Review

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Abstract: The first part of this review highlighted the evolving landscape of atherosclerosis, noting emerging cardiometabolic risk factors, the growing impact of exposomes, and social determinants of health. The prominent role of atherosclerosis in the bidirectional relationship between cardiovascular disease and cancer was also discussed. In this second part, we examine the complex interplay between multimorbid cardio-oncologic patients, cardiometabolic risk factors, and the harmful environments that lend a "syndemic" nature to these chronic diseases. We summarize management strategies targeting disordered cardiometabolic factors to mitigate cardiovascular disease and explore molecular mechanisms enabling more tailored therapies. Importantly, we emphasize the early interception of atherosclerosis through multifactorial interventions that detect subclinical signs (via biomarkers and imaging) to treat modifiable risk factors and prevent clinical events. A concerted preventive effort—referred to by some as a "preventome"—is essential to reduce the burden of atherosclerosis-driven chronic diseases, shifting from mere chronic disease management to the proactive promotion of "chronic health."

Keywords: atherosclerosis; cardiovascular disease; cancer; exposome; syndemic; preventome

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1. Introduction

The secular trend in hospital admissions indicates an increasing recognition of cancer among patients hospitalized for cardiovascular disease (CVD) [1]. Population-based studies further demonstrate that optimal control of atherosclerotic cardiovascular disease (ASCVD) risk factors—through appropriate behaviours and treatments as recommended by the American Heart Association (AHA) [2] — reduces the incidence of both cancer and CVD, as well as lowers all-cause, cardiovascular, and cancer-specific mortality [3,4]. These interventions include maintaining healthy sleep patterns, avoiding smoking, achieving normal plasma glucose and cholesterol levels, adopting a healthy diet, preventing obesity, engaging in regular physical activity, and managing blood pressure within the normal range. Importantly, these findings support the hypothesis of a shared pathophysiological "common soil" between cancer and CVD [5]. This notion is further emphasized by contemporary international clinical guidelines, which highlight cancer as a clinical condition warranting special attention in the management and prevention of ASCVD [6,7].

However, ASCVD risk is often underestimated and undertreated in oncological patients [8–13], and the interactions between environmental exposures (the exposome) and cardiometabolic risk factors remain dangerously neglected. This situation is no longer acceptable, especially given the progressive improvement in cancer patient survival, the aging of the general population, and the increasing incidence of early-onset cancer (before the age of 50). In the first part of this review, we discussed the evolving landscape of atherosclerosis and the central role of chronic low-grade inflammation in both CVD and cancer [14]. In this second part, we will explore the intricate interconnectedness of environmental exposures and cardiometabolic risk factors through a syndemic approach, which adds complexity to the management of contemporary oncological patients. From this perspective, we aim to define an updated strategy for managing ASCVD in patients with a history of or active cancer, with a particular focus on preventive cardio-oncology.

1. The Complexity of Current Oncologic Patients

Currently, at least 80% of heart disease, stroke, and type 2 diabetes, as well as 40-50% of cancers, are linked to an unhealthy lifestyle [15–19]. Cancer patients often present with a high cardiovascular (CV) risk or a history of heart disease, frequently associated with exposure to multiple risk factors, which often cluster together [20–23]. This includes both the direct and indirect CV effects of cancer and oncologic treatments, impacting not only physical health but also mental well-being [24,25].

Advancements in oncological diagnosis and therapy, along with the uncertainty surrounding prognosis, have led to the emergence of novel patient profiles, including long-term cancer survivors. A growing proportion of these individuals are living with advanced metastatic cancer, maintained in remission through prolonged and ongoing treatments. This expanding patient group requires vigilant and continuous surveillance to detect disease recurrence, CV complications, or second cancers [26].

