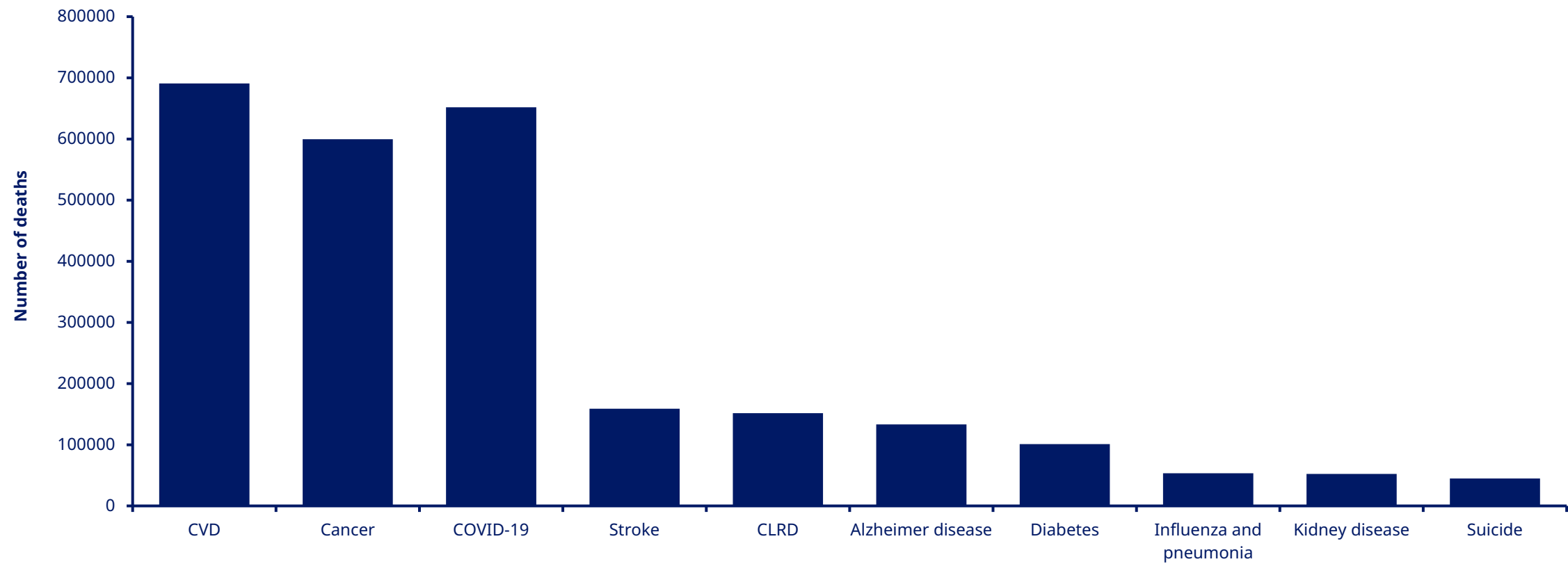


Atherosclerotic cardiovascular disease (ASCVD)



