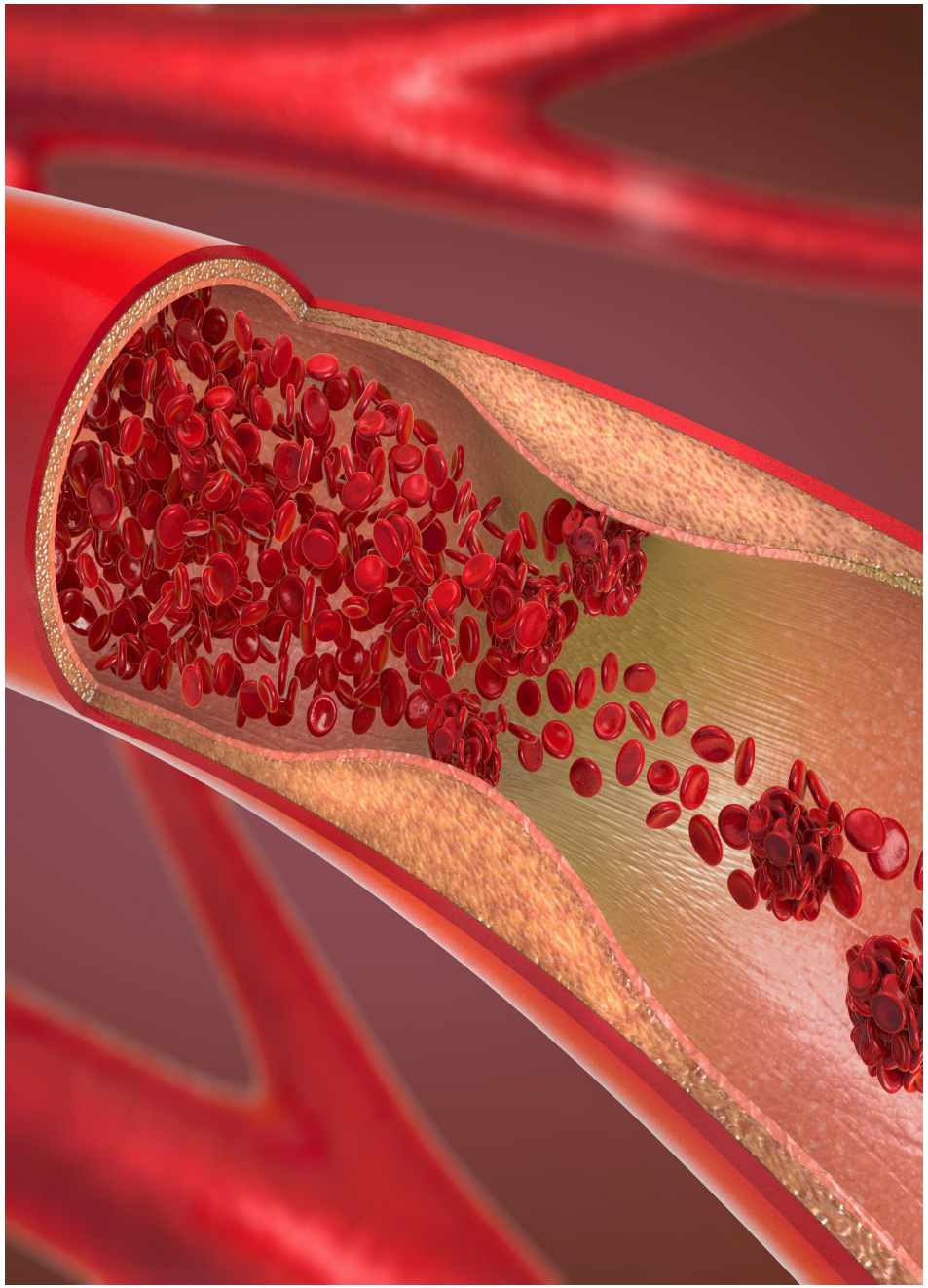
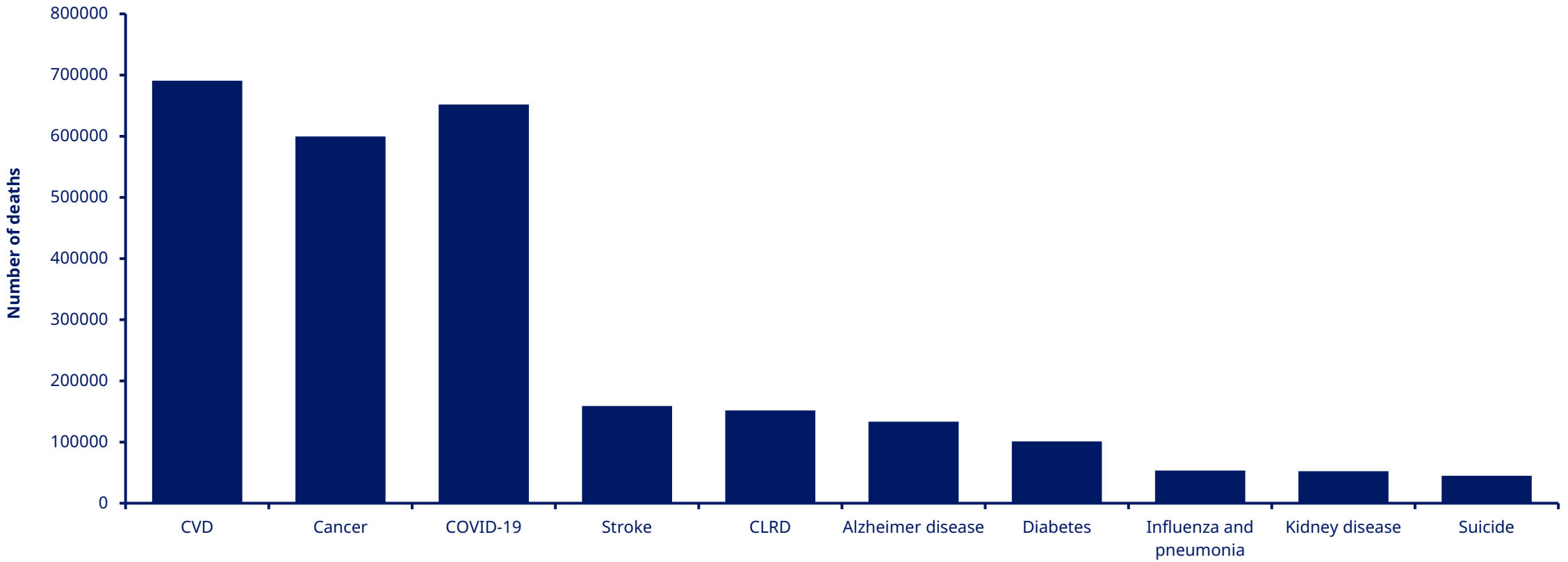