From this perspective, patient management must also address socio-economic factors associated with cancer treatment [27,28]. The improved survival rates and "chronicity" of cancer, facilitated by expensive therapies and continuous medical investigations, give rise to the issue of "financial toxicity"—the economic strain linked to long-term care necessary to maintain favourable outcomes and prevent complications particularly when cancer and CVD coexist in the same patient [29], given the fact that chronic CVDs, such as atherosclerosis and heart failure, are inherently associated with a high risk of financial distress [30–32]. Financial toxicity, encompassing both the objective financial burden and the subjective distress caused by a cancer diagnosis and its treatment, has significant implications not only for healthcare systems but also for the quality of life of cancer patients and their families. As highlighted by the ESMO expert consensus statements, socio-economic determinants play a critical role in this regard [33]. They include "intrinsic" factors (e.g. gender, age, ethnicity, lower income), "disease-related" factors (e.g. costs of systemic anticancer therapies), and "extrinsic" factors (e.g. travel expenses, out-of-pocket healthcare costs, lost wages, and medical appointments or tests). All of these contribute to financial toxicity, which can influence cancer diagnosis, treatment access, quality of life, and survival [34–37]. In addition, comorbidities have a relevant impact: in a cohort of

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long-term survivors of adolescent and young adult (AYA) cancer from the Kaiser Permanente database, 40% of patients had multiple comorbidities 10 years after diagnosis. The most common atherosclerosis-related comorbidities included dyslipidaemia (22 per 1,000 person-years), hypertension (16 per 1,000 person-years), diabetes (10 per 1,000 person-years), and severe depression or anxiety [38]. More recently, in the St. Jude Lifetime Cohort of childhood cancer survivors [39], 45.5% of individuals aged 40-49 had prediabetes, and 14% had diabetes. Over a median follow-up of 5.1 years, 10% of those with prediabetes progressed to diabetes. Survivors with a worse cardio-metabolic profile experienced significantly more CV events, including myocardial infarction (MI) in those with prediabetes and cardiomyopathy or stroke in diabetics. These findings underscore the need for comprehensive management strategies that address both the medical and socio-economic challenges faced by long-term cancer survivors.

Preventing and managing the risk of ASCVD is particularly important in patients with adult-onset cancer. Aging, which is often accompanied by chronic low-grade inflammation (inflammaging), is a major risk factor for non-communicable diseases (NCDs) such as CVD and cancer [40,41]. Many older adults present with comorbidities at the time of cancer diagnosis, and these conditions may worsen during and after cancer treatment [42–44]. Currently, more than 50% of elderly cancer patients live with two or more chronic conditions, with CVD, diabetes, lung disease, and chronic kidney disease (CKD) being the most prevalent [45–51]. The clinical complexity in these cases is often compounded by hazardous environments, further complicating the management of both cancer and comorbidities [52].

1.1. Assessing ASCVD Risk in Individual Cancer Patients

According to harmonized data from 112 cohort studies involving 1,518,028 participants (54.1% women) across 34 countries and 8 geographic regions, with a median age of 54.4 years and a median follow-up of 7.3 years, approximately 57.2% of incident CVD in women and 52.6% in men, as well as 22.2% and 19.1% of deaths from any cause, respectively, were attributable to five modifiable risk factors: body mass index (BMI), systolic blood pressure, non–high-density lipoprotein cholesterol (non-HDL-C), current smoking, and diabetes [19]. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 further emphasizes that a large proportion of cancer deaths are linked to modifiable risk factors, with smoking, alcohol use, and high BMI contributing the most. Additionally, metabolic risk factors saw the largest increase between 2010 and 2019 (34.7%) [17].

The rise in obesity and related conditions, particularly metabolic syndrome (MetS), is unsurprising given the increasing prevalence of energy-dense food consumption, sedentary behaviour, urbanization, and lower socio-economic status [53–55]. Obesity, a chronic low-grade inflammatory state, is commonly associated with hypertension, dyslipidaemia, and increased risk of several cancers, including colorectal, gallbladder, pancreatic, kidney, liver, and breast cancers (in post-menopausal women) [56,57]. Obesity also accelerates atherosclerosis progression [53,58]. Alarmingly, the incidence of obesity has risen sharply among children and adolescents. Overweight or obesity in childhood is linked to future cancer, type 2 diabetes, and ASCVD, often before the age of 50 [59–63]. In young patients with "obesity-related" cancer, ASCVD risk should not be underestimated, as cardiometabolic risk factors often emerge during childhood and adolescence [64,65]. For example, the PESA (Progression of Early Subclinical Atherosclerosis) study, which examined the vascular systems of 4,184 asymptomatic individuals aged 40-54, found that over 60% (71% of men and 48% of women) had silent atherosclerosis in one or more vascular regions [66], with progression observed in over 40% after a 3-year follow-up [67].