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

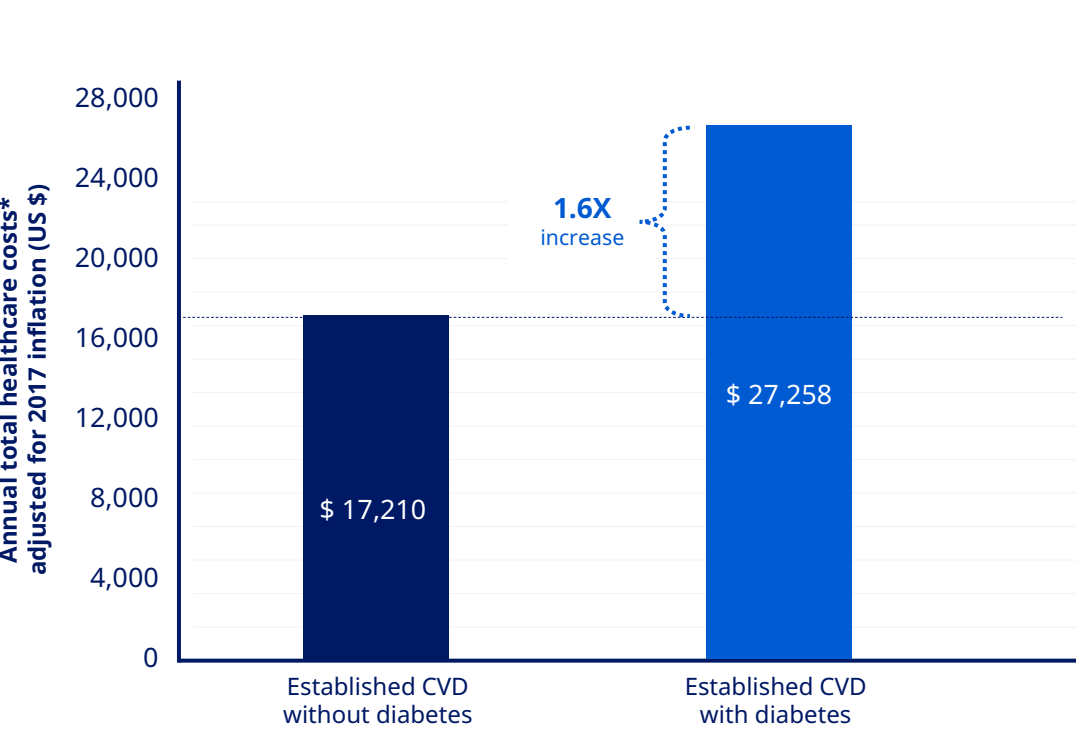


BURDEN OF ASCVD

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

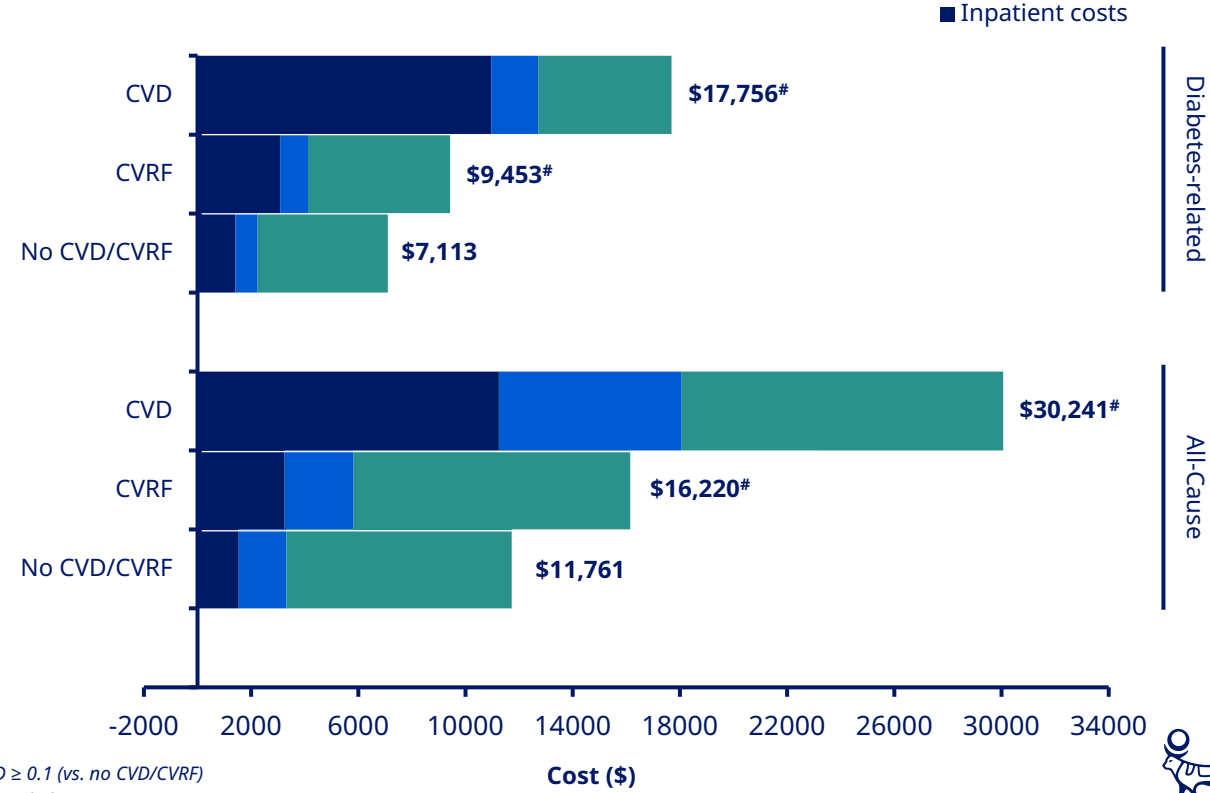
People with T2D (N=12,278)

