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Cardiometabolic-Based Chronic Disease, Addressing Knowledge and Clinical Practice Gaps

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Abstract

In the second part of this *JACC* State-of-the-Art Review, an early and sustainable preventive care plan is described for cardiometabolic-based chronic disease. This plan can improve cardiometabolic health by targeting early mechanistic events to decrease the risk for certain cardiovascular diseases (e.g., coronary heart disease, heart failure, and atrial fibrillation). Included are various prevention modalities, intensive lifestyle interventions, pharmacotherapy and cardiovascular outcome trial evidence, and bariatric/metabolic procedures. A tactical approach of implementing published clinical practice guidelines/algorithms for early behavioral, adiposity, and dysglycemia targeting is emphasized, as well as relevant educational and research implications. (J Am Coll Cardiol 2020;75:539–55) © 2020 by the American College of Cardiology Foundation.

Keywords

adipokines; adiposity; atherosclerosis; atrial fibrillation; cardiometabolic; cardiomyopathy; cardiovascular; chronic disease; dysglycemia; health; insulin; obesity; resistance; type 2 diabetes

In the first part of this *JACC* State-of-the-Art Review, a cardiometabolic-based chronic disease (CMBCD) model is described. This model is substantiated by scientific evidence and aggregated clinical experience, and configured with the intent to expose upstream clinical primary and metabolic drivers that are affected by modifiable risk factors and serve

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APPENDIX For a supplemental table, please see the online version of this paper.

as interventional targets to prevent downstream cardiovascular disease (CVD). The 3 upstream primary drivers of CMBCD are genetics, environment, and behavior. The 2 upstream metabolic drivers of CMBCD are adiposity and dysglycemia. These metabolic drivers interact at the level of insulin resistance, and have been previously configured as adiposity-based chronic disease (ABCD) and dysglycemia-based chronic disease (DBCD) (1,2) (Figure 1). In contrast with practice standards that focus on downstream CVD presentations and complications, which are associated with greater disease burden and intensive therapies, the CMBCD model is designed to facilitate earlier and sustainable interventions, primarily with structured lifestyle change and judicious pharmacotherapy.

The question remains: “Can targeting early metabolic events related to adiposity and dysglycemia effectively prevent later stages of CMBCD?” The answer is that success can occur by elucidating and modeling complex interactions of these primary and metabolic drivers (1–6). Prevention of disease progression and CVD events in patients with CMBCD has been challenging for multiple reasons. Care is often fragmented between cardiologists and endocrinologists, addressing the cardiovascular and metabolic dimensions of disease, respectively. Although cardiologists may be aware of the importance of metabolic factors for future CVD events, they are frequently hesitant to view management of dysglycemia and diabetes as within their scope. Finally, patients may not come to medical attention at early stages of CMBCD, where intensive prevention efforts may be most efficacious. There are 4 CMBCD stages: risk development, pre-disease, disease, and complications, which incorporate key mechanisms and lead to 3 specific CVD scenarios: coronary heart disease (CHD), heart failure (HF), and atrial fibrillation (AF). Although CHD, HF, and AF are viewed as 3 health outcomes representative of the atherosclerotic-ischemic, hemodynamic-myocardial, and electrophysiological processes frequently comorbid with CMBCD, cerebrovascular events and peripheral artery disease are important vascular outcomes outside the scope of this review. A CMBCD preventive care plan incorporates screening in stage 1, aggressive case finding in stage 2, and diagnostic testing in stages 3 and 4, followed by appropriate intervention that can slow or halt disease progression. This review focuses on adiposity and dysglycemia as drivers of risk in CMBCD. As a result, this review is limited to therapies and recent trial evidence supporting the use of newer agents to address dysglycemia and, secondarily, weight loss. Although critical to managing the risk of CVD events in CMBCD, the role of antihypertensive and lipid-lowering therapies in CMBCD is outside the scope of this review.

In the second part of this *JACC* State-of-the-Art Review, clinical management of CMBCD is described that concentrates on a preventive care framework. The discussion that follows is based on primordial prevention of cardiovascular risk development in the general population (stage 1), primary prevention of disease in patients at risk and with pre-disease (stage 2), secondary prevention of disease progression in patients with early disease (stage 3), and tertiary prevention of worsening symptom burden in patients with late disease (stage 4; the prevailing care plan today) (7–11). Of note, multiple prevention types, including quaternary prevention (the prevention of over-medicalization), are applied at each CMBCD stage, depending on pathophysiological targets and clinical goals.

MODIFIABLE RISKS

CORONARY HEART DISEASE.

Traditional risk factors for CHD are family history of premature disease (men age <55 years; women age <65 years), age (men age ≥45 years; women age ≥55 years), male sex, hypertension, dyslipidemia, smoking, and diabetes (12,13). Nontraditional risk factors for CHD include insulin resistance, metabolic syndrome (MetS), inflammation, autoimmune disease, human immunodeficiency status, gestational syndromes, psycho-social stressors, various social determinants, and other comorbidities (12). Another nontraditional risk factor for atherosclerosis may be somatic mutations leading to clonal hematopoiesis of indeterminate potential, which may be modifiable with cholesterol-lowering or inflammation-targeted medication (14). Validated risk scores include the American College of Cardiology (ACC)/American Heart Association (AHA) ASCVD Pooled Cohort Risk Calculator, European Systematic Coronary Risk Evaluation algorithm, QRISK calculator, Prospective Cardiovascular Münster model, and the Reynolds Risk Score. Biomarkers of risk include high-sensitivity C-reactive protein (hsCRP) and atherogenic lipid markers including lipoprotein(a). Noninvasive tests (e.g., ankle-brachial index and coronary artery calcium score) can also contribute valuable information to guide decision-making (12). However, adequately powered clinical trials validating many of these nontraditional biomarkers and tests are limited (15).

Levels of cardiorespiratory fitness also predict CHD risk (with incidence rates lowered by 20% for each maximally achieved metabolic equivalent of task unit) (16), incident coronary artery calcification (17), and CVD events (18). Cardiorespiratory fitness may also help explain discrepancies observed with metabolically healthy obese (modestly elevated body mass index [BMI] with low CHD risk) and metabolically unhealthy lean (low BMI and high CHD risk) profiles (19).

HEART FAILURE.

Various metabolic biomarkers and risk factors have been identified in HF (e.g., fasting proinsulin, apolipoprotein B/A1 ratio, serum β-carotene [20], IL-6, hsCRP, macroalbuminuria, obesity [21,22], diabetes [22], tobacco use, and HTN [22,23]). Patients with overweight or mild obesity may have lower risk for HF than those with lower or higher body weight classifications, but this obesity paradox only persists in women after adjusting for cardiorespiratory fitness and other factors, and appears to result from reverse causality (24). Leisure time and more structured physical activity improve cardiorespiratory fitness, cardiac structure and function, and HF incidence and hospitalization risk (25–27). In fact, for every metabolic equivalent of task unit increment, there is a 21% decrease in the multivariable adjusted risk for new-onset HF (28). Also, cardiorespiratory fitness, expressed as the cross product of BMI and the 6-min walk distance, is inversely proportional to HF mortality (29).

ATRIAL FIBRILLATION.

