either an ACE inhibitor or an ARB; if intolerant to one, substitute the other	ADA LOE: A, ACC/AHA LOE: A
Cholesterol	Diabetic patients 40–75 yrs of age with LDL 70–189 mg/dl should receive at least moderate-intensity statin [†] If age 40–75 yrs with CV risk factors,* high-intensity statin [‡] should be given	ACC/AHA Class I, LOE: A; ADA LOE: A
Anti platelet therapy	Aspirin 75–162 mg is reasonable for diabetic patients ≥50 yrs of age with at least 1 CV risk factor§ without increased GI bleeding risk Aspirin 75–162 mg might be reasonable for diabetic patients <50 yrs of age with 1 or more CV risk factors¶	ACC/AHA Class IIa, LOE: B; ADA LOE: C

*One or more of the following major CV risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD or albuminuria. †Moderate-intensity statin therapy lowers LDL cholesterol on average by 30% to 50%. ‡High-intensity statin lowers LDL cholesterol on average by >50%. §Corresponds to a 10-year ASCVD risk >10% (<http://tools.acc.org/ASCVD-Risk-Estimator/>). ¶Prior GI bleed, peptic ulcer disease, or concurrent use of medications that increase bleeding risk (e.g., nonsteroidal anti-inflammatory drugs or warfarin). ¶¶Corresponds to a 5% to 10% 10-year ASCVD risk.

ACC/AHA = American College of Cardiology/American Heart Association; ACE = angiotensin-converting enzyme; ADA = American diabetes Association; ARB = angiotensin II receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; GI = gastrointestinal; HbA1c = glycosylated hemoglobin; JNC-8 = Eighth Joint National Committee; LDL = low density lipoprotein; LOE = Level of Evidence; MPhR = maximum predicted heart rate

Summary

- Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality for individuals with diabetes
- Numerous studies have shown the efficacy of controlling individual CV risk factors in preventing or slowing ASCVD in people with diabetes
- Cardiovascular risk factors should be systematically assessed at least annually in all patients with diabetes.
- The uniform use of proven medical therapies as per the guidelines could reduce the CV risk for the patients with diabetes



THANKYOU