The total mean direct medical care costs for patients with established CVD were **\$18,953** per patient per year¹



People with T1D (N=12,687)

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

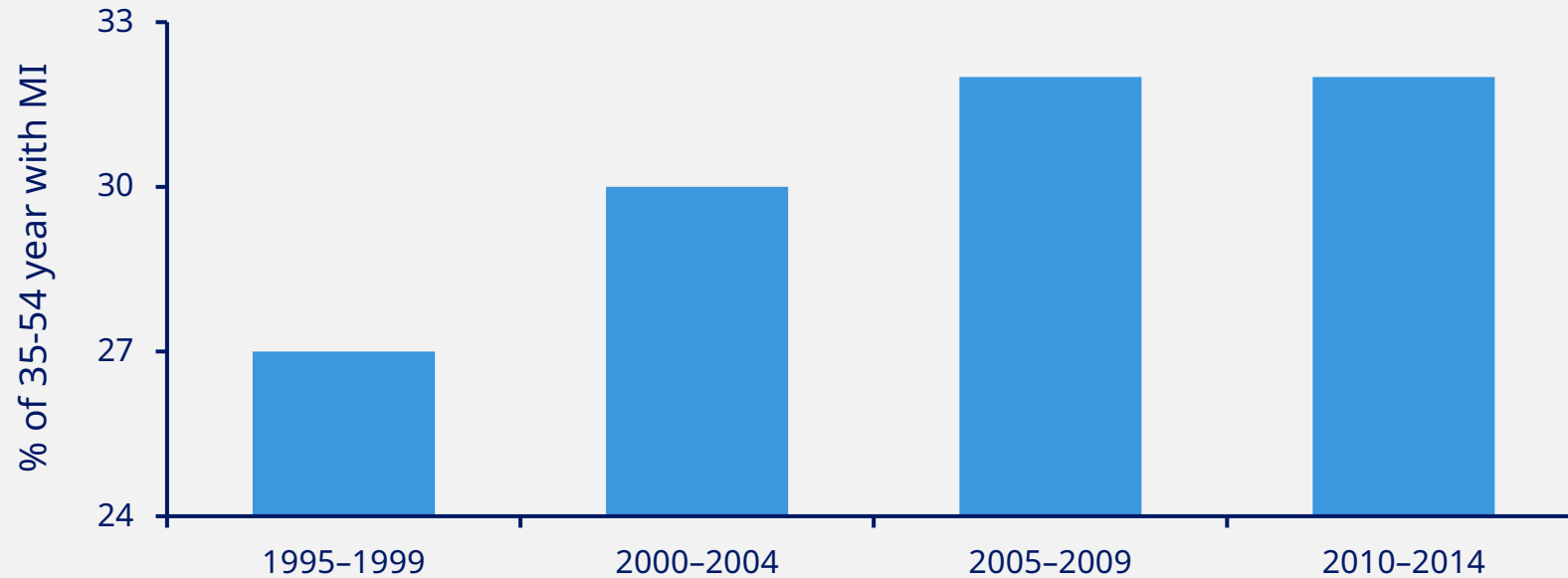


*Annual total healthcare costs included pharmacy costs, outpatient costs, inpatient costs; [#]Significant difference: $P < 0.05$ and $SMD \geq 0.1$ (vs. no CVD/ CVRF)
CVD, cardiovascular disease; CVRF, cardiovascular risk factors; SMD, standardized mean difference; T1D, type 1 diabetes; T2D, type 2 diabetes
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