There are 2 primary goals in the management of AF: symptomatic relief with rhythm control, and prevention of stroke and thromboembolic events. Weight reduction strategies

can improve not only the quality of life in patients with obesity, but also the clinical burden of AF (30,31). Prevention of AF in type 2 diabetes (T2D) may also succeed with an angiotensin-converting enzyme inhibitor or angiotensin-2 receptor blocker as part of upstream therapy (32).

In the Framingham Heart Study and other cohort studies, obesity was associated with approximately 50% greater risk for AF, with each BMI unit increase conferring a 4% increased AF risk (33,34). Clinical outcomes and mortality associated with AF were also adversely affected by abnormal adiposity (35–38). Both weight loss and increased cardiorespiratory fitness correlated with improved AF outcomes (39–44). Weight loss and risk factor modification targeting sleep apnea, hypertension (HTN), hyperlipidemia, glucose intolerance, and alcohol and tobacco use are included as new recommendations for patients with overweight/obesity and AF in the 2019 AHA/ACC/Heart Rhythm Society updated guidelines for AF management (45).

PREVENTION TYPES

PRIMORDIAL PREVENTION IN STAGE 1 CMBCD.

Primordial prevention applies to stage 1 ABCD, DBCD, and CMBCD. In ABCD, primordial prevention targets potential pathophysiological events that can cause abnormalities in adiposity, including increased adipose tissue mass, that lead to insulin resistance. In DBCD, primordial prevention mitigates abnormal adiposity and insulin resistance, insulin secretory exhaustion as β-cells can no longer compensate for insulin resistance, and adverse effects of hyperglycemia that exacerbate CMBCD progression. It should not be surprising that population-based societal measures, such as improving the built environment and health messaging, as well as screening for unhealthy behaviors and lifestyles early in life, are appropriate and advised in this setting.

Lifestyle interventions on community-based cohorts have been shown to improve the metabolic health of obese children, and the longitudinal FAMILIA (Family-Based Approach in a Minority Community Integrating Systems–Biology for Promotion of Health) studies targeting children ages 3 to 5 are underway to focus on improving cardiovascular risk factors throughout the lifecycle (46,47). In a 2017 updated systematic review by the U.S. Preventive Services Task Force on behavioral counseling for healthy eating and physical activity in patients without CVD risk factors, even modest changes in self-reported healthy activities, particularly in primary care settings, were associated with significant and potentially sustainable, patient-centered, cardiometabolic outcomes (48).

Human and animal studies have demonstrated the effects of various environmental exposures (over-nutrition/obesity, undernutrition, paternal factors, toxicants, stress, physical activity, longevity, and assisted reproductive technologies) on peri-conceptional and in utero development, adiposity and dysglycemia drivers, and CVD outcomes, moving the potential preventive target (e.g., optimizing nutrition during pregnancy) to even earlier in a person’s life (49–52). Healthy eating patterns, such as the DASH (Dietary Approaches to Stop Hypertension) diet (increased whole grains, fruits and vegetables, pulses [edible seeds of legumes: beans, lentils, dry peas, chickpeas, and so on], and nuts, with moderate intake of

low-fat dairy and decreased red/processed meats and sweetened beverages), are associated with improved cardiometabolic risk profiles, especially reducing hypertension in adults (53), but also preventing abnormal adiposity in children (54).

PRIMARY PREVENTION IN STAGE 2 CMBCD.

Primary prevention addresses stage 2 ABCD (progression of measurable abnormal adiposity to diagnostic thresholds), stage 2 DBCD (progression of hyperglycemia from pre-diabetes to T2D diagnostic criteria), and stage 2 CMBCD (progression of ABCD and DBCD metabolic drivers to early, detectible CVD). Initiated in 2015, ratified by health care professionals from 38 nations, and published in 2018, the Berlin Declaration proposed actionable policies for primary prevention focused on stage 2 DBCD in the context of decreasing CVD: early detection, prevention, early control, and fair access to high-quality interventions, with essential inclusion of specialist care (55).

Aggressive case finding to detect pre-disease or disease based on the presence of risk factors is appropriate in stage 2 CMBCD. For example, various imaging modalities are available for case finding that can detect abnormal adiposity amounts and distributions, correlating with MetS and CVD risk (56). This is relevant because certain interventions can mitigate the progression of ectopic adiposity to CVD, such as progressive resistance training, which reduces magnetic resonance-quantified epicardial and pericardial fat volume (57). These primary prevention concepts have been recently addressed in the 2019 ACC/AHA guidelines on CVD (58).

SECONDARY PREVENTION IN STAGE 3 CMBCD.

Individual patient-level secondary prevention strategies are implemented in stage 3 CMBCD when early CVD has been demonstrated by various diagnostic tests or a clinical event, with a goal of preventing disease progression of disease or a second event. More specifically, secondary prevention in CVD aims to reduce subsequent events and even mortality by addressing underlying pathophysiology (i.e., residual cholesterol, inflammatory, and thrombotic risks) (59). Moreover, in the CMBCD model, evidence is provided that secondary prevention also applies to specific metabolic drivers. In stage 3 ABCD, this is accomplished by decreasing the detrimental effects of abnormal adiposity on the cardiovascular system, and in stage 3 DBCD, by decreasing the detrimental effects of insulin resistance and/or hyperglycemia (pre-diabetes or T2D) on macrovascular/microvascular complications.

TERTIARY PREVENTION IN STAGE 4 CMBCD.

The majority of current preventive strategies take the form of tertiary prevention. These are interventions in the later course of disease, when symptom burdens and disability are more significant, leading to the usual patient presentation with complaints, so efforts must concentrate on management of complications to improve longevity and quality of life. Tertiary prevention addresses stage 4 ABCD (complications due to abnormal adiposity), stage 4 DBCD (vascular complications due to insulin resistance and/or hyperglycemia [pre-diabetes or T2D]), and stage 4 CMBCD (progressive and symptomatic CHD, HF, and/or AF).

QUATERNARY PREVENTION IN ALL CMBCD STAGES.

Quaternary prevention is a relatively new concept, first presented in 1986 as an intervention to identify patients with over-medicalization to deescalate these actions, avoid new but unnecessary or net harmful interventions, and overall, to behave in an ethical manner (60,61). In ABCD, DBCD, and CMBCD, quaternary prevention is effectively implemented at all stages by prioritizing early lifestyle interventions, and when necessary, judicious pharmacotherapy and procedures. Table 1 summarizes the features of the 5 prevention types discussed above.

INTERVENTIONAL MODALITIES

INTENSIVE LIFESTYLE CHANGE.

Eating patterns and physical activity are often evaluated together as part of a comprehensive lifestyle intervention to decrease the risks associated with CMBCD. Lifestyle medicine—the nonpharmacological and nonsurgical management of chronic disease—encompasses these interventions (Table 2) (62). Achieving a healthy weight (i.e., sufficient weight loss in those with an abnormally increased BMI to prevent or reverse ABCD complications) is a critical objective of lifestyle intervention. Current guideline recommendations and summary Level of Evidence (LOE) recommendations for lifestyle medicine interventions to prevent CVD in patients with diabetes are provided in Online Table 1.

