NOVEL APPROACHES IN PREVENTIVE CARDIOLOGY

Prepared by **Dr. Sidhartha Mullapudi**, DrNB (Cardiology), MD (General Medicine)
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I THE CARDIOVASCULAR-KIDNEY-METABOLIC (CKM) PARADIGM AND PREVENT EQUATIONS

- **The AHA CKM Syndrome Framework (Ndumele et al., *Circulation* 2023):** Contemporary preventive cardiology has shifted from managing isolated risk factors in silos to staging and treating the interconnected **Cardiovascular-Kidney-Metabolic (CKM) Syndrome** across **Stages 0 to 4** (Stage 0: no risk factors; Stage 1: excess/dysfunctional visceral adiposity; Stage 2: metabolic risk factors [T2DM, HTN, hypertriglyceridemia] or moderate-to-high-risk CKD; Stage 3: subclinical ASCVD/HF [CAC >0 or elevated NT-proBNP/troponin]; Stage 4: clinical CVD).
- **The AHA PREVENT Risk Equations (2023/2024):** Replaces the 2013 Pooled Cohort Equations (PCE) by removing race, starting risk estimation at **age 30 years** (estimating both **10-year and 30-year** risk of total CVD, ASCVD, and Heart Failure), and integrating **eGFR and urine albumin-to-creatinine ratio (uACR)** alongside **HbA1c** and social deprivation indices.
- **Incretin-Based Cardioprotection (GLP-1 and Dual GIP/GLP-1 Receptor Agonists):**
  - **SELECT Trial (*NEJM* 2023 — Semaglutide):** In 17,604 patients with established CVD and overweight/obesity (**BMI 27 kg/m2 or greater**) **without diabetes**, subcutaneous **Semaglutide (2.4 mg weekly)** reduced 3-point MACE (CV death, non-fatal MI, or non-fatal stroke) by **20 percent (HR 0.80)**, establishing GLP-1 receptor agonists as foundational cardiovascular secondary-prevention agents independent of glycemia.
  - **STEP-HFpEF (2023), FLOW (2024), and SUMMIT (2024 — Tirzepatide) Trials: Semaglutide** improved symptoms/6MWD in obese HFpEF (**STEP-HFpEF**) and reduced major kidney disease progression and CV death by 24 percent in diabetic CKD (**FLOW**), while the dual GIP/GLP-1 agonist **Tirzepatide** reduced the composite of CV death or worsening heart failure events by **38 percent** in obese HFpEF (**SUMMIT Trial**, *NEJM* 2024).
  - **SGLT2 Inhibitors and Non-Steroidal MRAs (Finerenone): Empagliflozin and Dapagliflozin** (**EMPA-KIDNEY, DAPA-CKD**) and the selective non-steroidal MRA **Finerenone** (**FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF** in HFmrEF/HFpEF, *NEJM* 2024) halt cardiorenal progression and prevent heart failure hospitalizations across the CKM spectrum.

II ADVANCED LIPID, GENETIC SILENCING AND ANTI-INFLAMMATORY THERAPIES

- **Small Interfering RNA (siRNA) Against PCSK9 (Inclisiran):** Conjugated with **Triantennary N-Acetylgalactosamine (GalNAc)** for selective hepatocyte uptake via asialoglycoprotein receptors, **Inclisiran** degrades *PCSK9* mRNA via the RISC complex. Dosed subcutaneously on **Day 1, Month 3, and every 6 months thereafter**, it provides sustained **~50 percent LDL-C reduction** (**ORION-9, -10, -11** trials; Phase III **VICTORION-2 PREVENT** and **ORION-4** MACE outcome trials ongoing).
- **ATP Citrate Lyase Inhibition (Bempedoic Acid — CLEAR Outcomes Trial, *NEJM* 2023):** Oral prodrug activated exclusively in the liver by **ACSVL1** (absent in skeletal muscle, avoiding myalgia) that inhibits cholesterol synthesis upstream of HMG-CoA reductase; reduced 4-point MACE by **13 percent** (and MI by 23 percent) in statin-intolerant patients.
- **Targeting Lipoprotein(a) [Lp(a)]:**
  - **Antisense Oligonucleotide (Pelacarsen) vs. Next-Generation siRNAs (Olpasiran, Zerlasiran, Lepodisiran) and Oral Muvalaplin:** While the Phase III **Lp(a)HORIZON Trial** of **Pelacarsen** (80% Lp(a) reduction) announced in September 2026 that it **did not reach statistical significance for its primary 4-point MACE endpoint**, deeper Lp(a) suppression (95 to 99 percent reduction) with quarterly/biannual **siRNAs** is being tested in ongoing Phase III outcome trials (**OCEAN(a)-Outcomes** with **Olpasiran** and **ACCLAIM-Lp(a)** with **Lepodisiran**), alongside the oral small-molecule Lp(a) assembly inhibitor **Muvalaplin** (**KRAKEN Trial**).
  - **RNAi for Resistant Hypertension and Hypertriglyceridemia:** Biannual subcutaneous **Zilebesiran** (siRNA silencing hepatic **angiotensinogen**; **KARDIA-1, KARDIA-2, KARDIA-3**) and **Olezarsen / Plozasiran** (targeting **APOC3**) or **Zodasiran** (targeting **ANGPTL3**).
  - **Residual Inflammatory Risk Targeting:** Low-dose **Colchicine (0.5 mg daily)** (**COLCOT** and **LoDoCo2** trials; **Class IIa** in the 2024 ESC Chronic Coronary Syndromes Guidelines) targets the **NLRP3 inflammasome / IL-1beta / IL-6** pathway in patients with chronic atherosclerotic disease.