In recent years, there has been increasing focus on refining traditional CV risk factors using indices derived from common lab tests. One promising parameter is the TyG index, calculated as logarithmized semi-product of fasting levels of triglycerides and glucose: ln [triglycerides (mg/dl) x blood glucose (mg/dl)/2]. The TyG index is highly sensitive and specific for insulin resistance [68], correlates with metabolic syndrome [69,70], and is a predictor of type 2 diabetes and CVD events [71,72], particularly in low- and middle-income countries [73]. Additionally, the TyG index has been associated with cancers of the kidney, liver, pancreas, and colon-rectum, and mediates a significant

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portion of the effect of BMI on cancer risk [74,75]. Recent metanalyses, finally, indicate that the Tyg index is a proxy for coronary artery disease (CAD) risk prediction, severity assessment and prognosis evaluation [76,77].

Despite its simplicity and affordability, the TyG index has limitations, as most studies are based on single measurements and lack data on confounding factors such as diet, physical activity, and alcohol intake. Furthermore, insights regarding demographic categories such as children, adolescents, and women remain at a preliminary stage [78]. Prognostic accuracy may be enhanced by incorporating inflammatory markers like high-sensitivity C-reactive protein (hsCRP) or cell-derived markers such as neutrophil-lymphocyte ratio (NLR) [79–87]. Another important risk factor is non-HDL-C, particularly triglyceride-rich lipoproteins, which have stronger atherogenic potential than low-density lipoprotein cholesterol (LDL-C) [88].

Addressing obesity requires a focus not just on the quantity of adipose tissue but also on its type (brown vs. white adipose tissue) and distribution [89,90]. Advanced body composition methods, such as dual-energy X-ray absorptiometry (DEXA) and computed tomography (CT), have shown the limitations of BMI in predicting CV risk, especially in oncologic patients with normal or reduced BMI [91–94]. These fat deposits, including intramuscular and pericardial fat, contribute to systemic inflammation and accelerated atherosclerosis. "Sarcopenic obesity," characterized by reduced muscle mass and strength alongside fat accumulation, is common in cancer patients [95] and linked to subclinical atherosclerosis and CVD events [89–100]. Chronic inflammation plays a major role in sarcopenia, with hsCRP and NLR serving as useful markers for silent atherosclerosis [101–104]. This is particularly relevant for patients on immune checkpoint inhibitors (ICIs), preliminary observations identify sarcopenia and high hsCRP as independent risk factors for poor outcomes in cancer patients treated with ICIs [105–107].

Inadequate treatment of CV risk factors is common in oncology patients and may worsen cancer prognosis while increasing the likelihood of CV events. In the prospective multicentre RADICAL-PC program, which involved newly diagnosed prostate cancer (PCa) patients scheduled for androgen deprivation therapy (ADT), obesity, hypertension, and hypercholesterolemia were the most common comorbidities, yet they were often inadequately managed [8]. Similar findings were reported by Sun in a retrospective analysis of PCa patients from the US Veterans Database [9]. Additionally, the CARDIOTOX Registry revealed that hypercholesterolemia and elevated blood pressure were frequently overlooked and poorly controlled [10]. A recent study by Lin et al. demonstrated that pretreatment lipid profiles may contribute to resistance to ADT with androgen receptor pathway inhibitors in localized cancer, based on findings from both human cohorts and explant models [108]. Likewise, non-adherence to Life's Simple 7 [109] was associated with increased risk of ASCVD (MI, angina, stroke, and heart failure) in long-term survivors of gastric, colorectal, and breast cancers enrolled in the Japanese National Registry [4]. This challenge is becoming increasingly unsustainable, given the improved survival rates offered by new cancer therapies [110–113].

Adherence to a healthy lifestyle, as recommended by guidelines, has been shown to reduce the risk of both cancer and ASCVD in the general population, as well as in high-risk groups such as individuals with high polygenic risk [114], diabetes [115], or CKD [116]. Emerging evidence suggests that these benefits may also extend to cardio-oncology patients [3].

Hypertension, the most common risk factor for ASCVD, is a leading comorbidity in cancer patients at all stages—before, during, and after treatment [19]. Many oncologic therapies can induce 'de novo' hypertension or worsen pre-existing high blood pressure [117]. Several mechanisms, including oxidative stress, endothelin-1 activity, prostaglandin imbalance, endothelial dysfunction, increased sympathetic activity, microvascular rarefaction and reduced nitric oxide production, contribute to hypertension, many of which overlap with those involved in atherogenesis [118,119]. Managing hypertension during cancer treatment is challenging, especially as it is often accompanied by a worsening cardiometabolic risk profile, such as during hormonal therapy for breast or prostate cancer [120–122]. In a large retrospective cohort of cancer survivors, maintaining blood pressure within normal ranges (<130/90 mmHg) per international guidelines was associated with a reduced incidence of CV complications, particularly in patients with elevated cardiometabolic risk [123].