The Diabetes Prevention Program (n > 3,200 with pre-diabetes with about 3-year follow-up) found that randomization to an intensive lifestyle intervention, with >7% weight reduction on a low-calorie, low-fat diet and incorporating moderate intensity physical activity ≥150 min/week, was associated with approximately 60% (hazard ratio [HR]: 0.42; 95% confidence interval [CI]: 0.44 to 0.52) and 40% (HR: 0.61; 95% CI: 0.49 to 0.76) lower incidence of T2D compared with placebo and metformin, respectively (63).

The Mediterranean diets describe a set of eating patterns with distinct foods, associated with decreased cardiometabolic risk and characterized by relatively high nutrient density, fiber, mono-unsaturated and n-3 polyunsaturated fatty acid, and polyphenol content (64). Adherence with this eating pattern is associated with decreased risk for MetS and other cardiometabolic risk factors, reduced inflammation and hepatic steatosis, and improved renal function (64). In an umbrella evaluation of the Mediterranean diet eating pattern, Galbete et al. (65) affirmed that despite substantial heterogeneity of published meta-analyses, a higher adherence with a Mediterranean eating pattern was associated with lower incidence of mortality from T2D and CVD.

Vegetarian eating patterns were associated with decreased CVD risks, Framingham risk score, and development of MetS (66). A vegan eating pattern, compared with the AHA diet, was found to lower hsCRP levels in patients with CHD (67).

The largest and most extensive trial of physical activity and CVD morbidity and mortality among patients with T2D was the Look AHEAD (Action for Health in Diabetes) trial, which randomized 5,145 patients with T2D to an intensive lifestyle intervention, including caloric restriction, pre-specified caloric intake of fats and protein, meal replacements, and ≥175

min/week of moderate-intensity physical activity by week 26, or to usual care with diabetes support and education (68). Despite weight loss of nearly 9% in the intervention group, and greater improvements in fitness and CVD risk factors after nearly 10 years of follow-up, the trial was stopped early for futility to reduce CVD events (403 with intervention vs. 418 with usual care; HR: 0.95; 95% CI: 0.83 to 1.09; p = 0.51) (68).

Earlier data from the Steno-2 (Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria) study randomized 160 patients with T2D and albuminuria to either conventional CVD risk factor management from their general practitioner or to multifactorial intervention over-seen by a diabetes center project team (69). The trial intervention included smoking cessation courses, restricted total and saturated fat intake, light-to-moderate exercise 3 to 5 days/week, and a stepwise intensive regimen that included more stringent control of blood glucose (target A1C <6.5%) and blood pressure (BP) (target <140/85 mm Hg for most of the study), along with lipid-lowering therapy and an angiotensin-converting enzyme inhibitor, regardless of BP (69,70). Patients randomized to the intensive treatment arm had a 53% (HR: 0.47; 95% CI: 0.24 to 0.73) reduction in the composite outcome of CVD death, nonfatal myocardial infarction (MI) or stroke, revascularization, or amputation, along with significant reductions in microvascular endpoints (69).

Various studies have focused on the nutritional component of intensive lifestyle intervention. Recently, the results of the DiRECT (Primary Care-Led Weight Management for Remission of Type 2 Diabetes) trial were published demonstrating 1-year (71) and 2-year (72) effects of total dietary replacement (825 to 853 kcal/day for 3 to 5 months and then stepped food reintroduction over 2 to 8 weeks, with structured support), compared with best practice, in patients with T2D. At 1 year, 24% of subjects in the treatment arm lost >15 kg (compared with none in the control arm), and 46% had T2D remission (compared with only 4% in the control arm) (71). Remission of T2D was related to the amount of weight lost (71). These significant beneficial effects affirm the need for structured lifestyle change in all patients with T2D and abnormal adiposity to prevent the event cascade that defines CMBCD progression.

Although moderate alcohol use (≤1 drink/day for women and 1 to 2 drinks/day for men) may be part of a healthy lifestyle, evidence for cardiometabolic benefit is limited (73). Red wine before or with the evening meal has been associated with improved long-term cardiovascular outcomes in some observational studies. However, data from the Saku study (74) in Japan demonstrated a positive association between alcohol consumption and the incidence of both insulin resistance and impaired insulin secretion. In a recent systematic analysis of the global burden of disease for 195 countries, the level of alcohol use that minimized harm across a broad range of health outcomes was *zero* (75). In the totality, nonusers should not be advised to begin drinking alcohol for CVD protection.

The Look AHEAD trial results were consistent with decades old scientific evidence on the benefit of and need to assess cardiorespiratory fitness (76,77). Strength training and cardiorespiratory fitness exert a magnitude of secondary prevention benefits similar to many pharmacotherapies (78). When offering lifestyle counseling, teasing out the subtle effects of

different physical activity levels, sedentary time, and sleep can be difficult. Using an isotemporal substitution analysis, Dumuid et al. (79) found that, of these variables, time spent engaging moderate-to-vigorous physical activity had the greatest beneficial impact on CVD outcomes.

PHARMACOTHERAPY.

The cardiovascular outcomes trials.—The evidence from cardiovascular outcomes trials (CVOTs) has been largely generated from the population of adults who have T2D and are at risk for atherosclerotic cardiovascular disease, and is based on the safety study experience of the newer medications.

The sodium-glucose cotransporter-2 inhibitors.

General mechanisms.: The sodium-glucose cotransporter-2 inhibitors (SGLT2i) decrease activity of the high-capacity, low-affinity SGLT2 receptor in the proximal tubule of the kidney, which is responsible for reabsorbing nearly 90% of filtered glucose (80). The activity of the SGLT2 is paradoxically increased in states of hyperglycemia, leading to enhanced glucose and sodium reabsorption (81). Four large CVOTs have been completed for SGLT2i in patients with T2D: empagliflozin (EMPA-REG OUTCOME [Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients] [82]), canagliflozin (CANVAS [CANagliflozin cardioVascular Assessment Study] [83] and CREDENCE [Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy] [84]), and dapagliflozin (DECLARE-TIMI 58 [Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events-Thrombolysis In Myocardial Infarction 58] [85]) (Table 3). Based on these CVOTs, the reduction in A1C between active and placebo arms was modest at only 0.1% to 0.6% (82–85), and therefore, is unlikely to account for the reduction in CVD events (86).

Analysis and comparisons of CVOT evidence.: Notably, all 4 of these CVOT were noninferior compared with placebo for cardiovascular safety (82–85). Additionally, EMPA-REG OUTCOME, CANVAS, and CREDENCE demonstrated reductions in a 3-point major adverse cardiac event (MACE) (CVD death, nonfatal MI, or nonfatal stroke) (82–84). DECLARE-TIMI 58 had 2 primary endpoints: a 3-point MACE and a 2-item composite of CVD death or hospitalization for heart failure (HHF) (85). In contrast to EMPA-REG OUTCOME and CANVAS, the 3-point composite MACE was not met in DECLARE-TIMI 58 (HR: 0.93; 95% CI: 0.84 to 1.03; p-superiority = 0.17) (85). However, in DECLARE-TIMI 58, there was a nearly 20% relative risk reduction in 1 of the primary endpoints—CVD death or HHF (HR: 0.83; 95% CI: 0.73 to 0.95; p-superiority = 0.005)—driven by a nearly 30% reduction in HHF (HR: 0.73; 95% CI: 0.61 to 0.88) (85). Consistent reductions in HHF and renal outcomes were observed in all 4 SGLT2i CVOT, but due to the pre-specified hierarchical testing plan in CANVAS, estimates for secondary outcomes were considered nonsignificant and exploratory only (83). Most recently, among 4,744 patients with heart failure and an ejection fraction <40%, dapagliflozin reduced heart failure or death from cardiovascular causes regardless of the presence or absence of diabetes (87).