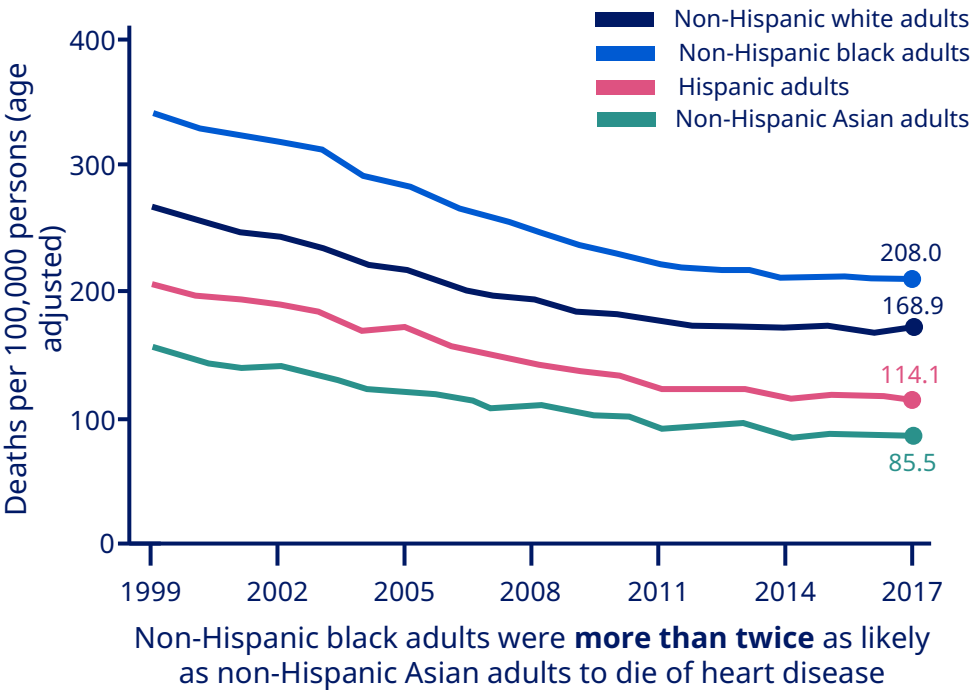
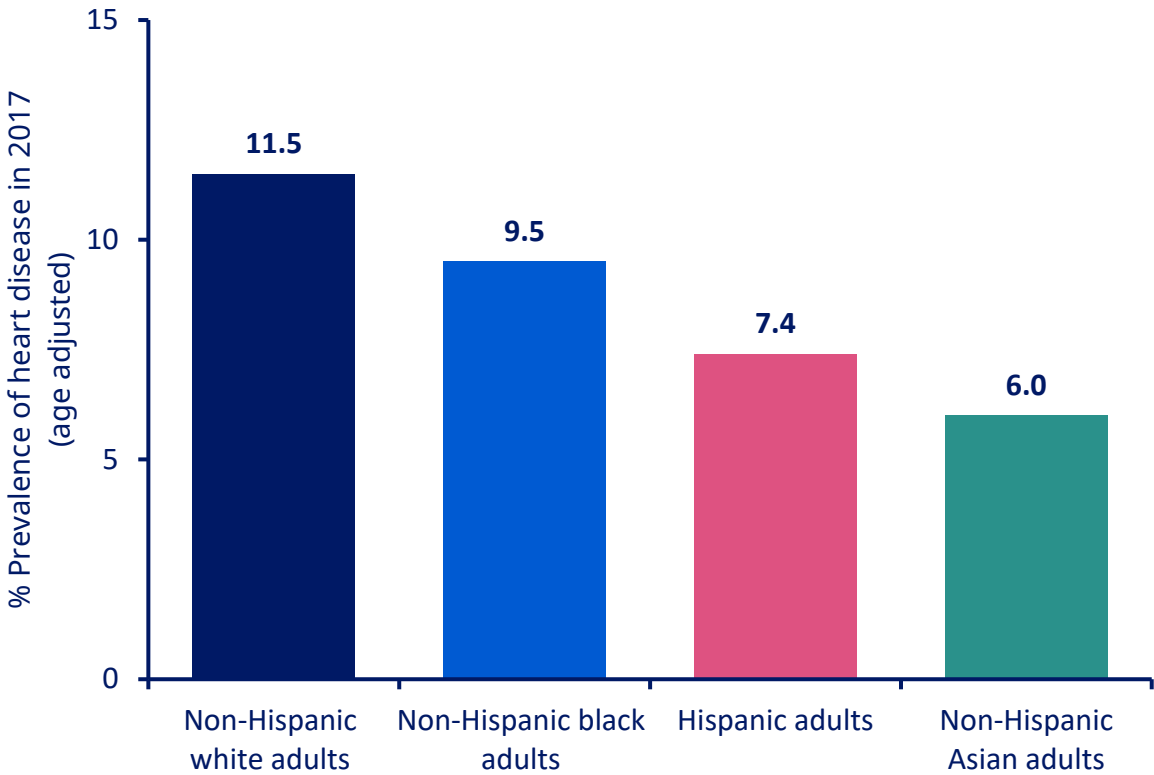
The proportion of **AMI hospitalizations attributable to young patients (35-54 years)** increased from 1995 to 2014² in the ARIC study



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)