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Although an individual's absolute CV risk is key to guiding treatment, especially in primary prevention, risk prediction models have evolved in recent years to reflect the growing prevalence of cardiovascular-kidney-metabolic (CKM) conditions, such as obesity, diabetes, and CKD, often clustering with adverse social factors like living in socioeconomically deprived neighbourhoods [124–126]. In Europe, the Systematic Coronary Risk Estimation 2 (SCORE2) and SCORE2-Older Persons (SCORE2-OP) are widely used [6]. In the U.S., the AHA's recent PREVENT equations have been validated to predict risk in adults aged 30–79 without known CVD [127], addressing the limitations of older models like the 2013 Pooled Cohort Equations (PCEs) [128]. PREVENT uses traditional risk factors (e.g., smoking, systolic blood pressure, cholesterol, diabetes) and estimated glomerular filtration rate, with models being sex-specific, race-neutral, age-scaled, and adjusted for non-CVD death [127]. However, none of these CV risk scores consider the unique challenges of cancer patients, including the elevated CV risk due to shared risk factors, the CV toxicity of cancer therapies, and cancer itself [129]. As recent research from the UK Biobank shows, established CV risk scores such as QRISK3, SCORE2, Framingham, and others do not perform as well in cancer survivors compared to non-cancer patients [13]. To address these limitations, coronary imaging—such as coronary artery calcium (CAC) scoring and coronary computed tomography angiography (CCTA)—can enhance the prognostic accuracy of clinical scores [130,131]. CCTA has shown promise in detecting coronary inflammation through radiological changes in perivascular adipose tissue (PVAT), measured via the Fat Attenuation Index (FAI) [132]. Inflammation biomarkers, such as hsCRP and interleukin-6 (IL-6), have long been associated with CV risk independent of cholesterol levels. Numerous trials demonstrate improved outcomes with reductions in both LDL-C and CRP [133–139]. A recent meta-analysis of 53 randomized controlled trials (RCTs) involving 171,668 participants showed significant reductions in CRP levels from treatments like statins, bempedoic acid, ezetimibe, and omega-3 fatty acids, independent of LDL-C reduction [140]. Notably, hsCRP predicted future CV events more effectively than LDL-C in high-risk, statin-intolerant patients [141].

2. How to Manage Atherosclerosis -Driven Chronic Diseases in Cancer Patient

NON pharmacologic treatments

The importance of lifestyle in preventing NCDs is well-established. Risk factors such as tobacco use; unhealthy diets high in saturated and trans fats, salt, and sugar; physical inactivity, and excessive alcohol consumption are responsible for more than two-thirds of all new NCD cases and significantly increase the risk of complications [19].

Diet. The EUROASPIRE V study highlights the importance of dietary guidance in managing patients at high CV risk [142]. Both vegetarian and Mediterranean diets, low in saturated fats and red meat, have been shown to improve blood lipid profiles, blood pressure, fasting glucose, and glycosylated haemoglobin levels. These diets also positively influence inflammation, oxidative stress markers, insulin sensitivity, and endothelial and antithrombotic function [143–147]. Meta-analyses of observational studies and randomized trials confirm the protective effect of Mediterranean diet against all-cause mortality, CVD, CAD, MI, cancer, neurodegenerative diseases, and diabetes [148] [149]. In the Women's Health Study, a 25-year cohort of 25,315 women, those with greater adherence to the Mediterranean diet had a 23% reduced risk of all-cause mortality. This effect was largely attributed to improvements in small molecule metabolites, inflammation, triglyceride-rich lipoproteins, insulin resistance, and BMI, with less impact from traditional cholesterol or glycaemic markers [150]. For patients with established CAD, the Mediterranean diet with extra virgin olive oil (EVOO) outperformed low-fat diets in preventing major CV events [151], slowing atherosclerosis progression [152], and preserving kidney function in obese patients with type 2 diabetes [153]. A strong inverse association between Mediterranean diet adherence and cancer risk has also been observed, particularly for breast cancer (BC). In the Women's Health Initiative study, postmenopausal women with BC following a diet rich in vegetables, whole grains, fruits, and reduced fat intake showed a 38% reduction in CV deaths over 10 years [154]. Similarly, the PREDIMED trial found that women at high CV risk who followed a Mediterranean diet enriched with EVOO had a reduced incidence of BC [155]. The MOLI-SANI study further underscored the