Atherosclerotic cardiovascular disease (ASCVD)

BURDEN OF ASCVD

CVD is the leading cause of death in the US, 2020



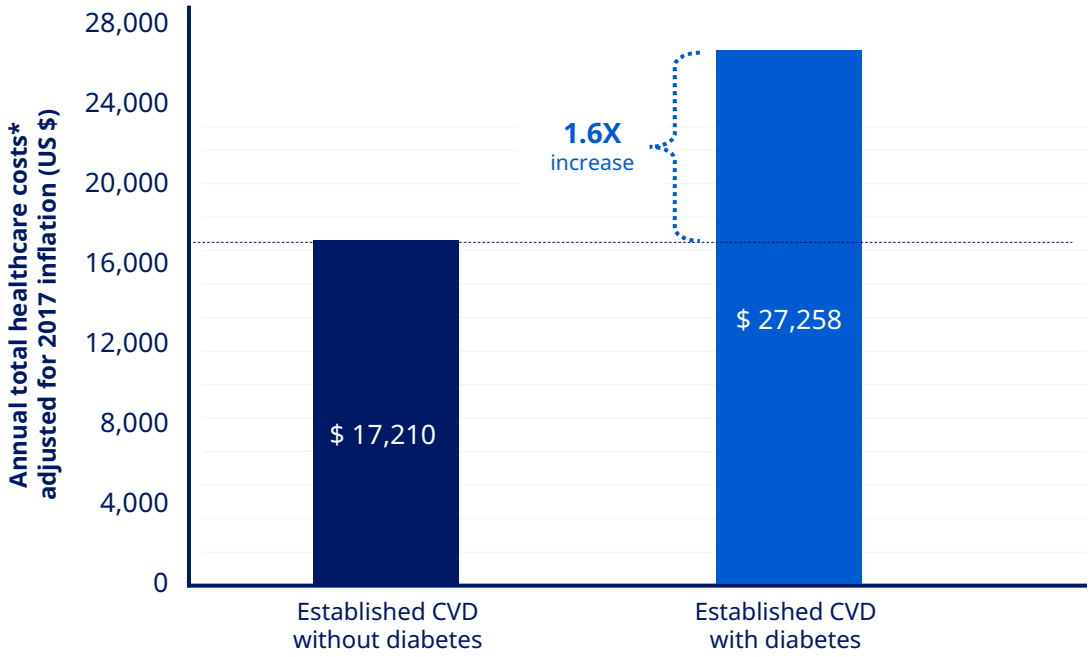
**Deaths of COVID-19 as of 7 December 2021.*
CLRD, chronic lower respiratory disease; CVD, cardiovascular diseases
1. Ahmad FB and Anderson RN. *JAMA*. 2021; doi:10.1001/jama.2021.5469; 2. *United States COVID: 50,148,680 Cases and 810,246 Deaths - Worldometer (worldometers.info)* Accessed on 7 December 2021; *3. An Update on Cancer Deaths in the United States | CDC* Accessed on 7 December 2021

BURDEN OF ASCVD

Higher annual total healthcare costs* in the US for people with T1D/T2D and with CVD