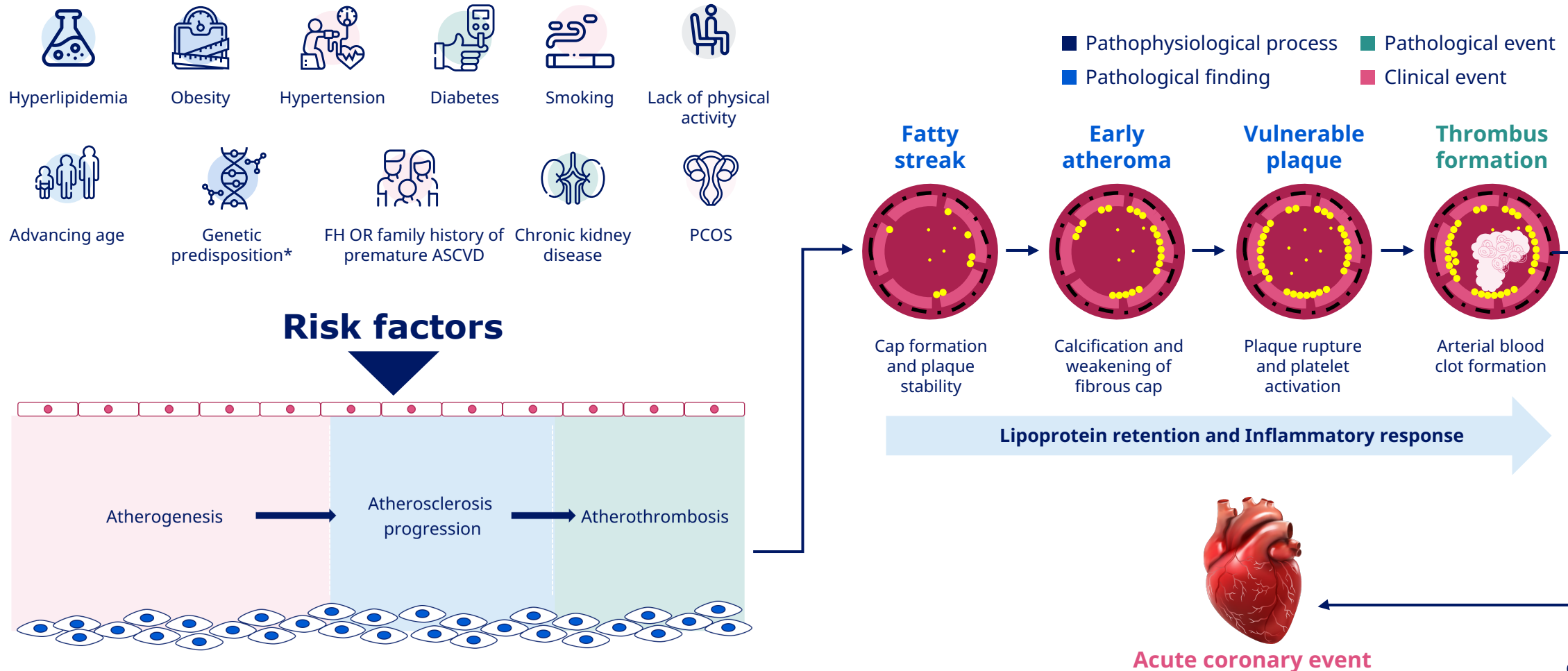


https://www.cdc.gov/nchs/hsu/spotlight/HeartDiseaseSpotlight_2019_0404.pdf Accessed on 1 December 2021