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importance of dietary quality, demonstrating that higher olive oil consumption was linked to lower rates of cancer, CV, and all-cause mortality, independent of overall diet quality [156]. In the Multi-Ethnic Study of Atherosclerosis (MESA), consumption of plant-based foods and beverages high in bioflavonoids was inversely associated with subclinical atherosclerosis in peripheral and carotid arteries [157].

In contrast, there is growing concern about the health impacts of ultra-processed foods (UPFs), which are typically high in energy, sugars, unhealthy fats, salt, and low in fibres, protein, vitamins, and minerals. Greater consumption of UPFs, as classified by the NOVA system [158], has been linked to increased cardiometabolic risk, depression, and mortality [159,160]. A systematic review of eight retrospective and three prospective cohort studies found that a 10% increase in UPF daily consumption was associated with a higher risk of overall cancer (HR = 1.13, 95% CI 1.07–1.18) [161]. Children are also affected by high UPF consumption. In the CORALS (Childhood Obesity Risk Assessment Longitudinal Study) cohort of 1,426 children (mean age 5.8 years), higher UPF intake was significantly associated with increased adiposity and worse cardiometabolic risk. Mothers of children with high UPF consumption tended to be younger, with higher BMIs, lower education levels, and lower employment rates [162]. Given these findings, reducing UPF consumption is crucial. The 2022 ESC Guidelines on Cardio-Oncology recommend dietary patterns rich in vegetables, fruits, and whole grains, which are associated with lower mortality and cancer recurrence compared to diets high in refined grains, processed and red meats, and high-fat dairy products [129]. According to the American Cancer Society Guidelines for Cancer Prevention the “healthy eating pattern includes a variety of vegetables (dark green, red, and orange), fiber-rich legumes (beans and peas), fruits, especially whole fruits with a variety of colors; and does not include red and processed meats, sugar-sweetened beverages and highly processed foods and refined grain products” [163].

Microbiota and microbiome. Diet plays a crucial role in regulating gut microbiota, a complex community of intestinal microorganisms, including bacteria, archaea, viruses, and fungi. The intestinal microbiota is often considered the largest endocrine organ in the human body, supporting immune responses against pathogens, aiding food digestion, and facilitating vitamin production [164]. A healthy gut microbiota stabilizes its host, contributing to CV health (CVH) and cardiovascular-kidney-metabolic health (CVKMH) [165], although the exact mechanisms and the influences of genetic and environmental factors on microbiota composition are not yet fully understood [166,167]. Dysregulated microbiota can exacerbate inflammatory pathways, including IL-6, CRP, lipopolysaccharide (LPS), short-chain fatty acids (SCFAs), mitogen-activated protein kinase (MAPK), nuclear factor-kB (NF-kB), and oncometabolite production [168]. Current research actively investigates the potential link between alterations in faecal microbial community composition and conditions such as obesity, insulin resistance, atherosclerosis, CVD, and cancer [169–172]. Preliminary pooled analyses suggest that manipulating intestinal flora may improve cardio-metabolic risk [173]. In a recent small randomized clinical trial, obese patients with type 2 diabetes who combined an appropriate lifestyle with "lean-associated" faecal microbiota transplantation showed significant improvements in lipid profiles and liver stiffness—markers of predisposition to atherosclerosis, cirrhosis, and hepatocellular carcinoma [174]. Initial studies exploring the causal relationship between the gut microbiome and CVD focused on trimethylamine N-oxide (TMAO), an intestinal microbiota-dependent metabolite derived from the choline head group of phosphatidylcholines, mainly found in Western dietary nutrients (e.g., lecithin, choline, carnitine). Elevated plasma levels of TMAO, produced by gut microbiota, are significantly predictive of major adverse CV events [175], facilitating atherosclerosis through dysregulated lipid metabolism, adiposity, impaired glucose homeostasis, high blood pressure, platelet reactivity, thrombosis, and vascular inflammation [176]. The relationship between dietary patterns and gut microbiota is evidenced by the correlation between prolonged red meat consumption and increased TMAO levels; conversely, an isocaloric-isoprotein diet without red meat can reduce TMAO levels [175]. Emerging data also suggest a link between microbiota and cancer development, as well as responses to oncological treatments [177–179]. Many bacterial species within the microbiome may play oncogenic roles, making the influence of bacterial flora potentially relevant in the context of personalized

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oncology treatments [180]. Recent observations indicate that intestinal flora may impact the development of early-onset cancer [181–183] and the response to immunotherapy [184–186].