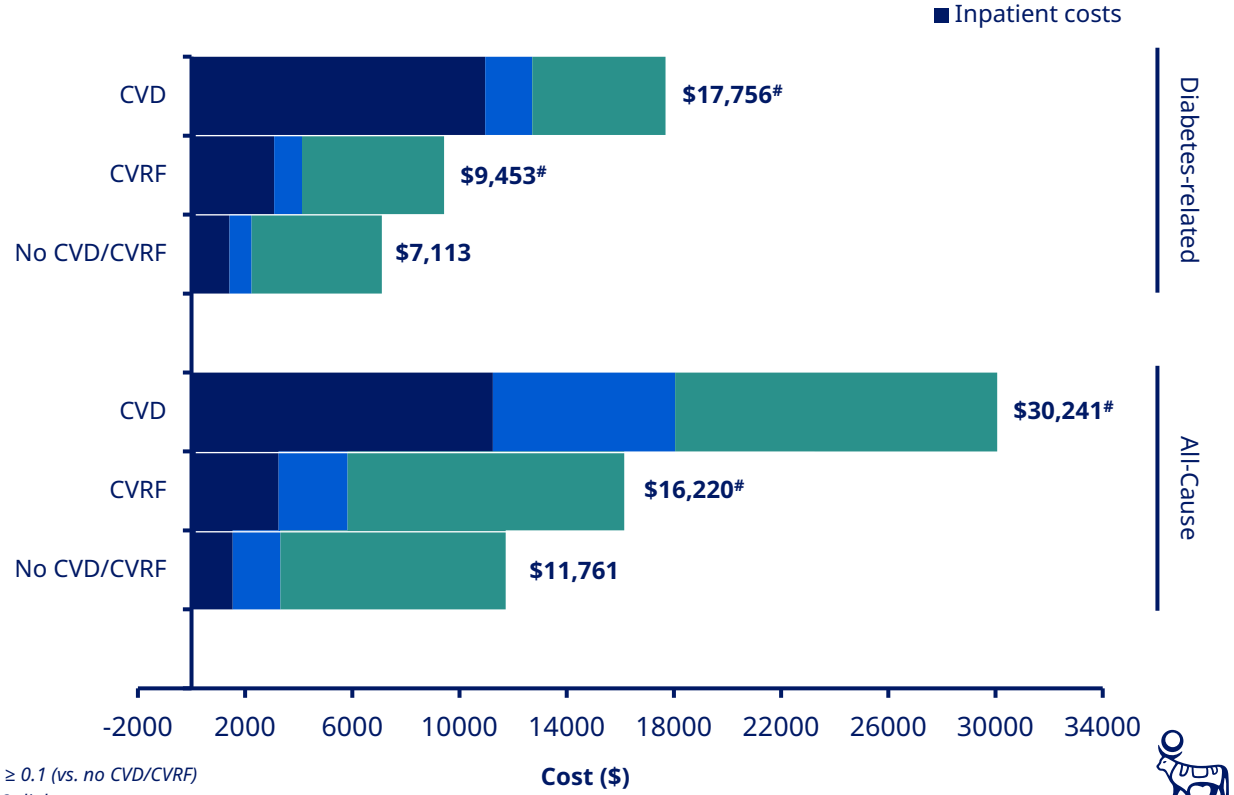
People with T2D (N=12,278)

The total mean direct medical care costs for patients with established CVD were **$18,953** per patient per year[1]



People with T1D (N=12,687)

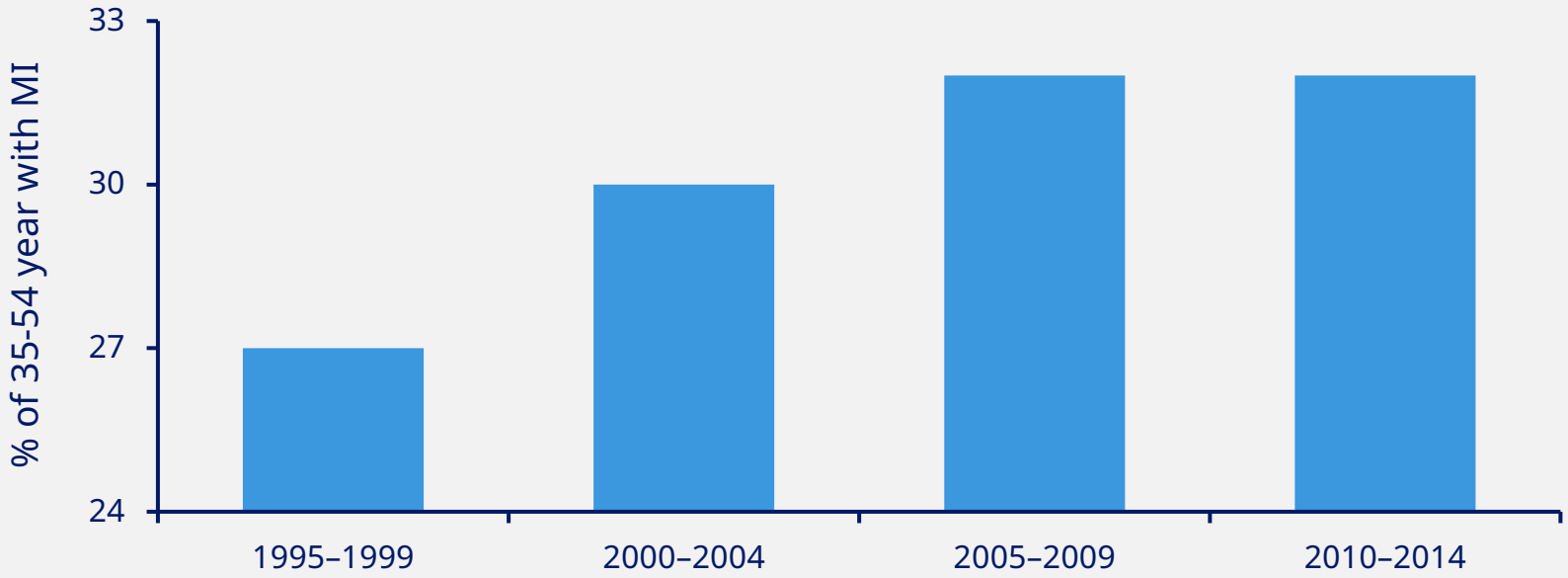
Data represents per patient per year healthcare costs at 12 months of follow-up (Jan-Dec 2016)[2]



**Annual total healthcare costs included pharmacy costs, outpatient costs, inpatient costs; #Significant difference: P < 0.05 and SMD ≥ 0.1 (vs. no CVD/CVRF)*
CVD, cardiovascular disease; CVRF, cardiovascular risk factors; SMD, standardized mean difference; T1D, type 1 diabetes; T2D, type 2 diabetes
1. Nichols GA, et al. Am J Manag Care. 2010;16(3):e86-e93; 2. Edelman S et al. PharmacoEconomics – Open. 2020;4:519–528

EPIDEMIOLOGY OF ASCVD

The proportion of **AMI hospitalizations attributable to young patients (35-54 years)** increased from 1995 to 2014[2] in the ARIC study