Safety concerns with SGLT2i.: The SGLT2i were well tolerated in the CVOT with some notable, albeit infrequent, exceptions. Genital infections were more common with SGLT2i than with placebo in all 4 trials (82–85). However, these infections infrequently (<1%) resulted in study drug discontinuation (82–85). Importantly, CANVAS identified amputations and fractures, captured as adverse events of special interest, as new safety concerns at the time (83). Increased fractures or amputations have not been consistently demonstrated with either empagliflozin or dapagliflozin (82,85). Of note, results from a recent search of the U.S. Food and Drug Administration Adverse Event Reporting System supported current warnings that SGLT2i use is associated with increased risk for euglycemic ketoacidosis (88).

The glucagon-like peptide 1 receptor agonists.

General mechanisms.: The incretin pathway plays a key role in the physiological response to oral glucose intake (89). Glucagon-like peptide 1 is an incretin polypeptide secreted by the distal intestinal L cells in response to oral nutrient ingestion, having several downstream effects prior to its degradation by dipeptidyl peptidase-4 (90).

At present, all but 1 glucagon-like peptide 1 receptor agonist (GLP1ra) approved for the treatment of T2D are administered subcutaneously, and differ in structure and duration of effect (91), the exception being oral semaglutide (92). Exenatide and lixisenatide are derived from exogenous Gila monster venom, whereas the remaining 4 commercially available GLP1ra are modifications of the endogenous molecule. Large CVOT have been completed for 6 of the GLP1ra, all of which demonstrated noninferiority compared with placebo (Table 4) (93–98). To date, liraglutide, semaglutide, albiglutide, and dulaglutide (but not exenatide and lixisenatide) each demonstrated superiority in reducing MACE compared with placebo (93–98). However, only liraglutide has demonstrated reductions in both CVD and all-cause mortality (94).

Weight reduction.: The GLP1ra lowered weight significantly more than placebo, with semaglutide 1.0 mg/week lowering body weight up to nearly 4 kg more than placebo (95). Overall, the weight loss associated with GLP1ra use is more than the 0.8 to 2.0 kg weight loss observed in the SGLT2i CVOT (82–85). The weight loss associated with GLP1ra is likely due to multiple mechanisms, including reduced caloric intake, versus the glycosuric caloric loss, and other effects associated with SGLT2i use (99).

Analysis of CVOT evidence.: There have been 6 completed GLP1ra CVOT with nearly all patients (70% to 100%) having CVD (93–98). Of these, only LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) (liraglutide [94]), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) (semaglutide [95]), and HARMONY (Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease) (albiglutide [97]) demonstrated superiority of the GLP1ra for the composite 3-point MACE outcome. In addition, the REWIND (Researching cardiovascular events with a Weekly INcretin in Diabetes) trial investigated weekly dulaglutide on CVD outcomes, and is more representative of a typical, middle-aged general medicine practice

population, with an international scope, primarily women, and a higher proportion (69%) of patients without prior CVD (100). REWIND randomized 9,901 participants to receive dulaglutide or placebo. During a median follow-up of 5.4 years, the primary composite outcome occurred in 12.0% in the dulaglutide group, compared with 13.4% in the placebo group (HR: 0.88; 95% CI: 0.79 to 0.99; p = 0.026) (98). Recently, in PIONEER-6 (Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes), oral semaglutide demonstrated cardiovascular noninferiority to placebo but not superiority, indicating cardiovascular safety and possible efficacy for oral GLP1ra for reduction of cardiovascular events in T2D (92).

The reasons other GLP1ra, such as lixisenatide or exenatide, did not demonstrate superiority compared with placebo for reductions in MACE were possibly due to differences in enrolled patient populations, pharmacokinetics, and composite outcome definitions (86). The main results from REWIND indicating superiority over placebo for CVD event reduction support a class effect of GLP1ra improving outcomes for patients with T2D and CMBCD.

Safety concerns with GLP1ra.: The LEADER and SUSTAIN-6 trials demonstrated potential side effects associated with GLP1ra use, including the risk of retinopathy and acute gallstone disease (86). Other gastrointestinal adverse effects, including nausea/vomiting, have been reported in CVOT with liraglutide (94) and semaglutide (95); albiglutide was associated with more diarrhea but not nausea/vomiting (97), and the occurrence of adverse gastrointestinal events was significantly more common with dulaglutide than placebo (98).

Nuanced decision-making based on CVOT.—To date, all SGLT2i and GLP1ra CVOT data pertain to T2D, and initiating these agents is currently part of T2D comprehensive care, requiring long-term follow-up. The SGLT2i and GLP1ra CVOT also afford the opportunity to compare events in patients with T2D, with and without established CVD. In a recent systematic review and meta-analysis, Zelniker et al. (101) demonstrated that the benefits of SGLT2i were observed in patients with established CVD (p for interaction = 0.05). This meta-analysis studied patients across EMPA-REG, CANVAS, and DECLARE-TIMI 58, with the risk factor–only populations composed of patients from CANVAS and DECLARE-TIMI 58 (101).

Tables 5 and 6 summarize the evidence for SGLT2i and GLP1ra benefits on the presence or absence of established CVD and demonstrated that a reduction in 3-point MACE was only definitive in those with established CVD (a secondary prevention effect). In addition, SGLT2i reduced the risk of CVD death or HHF by 23% (HR: 0.77; 95% CI: 0.71 to 0.84; p < 0.0001), with a similar benefit in patients with and without established CVD, and with and without a history of HF (both primary and secondary prevention effects) (101).

In these recent CVOTs, it is worth noting that background therapy with statins, aspirin, or metformin was not mandated per trial protocol, but approximately 70% to 90% of participants across the SGTL2i and GLP1ra CVOTs were recorded as receiving these agents depending on study participant characteristics. Notably, this percentage is likely greater than recorded use of these agents in adults with T2D, with and without CVD treated in the community (102–104).

Other agents.—Metformin generally occupies a position as first-line pharmacotherapy for primary prevention in stage 2 DBCD (pre-diabetes) or secondary prevention in stage 3 DBCD (T2D), but this is being reconsidered in patients with high-risk CMBCD, such as with HF (where metformin is associated with decreased mortality by retrospective analysis [105], but no demonstrable benefit based on meta-analyses [106]).

The dipeptidyl peptidase-4 inhibitors (DPP4i) augment levels of endogenously produced GLP1 and have also been studied in CVOT involving patients with T2D. Potential targets of DPP4i mirror those of GLP1ra in CMBCD. To date, 5 DPP4i CVOT have been completed—SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis In Myocardial Infarction 53) (107), EXAMINE (EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome) (108), TECOS (Evaluating Cardiovascular Outcomes with Sitagliptin) (109), CARMELINA (CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin) (110), and CAROLINA (CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes) (111)—in which saxagliptin, alogliptin, sitagliptin, linagliptin, and linagliptin versus glimepiride, respectively, were noninferior for MACE, but none satisfying superiority to placebo criteria in reducing CVD events (Table 7).