Alcohol. Traditional population studies have suggested a J- or U-shaped relationship between alcohol consumption and cardiovascular health (CVH), indicating that mild to moderate use may offer cardioprotective effects, while alcohol abuse is cardiotoxic [187]. However, recent findings have called into question the protective effects of moderate or mild alcohol consumption, citing potential confounding factors such as genetic polymorphisms, lifestyle behaviours among light drinkers, and inadequate analyses of social and economic influences [188–192]. In oncology, alcohol consumption has been causally linked to several types of cancer, with no safe level of intake. The risk of alcohol-associated cancer increases with consumption, and this risk is consistent across all ethanol-containing beverages. Regarding CV prevention, the 2021 ESC Guidelines on CVD prevention recommend limiting alcohol consumption to a maximum of 100 g per week (about 5–6 standard UK glasses of wine or pints of beer per week) [6] while the American Cancer Society's Guidelines for Diet and Physical Activity for Cancer Prevention advise against alcohol consumption, stating that individuals who choose to drink should limit their intake to no more than one drink per day for women and two drinks per day for men [163].

Physical activity (PA) In oncology, PA significantly impacts cellular processes and tumour growth [193] by modulating insulin and glucose metabolism, immune function, inflammation, sex hormones, oxidative stress, genomic instability, and myokines [163,194,195]. Furthermore, PA may reduce cancer risk related to obesity. The physical effects of PA, such as increased blood flow, shear stress on the vascular system, pH regulation, heat production, and sympathetic activation, along with endocrine effects like stress hormones, myokines, and circulating exosomes, may help regulate cancer progression and biology by affecting tumour growth, metastatic potential, tumour metabolism, and the immunogenic profile of tumours. Exercise also has beneficial effects on cancer symptoms and treatment-related adverse effects [196].

Smoking cessation is a critical priority for preventing both CVD and cancer. Smoking significantly increases mortality from all causes and is a leading contributor to ASCVD. Cigarette smoke contains over 7,000 chemical compounds, including at least 72 known carcinogens and numerous pro-carcinogens [197,198]. Tobacco use is causally linked to various CVD phenotypes, ranging from early-onset atherosclerosis in adolescents and young adults to increased risks of acute MI, stroke, peripheral artery disease, aortic aneurysm, and sudden death [199]. Both cigarette smoke and second-hand smoke activate, damage, and kill endothelial cells, leading to lipid and inflammatory cell infiltration. Additionally, activated leukocytes release inflammatory cytokines and enhance the expression of adhesion molecules, contributing to the formation of vulnerable plaques, a pro-thrombotic environment, and reduced fibrinolytic capacity [200]. Smoking also contributes to the development of diabetes and dyslipidaemia [201]. In 1964, the Surgeon General's report first established the causal link between smoking and lung cancer [202]. Fifty years later, the 2014 report highlighted the increased risk of smoking exposure for several other cancers. While lung, laryngeal, and pharyngeal cancers have the highest relative risks for current smokers, elevated risks have also been observed for cancers of the upper digestive tract, oral cavity, lower urinary tract, oesophagus, nasopharynx, cervix, pancreas, stomach, kidney, liver, and colorectal regions [199,203]. Meta-analyses have confirmed smoking as a major risk factor for urothelial bladder cancer [204,205] and for an unfavourable course of prostate cancer [206].

Social and psychological determinants of health. Inequalities in wealth, income, and education are key factors in the development and progression of multimorbidity. Low socioeconomic status is a recognized risk factor for many mental and behavioral problems, that eventually lead to lifelong physical diseases [207,208]. Food insecurity (FI), or "the lack of consistent access to enough food for an active and healthy life" [209] has indeed been associated to ASCVD risk through the nutrition/anthropometric, psychological/mental health, and access to care pathways [210].