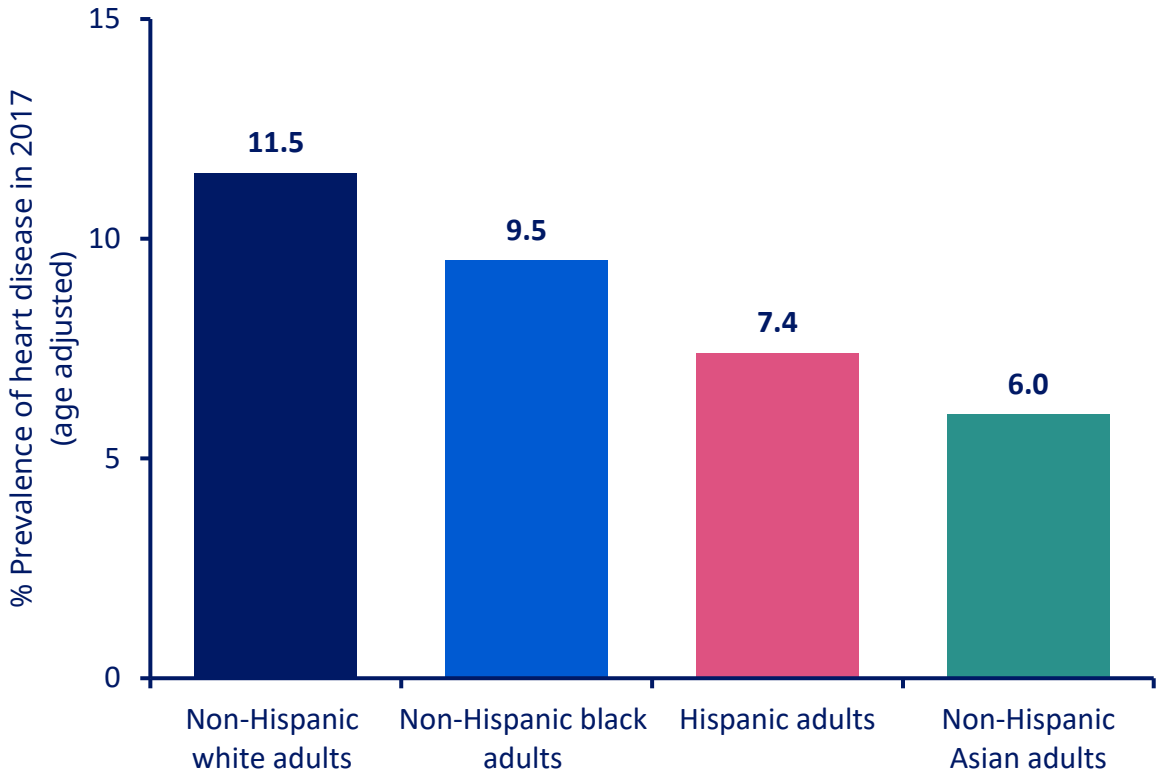


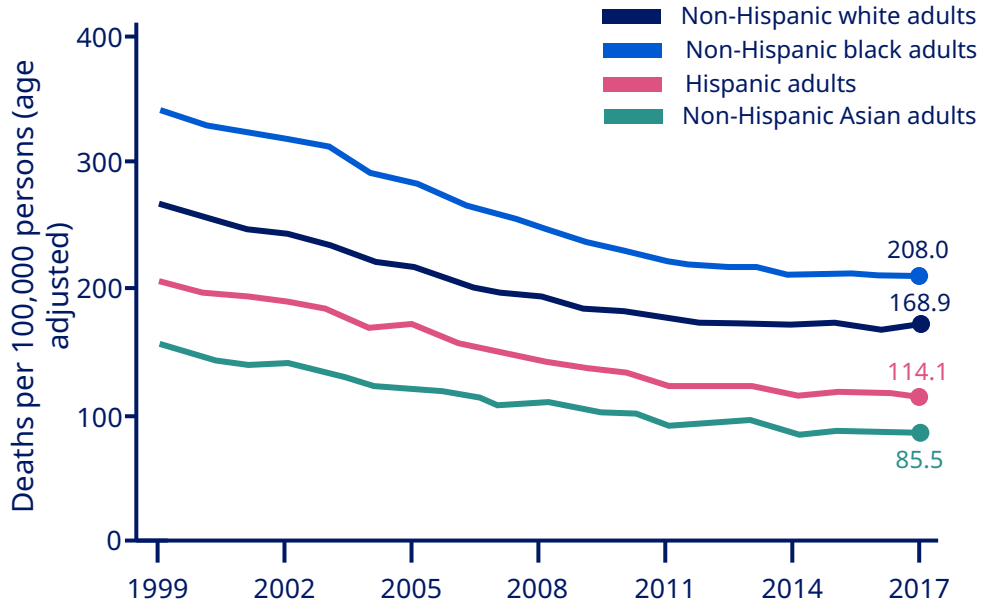
AMI, acute myocardial infarction; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey

1. Virani SS et al. Circulation. 2020;141:e139–e596. DOI: 10.1161/CIR.0000000000000757; 2. Arora S et al. Circulation. 2019 Feb 19;139(8):1047-1056)

EPIDEMIOLOGY OF ASCVD

Racial and ethnic disparities in prevalence and mortality of heart disease, 1999-2017 (≥18 years)





Non-Hispanic black adults were **more than twice** as likely as non-Hispanic Asian adults to die of heart disease

https://www.cdc.gov/nchs/hus/spotlight/HeartDiseaseSpotlight_2019_0404.pdf *Accessed on 1 December 2021*