Hypertriglyceridemia is a MetS trait that can affect the progression of CMBCD. In REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial) (112,113), patients with persistently elevated triglycerides in the setting of atherosclerosis (71%) or diabetes (29%), and despite statin dosing, experienced decreased first, subsequent, and total ischemic CVD events with icosapent ethyl, 2 g twice daily, compared with placebo control subjects.

Obesity medications used with lifestyle interventions produce greater weight loss and durable effects when compared with lifestyle alone (114). Five U.S. Food and Drug Administration–approved medications are currently available for the chronic treatment of obesity: orlistat, lorcaserin, phentermine/topiramate ER, naltrexone ER/bupropion ER, and liraglutide 3 mg. These medications are effective in treating multiple manifestations of CMBCD including improvements in glycemia, lipids, and BP (114). Phentermine/topiramate ER (115) and liraglutide 3 mg (116) have been shown to prevent progression to T2D by w80% in patients with pre-diabetes at baseline over the 2- to 3-year course of these studies. A CVOT for lorcaserin, primarily designed as a noninferiority trial, demonstrated that metabolic benefits were not accompanied by an increase in MACE (117). Cardioprotection against MACE was demonstrated in high-risk patients with T2D at the lower 1.8 mg/day dose of liraglutide (94) and at a dose of 1.0 mg/week of semaglutide (95).

BARIATRIC SURGERY.

Bariatric surgery primarily targets weight loss in patients with obesity, but can also target cardiometabolic risk factors under the designation of metabolic surgery. Two key studies (118,119) that focused on T2D endpoints with bariatric surgery found not only significant reductions in A1C and reduction in T2D medications, but also reductions in HTN,

dyslipidemia, inflammation, symptom burden, and health care costs (120). However, there are no CVOT data available for patients undergoing bariatric surgery.

Coronary heart disease.—Bariatric surgery with significant and sustained weight loss is associated with decreased future rates of MI and mortality (121). This may be related, in part, to decreased insulin resistance and inflammation (decreased hsCRP), increased adiponectin, and improved arterial remodeling markers after bariatric surgery (122).

Heart failure.—Based on the Swedish National Patient Registry (123) and analysis of the Swedish Obese Subjects study (124), patients undergoing bariatric surgery have decreased risk of HF post-operatively. Based on 2 large Scandinavian nationwide registries (125), and a retrospective analysis of data from the United States (126), Roux-en-Y gastric bypass was found to be associated with significant reductions in HF incidence, post-operatively. Prior bariatric surgery with successful weight loss has also been associated with better inpatient outcomes (e.g., mortality and length of stay) among those patients with HF (127,128).

Atrial fibrillation.—Unfortunately, the effects of bariatric procedures on AF are inconclusive, with divergent results stemming from different populations and risk profiles studied. From 2008 to 2012, the prevalence of AF among patients undergoing bariatric surgery was 1.9%, primarily in the older population and in men, but not influenced by BMI (129). Although bariatric procedures may be associated with decreased incident AF (130,131), possibly associated with attenuated P-wave dispersions (132), these procedures have also been found to be associated with increased risk of AF requiring emergency room visits or hospitalization for up to 2 years post-operatively (133). Nevertheless, in a retrospective observational cohort study of patients with severe obesity, Donnellan et al. (134) found a lower AF recurrence rate after ablation, performed a mean of 22 months after bariatric surgery, compared with those not having bariatric surgery. These effects have been reviewed (135) and the role of bariatric surgery to decrease CMBCD risk has been incorporated into clinical practice guidelines (CPG) recommendations (136).

IMPLEMENTING THE CMBCD PREVENTION CARE PLAN

In the CMBCD preventive care plan presented here (Central Illustration), strategic targets corresponding to mechanistic events are identified, and then, tactically, published CPG/clinical practice algorithms (CPAs) are selected and implemented by the clinician. Table 8 provides the references for many of the current CPG/CPAs that are relevant for each of these targets and can be used to implement the CMBCD preventive care plan (45,102,114,137–161).

CONCLUSIONS

In parts 1 and 2 of this *JACC* State-of-the-Art Review, a new model for CMBCD is presented with an emphasis on early and sustainable prevention with consequent optimization of cardiometabolic health. The purpose of this new pathophysiological construct is to provide a template for the implementation of specific preventive strategies to improve outcomes.

If this new CMBCD model is to be accepted and disseminated, then an appropriate infrastructure should be established to optimize implementations for populations and individuals. The implementation Science Work Group of the National Heart, Lung, and Blood Institute addressed this issue with respect to CPG and found that potential strategies include educational outreach, multifaceted interventions, and more research (162). Educational initiatives will also need to focus on lifestyle medicine, the interactions with cardiometabolic pathophysiology, and suitable implementation tactics that can be incorporated into formal training programs, such as a preventive cardiology fellowship, clinic, and inpatient service (163,164).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

ABCD	adiposity-based chronic disease
AF	atrial fibrillation
AHA	American Heart Association
BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
CI	confidence interval
CMBCD	cardiometabolic-based chronic disease
CPA	clinical practice algorithm
CPG	clinical practice guidelines
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trials
DBCD	dysglycemia-based chronic disease
DPP4i	dipeptidyl peptidase-4 inhibitor(s)

GLP1ra	glucagon-like peptide 1 receptor agonist
HF	heart failure
hsCRP	high-sensitivity C-reactive protein
MACE	major adverse cardiac events
MET	metabolic equivalent of task
MetS	metabolic syndrome
MI	myocardial infarction
PA	physical activity
SGLT2i	sodium-glucose cotransporter-2 inhibitors
T2D	type 2 diabetes

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HIGHLIGHTS

- The CMBCD prevention care plan is designed to implement early, sustainable, and multimodality protocols for all patients with CVD.
- Behavior, adiposity, insulin resistance, dysglycemia, and other MetS traits are the principal targets of the CMBCD preventive care plan for CHD, HF, and AF.
- Structured lifestyle change involving healthy eating patterns and physical activity, judicious use of cardioprotective pharmacotherapy based on cardiovascular outcome trial data, and bariatric procedures are emphasized.