PATHOGENESIS OF ATHEROSCLEROSIS

Atherosclerotic plaque lifecycle ¹⁻⁵



ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia

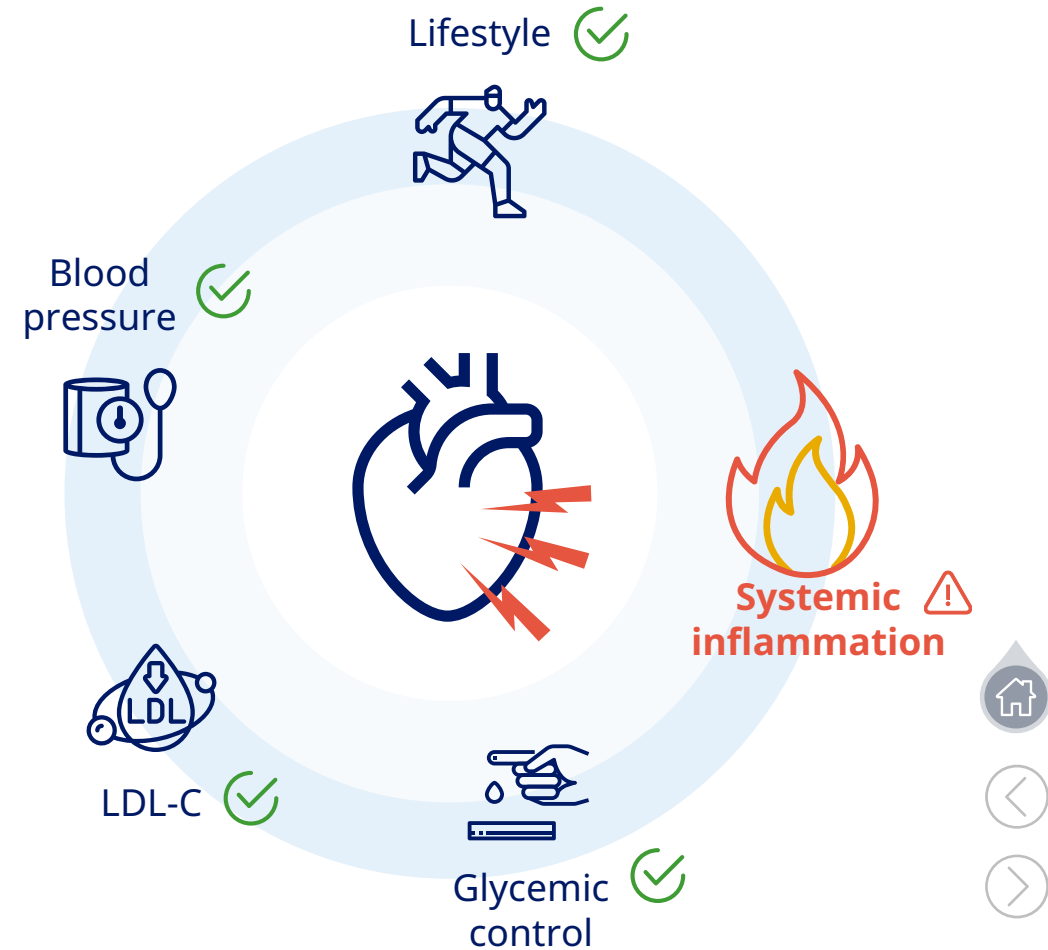
1. Herrington W et al. *Circ Res* 2016;118:535–546; 2. Agrawal S et al. *Am J Cardiol.* 2017;119(10):1532–1541; 3. Hudspeth B. *Am J Manag Care.* 2018;24(13 Suppl):S268–S272; 3. Handelsman Y et al. *Endocr Pract.* 2020;26(No.10); 4. Grundy SM et al. *Journal of the American College of Cardiology.* 2019;73(24). 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 events²
- The most widely used marker of this pathway is **hsCRP**²