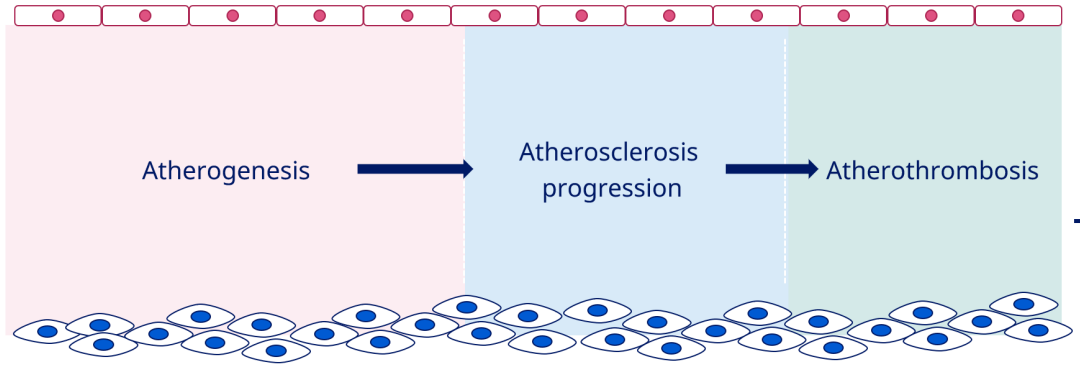
PATHOGENESIS OF ATHEROSCLEROSIS

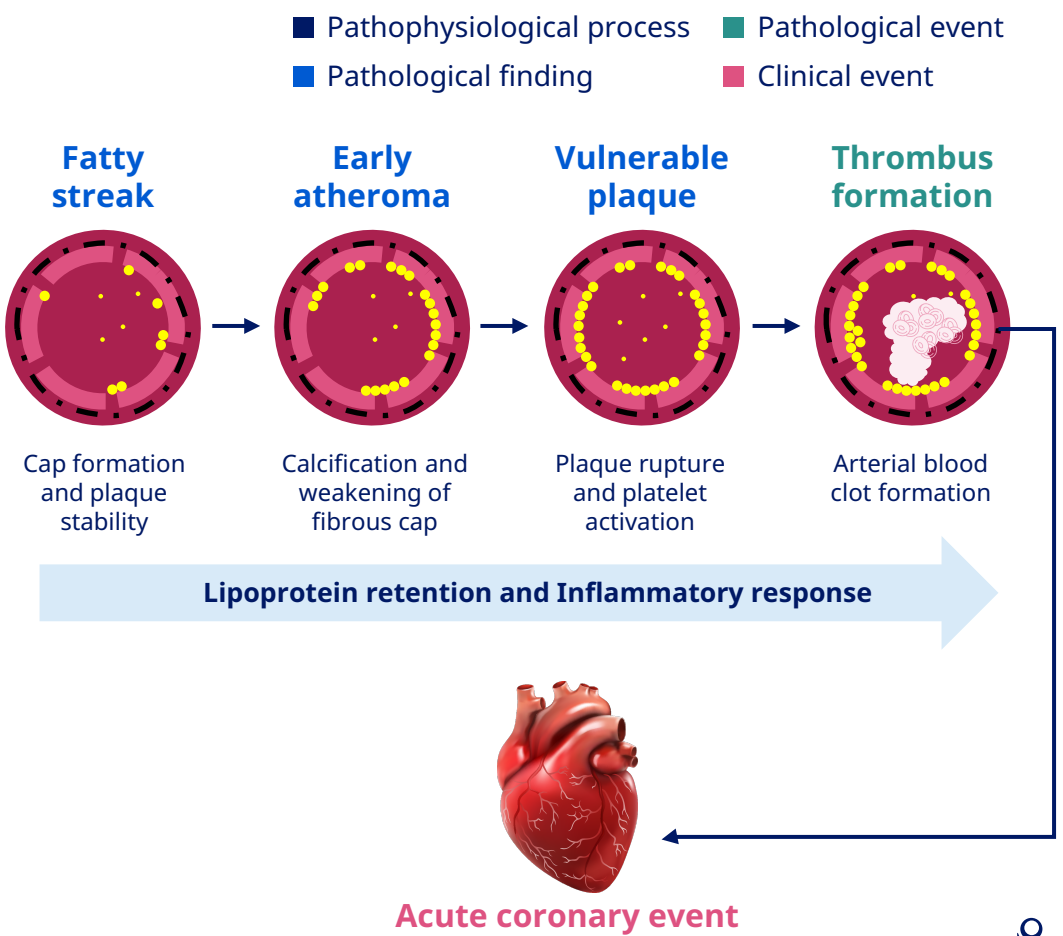
Atherosclerotic plaque lifecycle [1-5]

Hyperlipidemia | Obesity | Hypertension | Diabetes | Smoking | Lack of physical activity

Advancing age | Genetic predisposition* | FH OR family history of premature ASCVD | Chronic kidney disease | PCOS