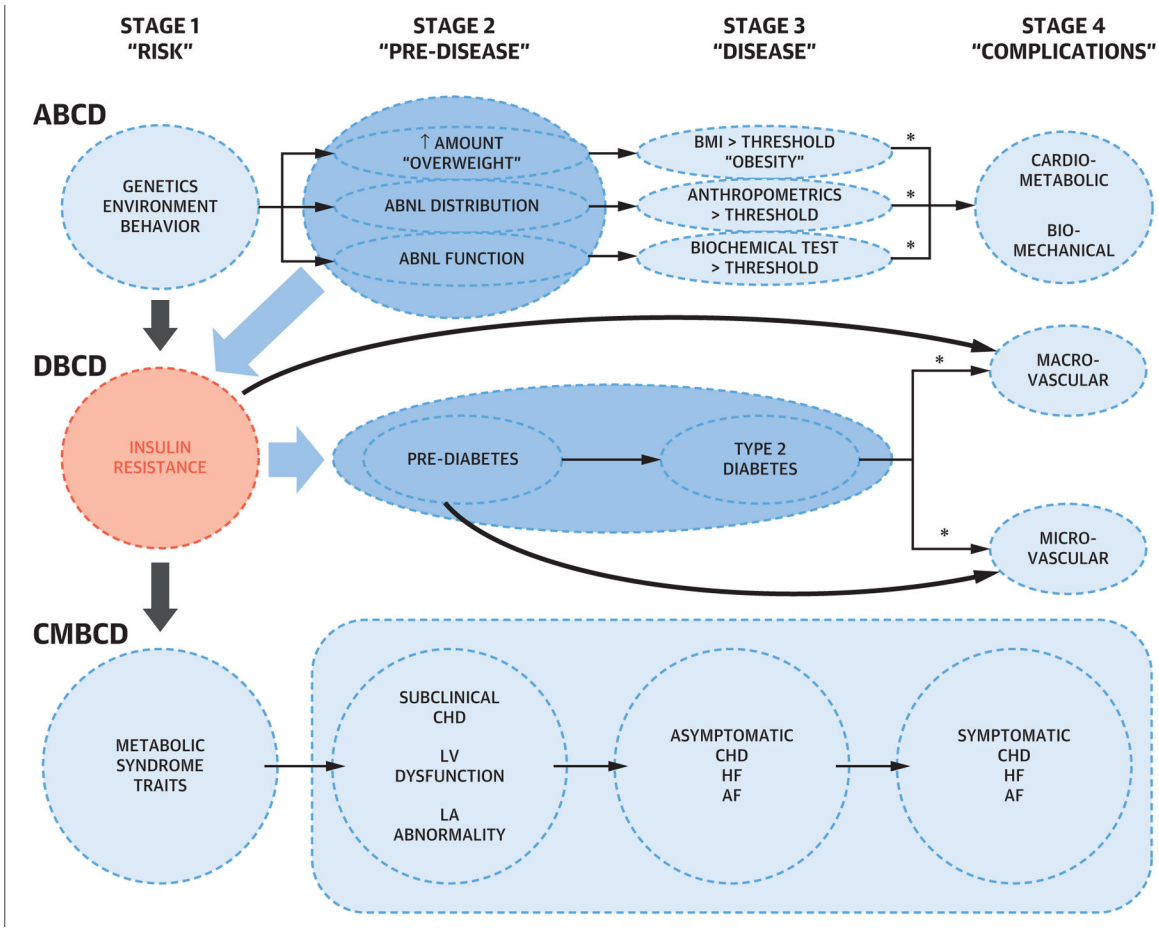
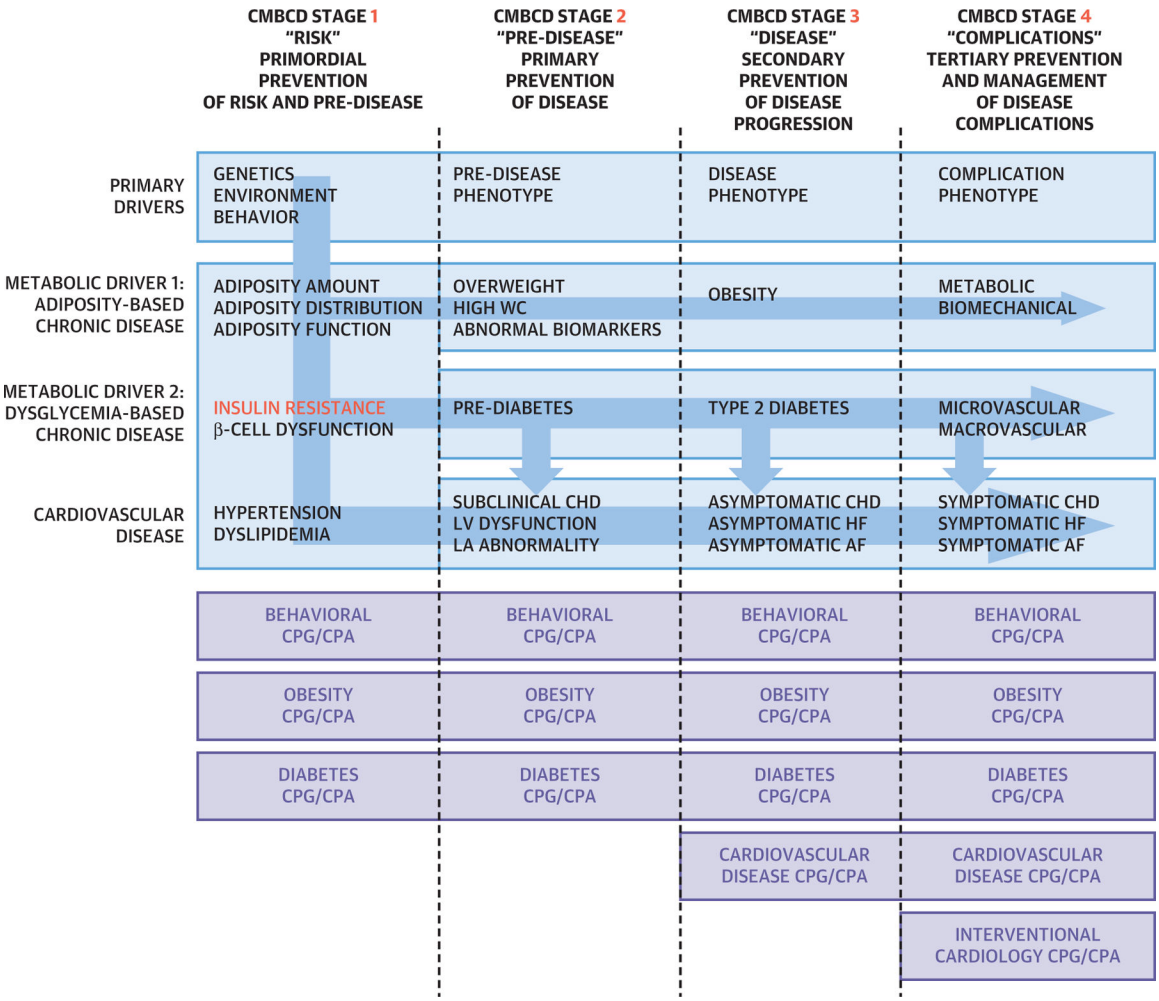


FIGURE 1. The Adiposity-, Dysglycemia-, and Cardiometabolic-Based Chronic Disease Models

Four distinct chronic disease stages are based on a logical clustering of pathophysiological events for ABCD, DBCD, and CMBCD models. **Shaded areas and arrows** indicate main causal relationships: abnormal adiposity to insulin resistance to dysglycemia to cardiovascular disease. **Asterisks** indicate exertions of other metabolic syndrome traits. ABCD = adiposity-based chronic disease; AF = atrial fibrillation; CHD = coronary heart disease; CMBCD = cardiometabolic-based chronic disease; DBCD = dysglycemia-based chronic disease; HF = heart failure; LA = left atrial; LV = left ventricular.