Residual inflammatory risk is classified as levels of hsCRP ≥ 2 mg/L³



GUIDELINE-BASED TREATMENT APPROACHES FOR CVD

Managing risk factors to reduce ASCVD risk



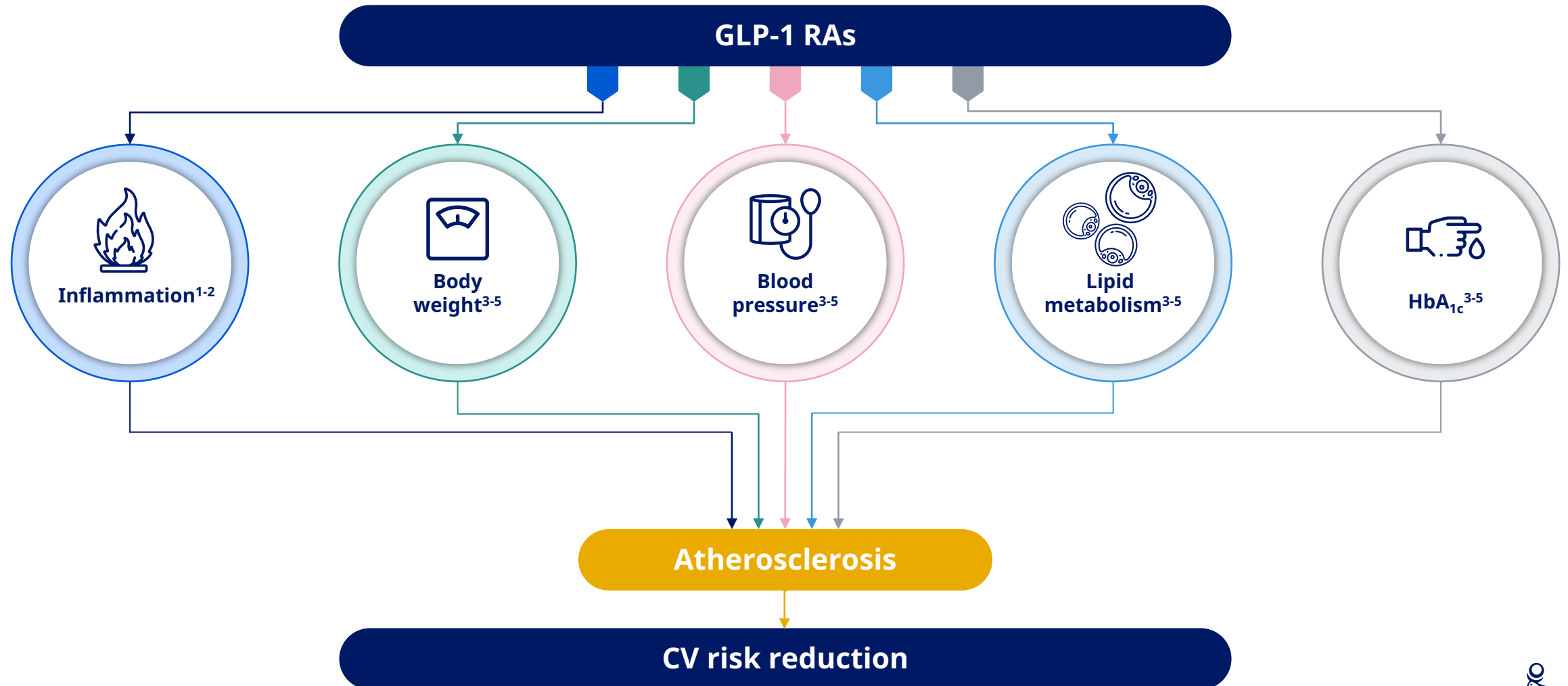
Product classes in highlighted boxes are discussed in this section

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.