Risk factors





ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia

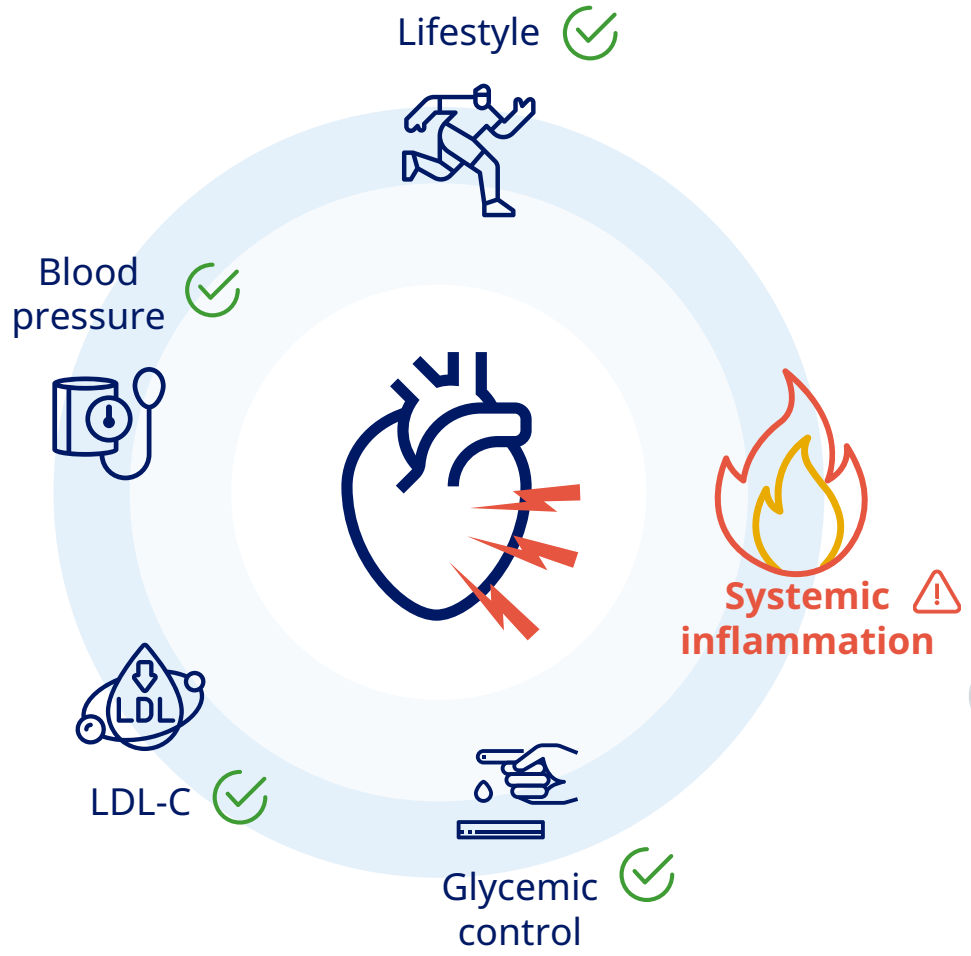
1. Herrington W et al. Circ Res 2016;118:535–546; 2. Agrawal S et al. Am J Cardiol. 2017;119(10):1532-1541; 3. Hudspeth B. Am J Manag Care. 2018;24(13 Suppl):S268-S272; 3. Handelsman Y et al. Endocr Pract. 2020;26(No.10); 4. Grundy SM et al. Journal of the American College of Cardiology. 2019;73(24). DOI: 10.1016/j.jacc.2018.11.003; 5. Nauck MA et al 2020. Molecular metabolism. https://doi.org/10.1016/j.molmet.2020.101102

PATHOGENESIS OF ATHEROSCLEROSIS

The concept of residual inflammatory risk

- Cardiovascular events occur despite control of conventional risk factors. This is recognised as **'residual cardiovascular risk'**[1]
- **Systemic inflammation,** driven by the NLRP3 inflammasome pathway, contributes to the risk of cardiovascular events[2]
- The most widely used marker of this pathway is **hsCRP**[2]

Residual inflammatory risk is classified as levels of hsCRP **≥2 mg/L**[3]



hsCRP, high-sensitivity C-reactive protein; LDL-C, low density lipoprotein cholesterol; NLRP3, NOD [nucleotide oligomerization domain]-, LRR [leucine-rich repeat]- and PYD [pyrin domain]-containing protein 3

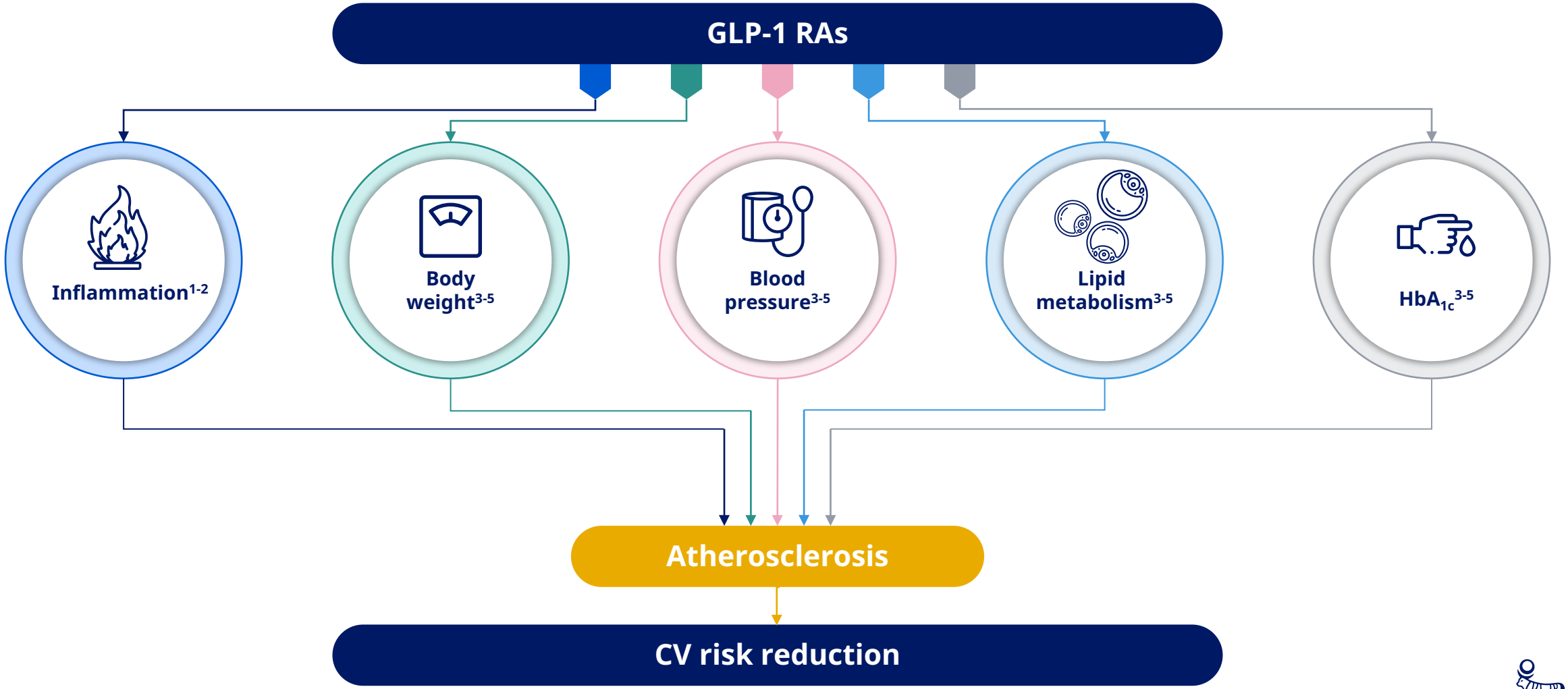
1. Vanuzzo. Intern Emerg Med 2011;6:Suppl 1:45–51; 2. Ridker PM et al. Circulation 2020;141:787–789; 3. Ridker PM. Circ Res. 2017;120(4):617-619.