Novel Preventive Pillar	Target & Mechanism	Key Clinical Trial / Evidence	Primary Preventive Impact
Semaglutide / Tirzepatide	GLP-1 RA / Dual GIP-GLP-1 RA	**SELECT** (2023), **FLOW** (2024), **SUMMIT** (2024)	**20% MACE reduction** in non-DM obesity (**SELECT**); **38% CV death/HF reduction** in obese HFpEF (**SUMMIT**)
Bempedoic Acid	Hepatic ATP Citrate Lyase (ACL) inhibitor (ACSVL1 prodrug)	**CLEAR Outcomes** (*NEJM* 2023)	**13% 4-point MACE reduction** (23% MI reduction) in statin-intolerant primary/secondary prevention
Inclisiran	GalNAc-conjugated *PCSK9* siRNA	**ORION-9/10/11**; **VICTORION-2 PREVENT** (ongoing)	**~50% sustained LDL-C reduction** with **biannual dosing**, overcoming daily pill non-adherence
Lp(a) RNA Therapeutics	*LPA* mRNA ASO (Pelacarsen) & siRNAs (Olpasiran, Lepodisiran)	**Lp(a)HORIZON** (neutral MACE, Sept 2026); **OCEAN(a)-Outcomes** (ongoing)	80–98% Lp(a) reduction; testing whether ultra-deep siRNA suppression reduces MACE
Low-Dose Colchicine (0.5 mg)	Tubulin / NLRP3 inflammasome inhibitor	**COLCOT** (2019), **LoDoCo2** (2020)	**23–31% MACE reduction** in chronic CAD (**Class IIa** in 2024 ESC CCS Guidelines)

III PRECISION IMAGING AND GENOMIC PLAQUE CHARACTERIZATION

- **Coronary Artery Calcium (CAC) and AI-Enabled Quantitative Coronary CTA (AI-QCT):** Moves risk stratification from population probability equations to **direct visualization of individual atherosclerotic plaque burden**:
- **High-Risk Vulnerable Plaque Features on CCTA:** Identifies **Low-Attenuation Plaque (necrotic lipid core <30 Hounsfield Units)**, **Positive Vessel Remodeling (remodeling index >=1.1)**, **Spotty Calcification**, and the **Napkin-Ring Sign** (high-risk plaque features, particularly low-attenuation plaque, predicted future MI independent of stenosis severity in the **SCOT-HEART** and **PROMISE** trials).

- **Perivascular Fat Attenuation Index (FAI):** CT measurement of perivascular adipose tissue inflammation around the proximal coronary arteries (**CRISP-CT / ORFAN** studies), identifying inflamed coronary arteries prior to plaque rupture.
- **Polygenic Risk Scores (PRS):** Aggregates the weighted effect of millions of common SNPs to identify young individuals in the **top 8 percent of genetic risk** (who carry a **3-fold or greater CAD risk**, equivalent to monogenic Familial Hypercholesterolemia) decades before clinical events occur.

IV DIGITAL HEALTH AND WEARABLE DIAGNOSTICS

- **Validated Out-of-Office BP and Wearable PPG/ECG:** While **cuff-based HBPM and 24-hour ABPM** remain the **2024 ESC Guideline Class I standard** (as cuffless photoplethysmography [PPG] smartwatch blood pressure devices are **not yet recommended** for clinical decision-making due to calibration drift), smartwatch PPG with single-lead ECG confirmation is validated for **opportunistic Atrial Fibrillation detection** (**Apple Heart Study, Huawei Heart Study**) and is being tested for rhythm-guided anticoagulation (**REACT-AF Trial**).

V PRACTICAL CONSIDERATIONS IN THE INDIAN CLINICAL CONTEXT (CSI / LAI CONSENSUS)

- **Addressing Early-Onset Malignant CAD in South Asians:** Because Indians develop first myocardial infarction 8 to 10 years earlier than Western populations with high rates of visceral adiposity ("thin-fat" phenotype), insulin resistance, and elevated **Lipoprotein(a)**, the **Lipid Association of India (LAI) and CSI** recommend starting formal ASCVD risk screening by **age 20 to 30 years**, measuring **Lp(a) at least once in every adult**, and targeting **LDL-C less than 50 to 55 mg/dL** in very-high-risk and **less than 30 to 40 mg/dL** in extreme-risk secondary prevention patients.

KEY REFERENCES

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