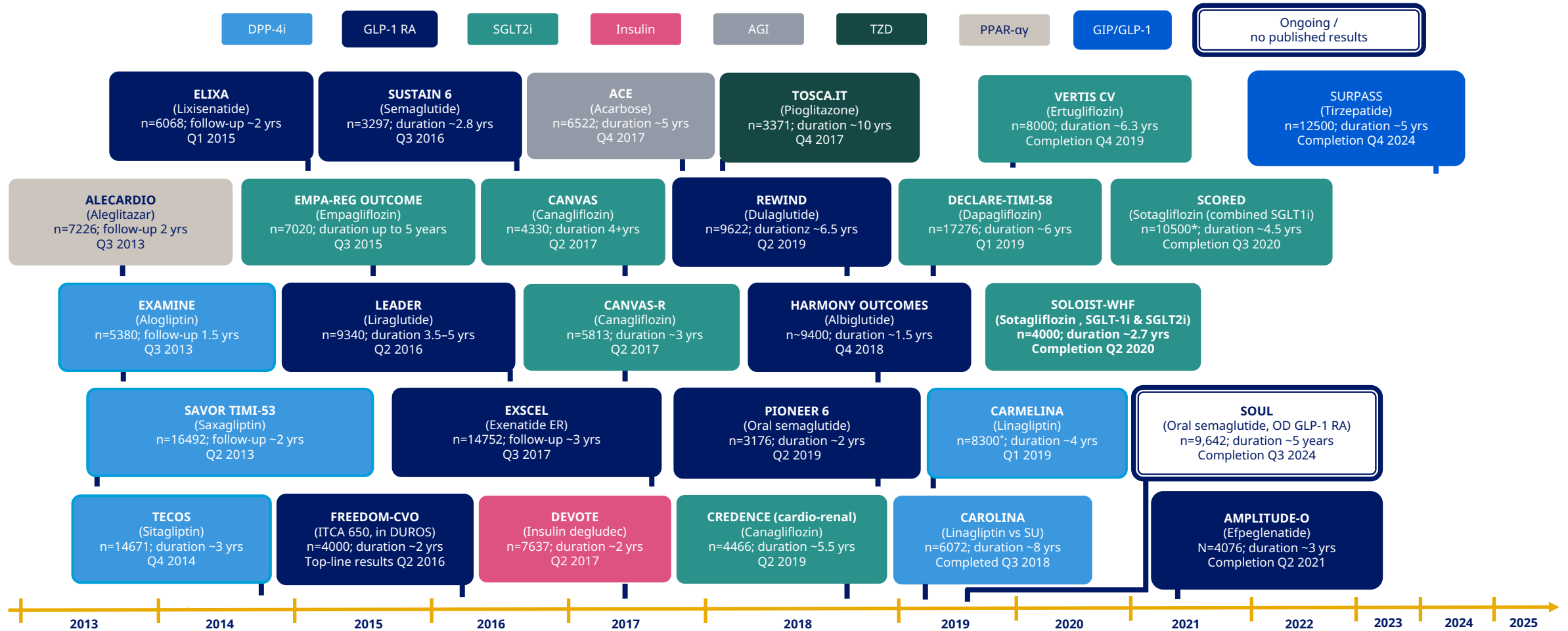


Potential mechanisms of CV risk reduction by GLP-1 RAs



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



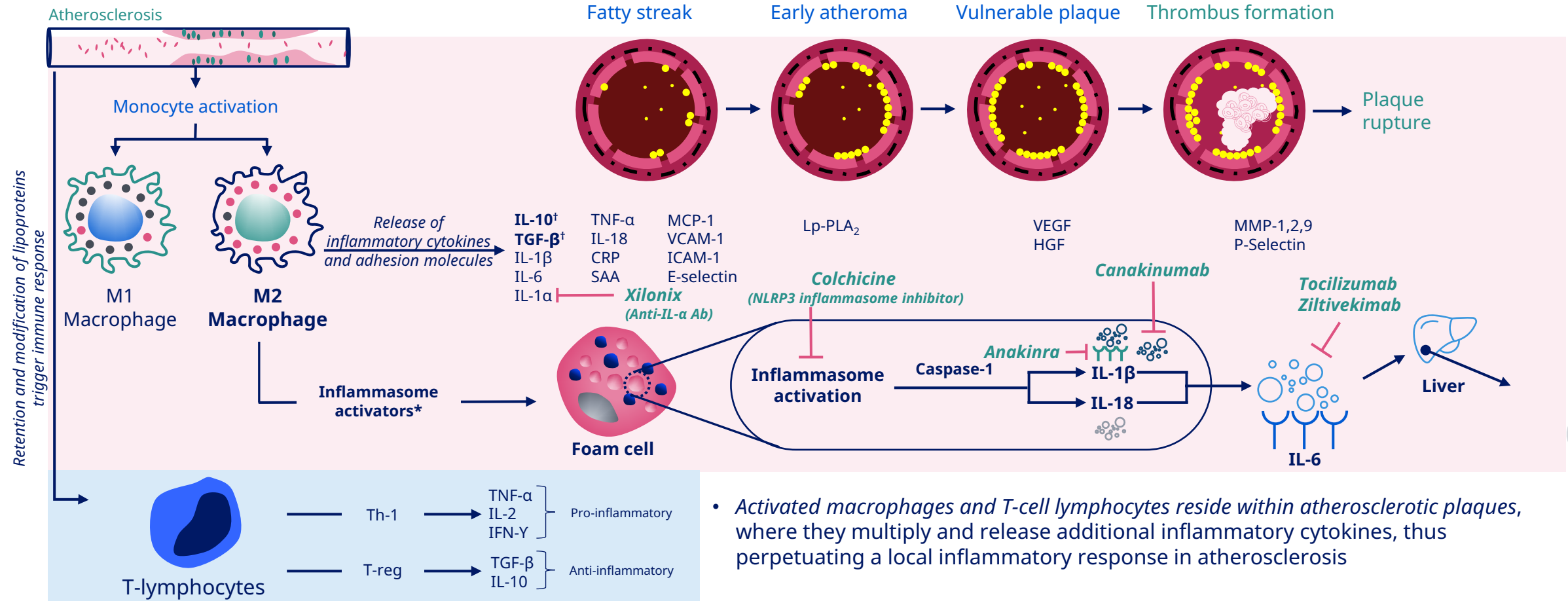
*Estimated enrolment;

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-α, 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



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. Montarelli 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 \geq 2 mg/L	LDL-C \geq 100 mg/dL	No simple biomarker	TG \geq 150 mg/dL	Lp(a) \geq 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; HbA_{1c}, 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.