CENTRAL ILLUSTRATION. Cardiometabolic Prevention Care Plan

The 4 stages of cardiometabolic-based chronic disease (CMBCD) are depicted at the top. In CMBCD stage I **(first column)**, adiposity, dysglycemia, and other metabolic drivers act concurrently and independently to produce cardiovascular disease. For cardiovascular pre-disease **(bottom row, second column)**, subclinical coronary heart disease is suspected by interrogating 3 vascular beds: increased coronary calcium score, 3-dimensional carotid ultrasound, and ankle-brachial index; left ventricular dysfunction by echocardiography; and left atrial abnormality by electrocardiogram and echocardiogram. Stages are currently defined by artificial boundaries, determined by thresholds of detectability, and positioned along a continuum. **Blue arrows** indicate complex causal relationships among drivers and stages. Insulin resistance **(red)** occupies a critical integrating pathophysiological role. Preventive care modalities are depicted in the **bottom purple panel** and represented by the most current evidence-based clinical practice guidelines and clinical practice algorithm applicable for the specific CMBCD stage and targets. **Dotted lines** are demarcations between stages in column headings. AF = atrial fibrillation; CHD = coronary heart disease; CI = confidence interval; CMBCD = cardiometabolic-based chronic disease; CPA = clinical

practice algorithm; CPG = clinical practice guidelines; HF = heart failure; LA = left atrial; LV = left ventricular; wc = waist circumference.

TABLE 1

Cardiometabolic-Based Chronic Disease Prevention Types and Features

Primordial	Primary	Secondary	Tertiary	Quaternary
Entire population (especially youth)	Primordial prevention plus:	Primary prevention plus:	Secondary prevention plus:	Ethical behavior
Screening	At-risk population	Diagnostic testing	Noninvasive procedures	Avoid over-medicalization
Healthy lifestyle	Case finding	Risk stratification	Surgical procedures	Avoid action if in doubt
Behavioral programs	Body imaging	Inflammation focus	↑ Cost	
Health promotion curricula	Specialist care	Cardiac rehabilitation	↑ Iatrogenesis	
Family-based	Atherosclerosis focus	SGLT2i/GLP1ra		
Plant-based eating pattern	Adiposity focus	Other pharmacology		
High fiber	Dysglycemia focus			
Minimally processed food	Metformin			
Aerobic physical activity	Weight-loss medications			
Progressive resistance training	Possibly SGLT2i			

GLP1ra = glucagon-like peptide 1 receptor agonist; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

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TABLE 2

Intensive Lifestyle Interventions for Cardiometabolic-Based Chronic Disease

Healthy eating patterns
Aerobic physical activity
Progressive resistance and strength training
Healthy behavior
Weight loss/healthy body composition
Sleep hygiene
Tobacco cessation
Alcohol moderation
Community engagement
Meal replacements as needed
Avoid social-business eating and skipping breakfast

TABLE 3

SGLT2i Cardiovascular Outcomes Trials

	EMPA-REG (82)	CANVAS Program (83)	CREDENCE(84)	DECLARE (85)
	Empagliflozin (n = 7,020)	**Canagliflozin (n = 10,142)**	**Canagliflozin (n = 4,401)**	**Dapagliflozin (n = 17,160)**
Median follow-up, yrs	3.1	2.4	2.6	4.2
Mean age, yrs	63	63	63	64
Female, %	29	36	34	37
BMI, kg/m^2, mean	30.6	32.0	31.3	32.1
HbA1c, %	8.1	8.3	8.3	8.3
Baseline eGFR, ml/min, mean	74	77	56	85
eGFR <60 ml/min, %	26	20	59	7
Prior CVD, %	99	66	50	41
Prior HF, %	10	14	15	10
3P-MACE	**0.86 (0.74–0.99)**	**0.86 (0.67–0.91)**	**0.80 (0.67–0.95)**	0.93 (0.84–1.03)
CV death	**0.62 (0.49–0.77)**	0.87 (0.72–1.06)	**0.78 (0.61–1.00)**	0.98 (0.82–1.17)
Nonfatal MI	0.87 (0.70–1.09)	0.89 (0.73–1.09)	NA	0.89 (0.77–1.01)
Nonfatal stroke	1.18 (0.89–1.56)	0.87 (0.69–1.09)	NA	1.01 (0.84–1.21)
CV death or HHF	**0.66 (0.55–0.79)**	**0.78 (0.67–0.91)**	**0.69 (0.57–0.83)**	**0.83 (0.73–0.95)**
HHF	**0.65 (0.50–0.85)**	0.67 (0.52–0.87)	**0.61 (0.47–0.80)**	**0.73 (0.61–0.88)**
All-cause mortality	**0.68 (0.57–0.82)**	0.87 (0.74–1.01)	0.83 (0.68–1.02)	0.93 (0.82–1.04)
Renal events*	**0.61 (0.53–0.70)**	0.60 (0.47–0.77)	**0.70 (0.59–0.82)**	**0.53 (0.43–0.66)**

Values in parenthesis are HR (95% CI).

*Definition varied across trials.

Values in **bold** are statistically significant at $p < 0.05$.

3P-MACE = 3-point major adverse cardiac events; BMI = body mass index; CV = cardiovascular; CANVAS = CANagliflozin cardioVascular Assessment Study; CREDENCE = Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; CVD = cardiovascular disease; DECLARE-TIMI = Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events-Thrombolysis In Myocardial Infarction; eGFR = estimated glomerular filtration rate; EMPA-REG = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HbA1c = hemoglobin A1c; HF = heart failure; HHF = hospitalization for heart failure; MI = myocardial infarction; NA = not available.

TABLE 4

GLP1ra Cardiovascular Outcomes Trials

	ELIXA (93)	LEADER (94)	SUSTAIN-6 (95)	EXSCEL (96)	HARMONY (97)	REWIND (98)	PIONEER 6 (92)
	Lixisenatide (n = 6,068)	**Liraglutide (n = 9,340)**	**Semaglutide (n = 3,297)**	**Exenatide QW (n = 14,752)**	**Albiglutide QW (n = 9,463)**	**Dulaglutide QW (n = 9,901)**	**Oral Semaglutide (n = 3,183)**
Median follow-up, yrs	2.1	3.8	2.1	3.2	1.6	5.4	1.3
Mean age, yrs	60	64	54	62	64	66	66
Female, %	30	36	39	38	31	46	32
BMI, kg/m^2, mean	30.2	NA	NA	NA	32.3	32.3	32.3
HbA1c, %	7.7	8.7	8.7	8.1	8.8	7.3	8.2
Baseline eGFR, ml/min, mean	76	75	75	76	79	75	74
eGFR <60 ml/min, %	23	23	28.5	18	23	22	27
Prior CVD, %	100	81	83	73	100	32	85
Prior HF, %	22	18	24	16	20	9	12
3P-MACE	1.02 (0.89–1.17)	**0.87 (0.78–0.97)**	**0.74 (0.58–0.95)**	0.91 (0.83–1.00)	**0.78 (0.68–0.90)**	**0.88 (0.79–0.99)**	0.79 (0.51–1.11)
CV death	0.98 (0.78–1.22)	**0.78 (0.66–0.93)**	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.93 (0.73–1.19)	0.91 (0.78–1.06)	0.49 (0.27–0.92)
Nonfatal MI	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.95 (0.84–1.09)	**0.75 (0.61–0.90)****	0.96 (0.79–1.16)	1.18 (0.73–1.90)
Nonfatal stroke	1.12 (0.79–1.58)	0.86 (0.71–1.06)	**0.61 (0.38–0.99)**	0.86 (0.70–1.07)	0.86 (0.66–1.14)	**0.76 (0.61–0.95)**	0.74 (0.35–1.57)
All-cause mortality	0.94 (0.78–1.13)	**0.85 (0.74–0.97)**	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.95 (0.79–1.16)	0.90 (0.80–1.01)	0.51 (0.31–0.84)
HHF	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	NA	0.93 (0.77–1.12)	0.86 (0.48–1.55)
Renal events*	0.81 (0.66–0.99)	**0.78 (0.67–0.92)**	**0.64 (0.46–0.88)**	0.85 (0.73–0.98)	NA	**0.85 (0.77–0.93)**	NA

Values in parenthesis are HR (95% CI).