GUIDELINE-BASED TREATMENT APPROACHES FOR CVD

Managing risk factors to reduce ASCVD risk

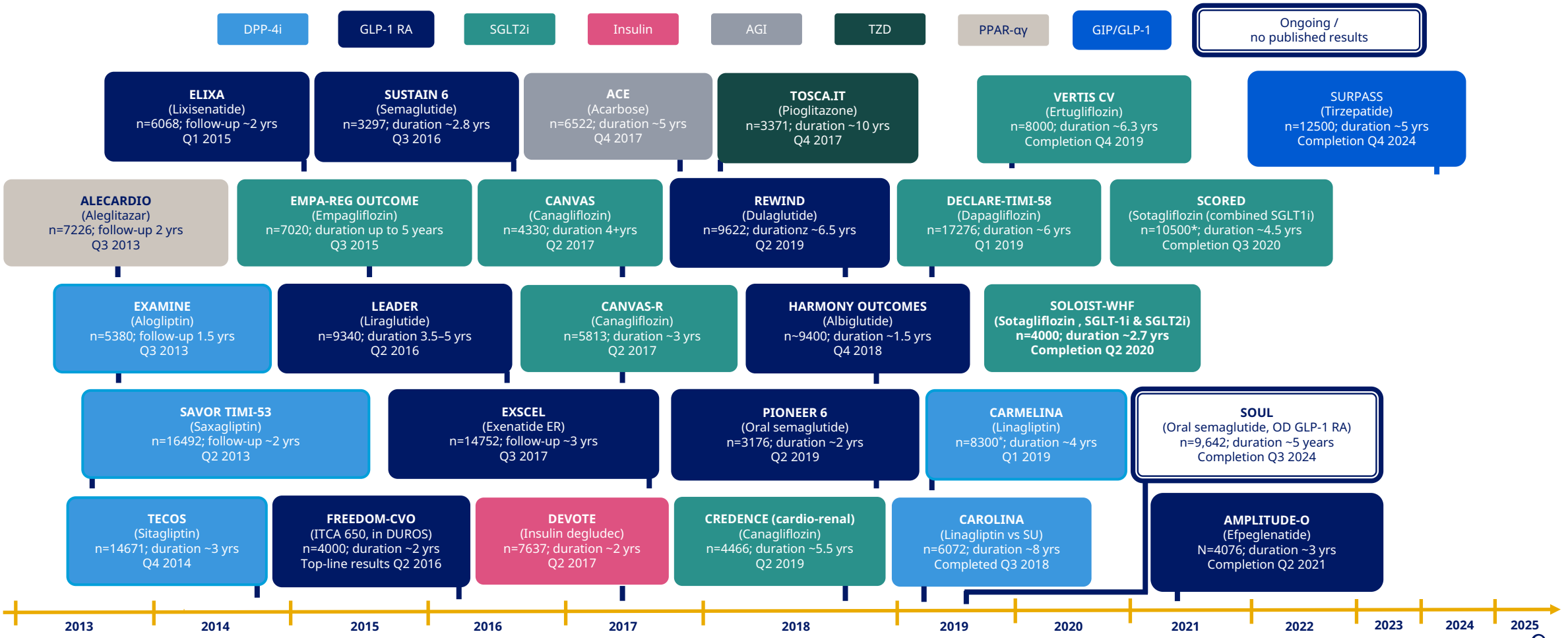
Product classes in highlighted boxes are discussed in this section
ASCVD, atherosclerotic CVD; CV, cardiovascular
1. Gaede P et al. N Engl J Med. 2008;358(6):580-591. 2. American Diabetes Association. Diabetes Care. 2020; 43 (Supplement 1):S1-S212.

Potential mechanisms of CV risk reduction by GLP-1RAs



1. Aroda V, et al. Diabetes Care 2019;42:1724-32; 2. Rodbard HW, et al. Diabetes Care. 2019;42(12):2272-2281; 3. Marso SP et al. N Engl J Med. 2016;375(4):311-22; 4. Marso SP et al. N Engl J Med. 2016;375:1834–1844; 5. Hussain M et al. N Engl J Med. 2019;381(9):841-851.

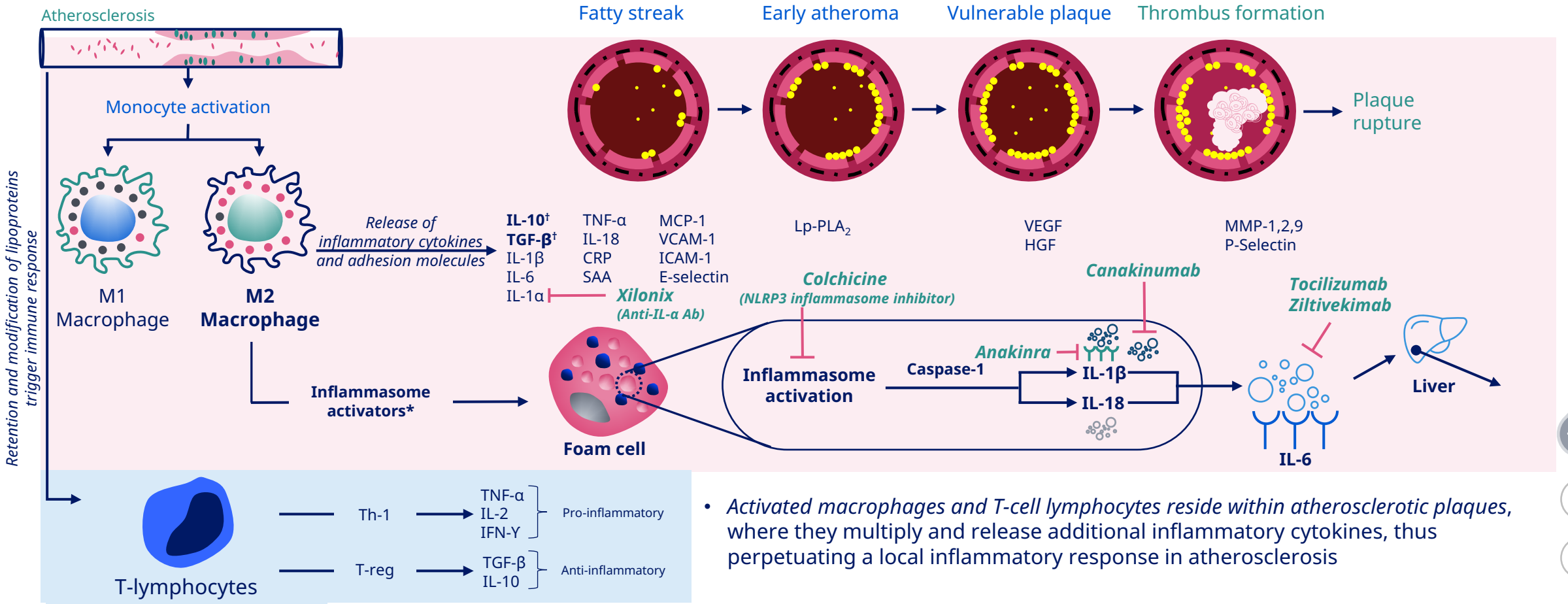
Recent CVOTs in diabetes



**Estimated enrolment;*
AGI, alpha-glucosidase inhibitor; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; ER, extended release; GIP, gastric inhibitory peptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; ITCA 650, continuous subcutaneous delivery of exenatide; PPAR-αγ, peroxisome proliferator-activated receptors-α and γ; QW, once weekly; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione. ClinicalTrials.gov. Accessed October, 2019.

ANTI-INFLAMMATORY THERAPY FOR CVD

Mechanism of action of anti-inflammatory drugs



- *Activated macrophages and T-cell lymphocytes reside within atherosclerotic plaques*, where they multiply and release additional inflammatory cytokines, thus perpetuating a local inflammatory response in atherosclerosis

*Please find abbreviations in the speaker notes; **Bolded text** indicates cytokines IL-10 and TGF-β that reduce the inflammatory state of plaque macrophages and be particularly important in regressing atherosclerosis plaque; *Due to hypoxia, oxidized LDL, cholesterol crystals, atheroprone flow, somatic mutations; neutrophil extracellular traps*

1. Montarello NJ et al. Cardiovasc Drugs Ther. 2020; https://doi.org/10.1007/s10557-020-07106-6; 2. Chan Y and Ramji DP. Future Med Chem.2020;12(7):613-626; 3. Nguyen MT et al. J Clin Med. 2019; 8(8):1109 ; 4. Aday AW and Ridker PM. Review Front Cardiovasc Med. 2019;6:16

ANTI-INFLAMMATORY THERAPY FOR CVD

Factors contributing to the residual CVD risk

Patients with or at high risk for ASCVD

Despite contemporary evidence -based therapies*, residual risk of ASCVD events persists

	Residual inflammatory risk	Residual cholesterol risk	Residual thrombotic risk	Residual triglyceride risk	Residual Lp(a) risk	Residual diabetes risk
Critical biomarker	hsCRP ≥ 2 mg/L	LDL-C ≥ 100 mg/dL	No simple biomarker	TG ≥ 150 mg/dL	Lp(a) ≥ 50 mg/dL	HbA_{1c} fasting glucose
Potential intervention	Targeted inflammation reduction	Targeted LDL/Apo B reduction	Targeted antithrombotic reduction	Targeted triglyceride reduction	Targeted Lp(a) reduction	SGLT2is GLP-1 RAs
Randomized trial evidence	CANTOS COLCOT LoDoCo2 OASIS-9	IMPROVE-IT FOURIER SPIRE ODYSSEY	PEGASUS COMPASS THEMIS	REDUCE-IT PROMINENT	HORIZON	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

**In addition to standard evidence-based therapies, more aggressive blood pressure targets may be considered*
Apo B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycosylated haemoglobin; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein C; Lp(a), lipoprotein (a); SGLT2i, sodium–glucose cotransporter 2 inhibitor; TG, triglyceride
Lawler PR et al. Eur Heart J. 2021;42(1):113-131.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