Values in **bold** are statistically significant at $p < 0.05$.

*Definition varied across trials.

**Hazard ratio for fatal or non-fatal MI.

ELIXA = Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010; EXSCEL = Exenatide Study of Cardiovascular Event Lowering Trial; HARMONY = Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PIONEER-6 = Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; REWIND = Researching cardiovascular events with a Weekly INcretin in Diabetes; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; other abbreviations as in Table 3.

TABLE 5

Heterogeneity of SGLT2i on Primary Outcome 3-Point MACE *

	Established CVD	CVD Risk Factors	p Value for Interaction
	HR (95% CI)	HR (95% CI)	
EMPA-REG (82)	0.66 (0.55–0.79)	NA	
CANVAS (83)	0.82 (0.72–0.95)	0.98 (0.77–1.03)	0.18
CREDENCE (84)	0.70 (0.56–0.88)	0.69 (0.54–0.88)	0.91
DECLARE-TIMI 58 (85)	0.90 (0.79–1.02)	1.01 (0.86–1.02)	0.25

* There is a class effect of SGLT2i for secondary prevention of 3-point MACE.

CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; MACE = major adverse cardiovascular events; SGLT2i = sodium-glucose cotransporter-2 inhibitor; other abbreviations as in Tables 3 and 4.

TABLE 6

Heterogeneity of GLP1ra on Primary Outcome 3-Point MACE *

	Established CVD	CVD Risk Factors	p Value for Interaction
	HR (95% CI)	HR (95% CI)	
ELIXA (93)	1.02 (0.89–1.17)	NA	
LEADER (94)	0.83 (0.74–0.93)	1.20 (0.86–1.67)	0.04
SUSTAIN-6 (95)	0.72 (0.55–0.93)	1.00 (0.41–2.46)	0.49
EXSCEL (96)	0.90 (0.82–1.00)	0.99 (0.77–1.28)	0.50
HARMONY (97)	0.78 (0.68–0.90)	NA	
REWIND (98)	0.87 (0.74–1.02)	0.87 (0.74–1.02)	0.92

* There is a class effect of GLP1ra for secondary prevention of 3-point MACE.

GLP1ra = glucagon-like peptide 1 receptor agonist; other abbreviations as in Tables 3 and 5.

TABLE 7

DPP4i Cardiovascular Outcomes Trials*

	SAVOR-TIMI 53 (107)	EXAMINE (108)	TECOS (109)**	CARMELINA (110)	CAROLINA (111)
	Saxagliptin (n = 16,492)	**Alogliptin (n = 5,380)**	**Sitagliptin (n = 14,523)**	**Linagliptin (n = 6,979)**	**Linagliptin vs. Glimepiride (n = 6,033)**
Median follow-up, yrs	2.1	1.5	3.0	2.2	5.9
Mean age, yrs	65	61	65	66	64
Female, %	33	32	29	37	40
BMI, kg/m^2, mean	31.2	28.7	30.2	31.4	30.1
HbA1c, %	8.0	8.0	7.2	8.0	7.2
Baseline eGFR, ml/min, mean	73	71	75	55	77
eGFR <6O ml/min, %	<50 ml/min: 16	29	NA	62	19
Prior CVD, %	78	100	100	57	42
Prior HF, %	13	28	18	27	4
3P-MACE	1.00 (0.89–1.12)	0.96 (≤1.16)	0.99 (0.89–1.10)	1.02 (0.89–1.17)	0.98 (0.84–1.13)
CV death	1.03 (0.87–1.22)	0.85 (0.66–1.10)	1.03 (0.89–1.19)	0.96 (0.81–1.14)	1.00 (0.81–1.24)
Nonfatal MI	0.95 (0.80–1.12)	1.08 (0.88–1.33)	0.95 (0.81–1.11)	1.15 (0.91–1.40)	1.01 (0.80–1.28)
Nonfatal stroke	1.11 (0.88–1.39)	0.95 (≤ 1.14)	0.97 (0.79–1.19)	0.88 (0.63–1.23)	0.86 (0.66–1.12)
CV death or HHF	NA	1.00 (0.82–1.20)	1.02 (0.90–1.15)	NA	1.00 (0.84–1.20)
HHF	**1.27 (1.07–1.51)**	1.07 (0.79–1.46)	1.00 (0.83–1.20)	0.90 (0.74–1.08)	1.21 (0.92–1.59)
All-cause mortality	1.11 (0.96–1.27)	0.88 (0.71–1.09)	1.01 (0.90–1.14)	0.98 (0.84–1.13)	0.91 (0.78–1.06)
Renal events*	1.08 (0.88–1.3)	NA	NA	0.98 (0.82–1.18)	NA

Values in parenthesis are HR (95% CI).

Values in **bold** are statistically significant at $p < 0.05$.

*Definition varied across trials.

**CV death, nonfatal MI and nonfatal stroke was a pre-specified secondary composite outcome in TECOS.

SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis In Myocardial Infarction 53; EXAMINE = EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA = CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin; CAROLINA = CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes; other abbreviations as in Table 3.

TABLE 8

Implementation of Clinical Practice Guidelines for Targeted Early and Sustainable Prevention of CMBCD*

CMBCD Target	Timing by CMBCD Stage†	Clinical Practice Guideline Topics (Ref. #)
Behavioral	Early: 1 > 2 > 3 > 4	Weight loss (137)
		Healthy eating and physical activity (138)
		Modifiable cardiovascular risk factors (139)
Obesity	Early: 1 > 2 > 3 > 4	Comprehensive (114)
		Pharmacotherapy (140)
		Type 2 diabetes (141)
		Cardiovascular risk (142,143)
Diabetes	Early: 1 > 2 > 3 > 4	Comprehensive (144)
		Nutrition (148)
		Algorithm (145)
		Cardiovascular (102,145,149)
		Hyperglycemia (146)
		Comorbidities (150)
		Lifestyle (147)
		Transcultural (151)
Cardiovascular disease	Late: 3 > 4	Hypertension (152)
		Coronary heart disease (153–155)
		Heart failure (156–158)
		Atrial fibrillation (45)
Cardiovascular disease	Late:4	Coronary revascularization (159) complications
		Ventricular arrhythmias and sudden death (160)
		Advanced heart failure and transplantation (161)

*See Central Illustration for schematic representation. For primary drivers, there are no evidence-based clinical practice guidelines/clinical practice algorithms relevant for health care professionals on genetic or environmental interventions.

†Timing for preventive care actions should be as early as possible. Behavioral, obesity, and diabetes targets can still be addressed at all stages. Cardiovascular disease with or without complications are addressed in later stages. Stage 1 is “risk”; stage 2 is “pre-disease”; stage 3 is “disease”; and stage 4 is “complications.”