In 2019, Tawakol et al. documented a link between socioeconomic disparities and CVD through a stress-related neurobiological pathway [211]. In 2022, the American Heart Association (AHA) included sleep as an essential component of CVH and addressed social determinants of health

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(SDOH) and psychological well-being, recognizing their importance for achieving equitable CVH outcomes [2]. Positive psychological traits, such as optimism, purpose in life, environmental mastery, perceived social role reward, and resilient coping, have been associated with better CVH, while psychosocial stress and depression are linked to worse outcomes [2,212]. Loneliness, a recognized SDOH, is also a risk factor for both CVD and cancer [213–215]. In a systematic review of 51 cohort studies involving 2,611,907 participants with an average follow-up period of 10.3 years, depression and anxiety were associated with a significantly higher risk of cancer incidence (adjusted RR: 1.13; 95% CI: 1.06-1.19), specific cancer mortality (1.21; 1.16-1.26) and all-cause mortality in cancer patients (1.24; 1.13-1.35) [216]. Psychological distress is common in cancer [217,218] and may intersect with the cognitive change associated with therapy, or "chemo-brain" [219], an entity that has been identified in people with a variety of cancers who have undergone chemotherapy and/or hormone treatment. These patients may have difficulties in executive functions, multitasking, short-term memory and attention and coping ability. Anxiety and depression are emerging as significant risk factors for subclinical atherosclerosis [220–222], in the context of cardio-oncology there is an urgent need to address these novel risk enhancers. An example is offered by the positive impact of spirituality in serious health conditions and its ability to counter loneliness, hopelessness, and depersonalization, often overlooked in patient-centred care [223]. Spirituality can enhance coping abilities [224] and potentially improve outcomes through effects on the autonomic nervous system, and hormonal, immunological, and neurological pathways [225]. Since 2008 The Institute of Medicine (IOM) stated: "Attending psychosocial needs should be an integral part of quality cancer care. All components of the health care system involved in cancer patient management should explicitly incorporate attention to psychosocial needs into their policies, practices, and standards addressing clinical care" [226,227]. Psychotherapeutic interventions useful for mental health in cancer patients are based on emotional support and include education, behavioural training, group interventions and individual psychotherapy.

Pollution is an increasingly significant health issue, acting as a "syndemic" risk factor when combined with traditional risk factors. Air and noise pollution, light disruption at night, climate change, and chemical exposure contribute to the development and progression of cardiometabolic multimorbidity [228]. Studies on populations living near airports, heavy road traffic, and industrial zones highlight the impact of environmental pollution on cardio-metabolic and oncological risks [229–233]. These stressors—through mechanisms such as altered stress responses, circadian rhythm disruption, immune activation, inflammation, oxidative stress, microvascular dysfunction, heart rate variability, and hypercoagulability—heighten CV risk and burden [52**]**. For example, air pollution amplifies the adverse effects of heat, particularly in vulnerable elderly populations, while exposure to heavy metals like lead and mercury has been linked to hyperlipidaemia [234]. Addressing pollution from an "exposomic" perspective, which considers the total environmental exposure across an individual's life, is a crucial issue. Simply controlling traditional risk factors will not be enough to reverse the rising trend of NCDs. Efforts must focus on improving environmental conditions alongside traditional risk factor management.

Pharmacologic therapies: cardiometabolic and anti-inflammatory agent

2.2.1. Cardiometabolic Therapies and Their Impact on Atherosclerotic Plaque

(i) **Lipid-lowering therapies** (LLTs), including statins, ezetimibe, polyunsaturated fatty acids (PUFAs), and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have been extensively studied for their beneficial effects on atherosclerotic plaque regression, both as monotherapies and in combination [235–256]. LLTs also influence platelets and interact with various atherosclerosis mediators, including the endothelium, monocytes, and smooth muscle cells [257]. Table 1 summarizes key studies on LLTs and their effects on atherosclerotic plaques.

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Table 1. The impact of Lipid Lowering therapies on the atherosclerotic plaque: some studies.

Study/year/Reference	Type of study	Lipid –lowering therapy	Population	Imaging modality	Endpoints	Results
REVERSAL Nissen SE et al./2004/Ref. [235]	double-blind, randomized active control multicenter	Pravastatin 40 mg versus Atorvastatin 80 mg (for 18 months)	600 US patients	IVUS	Δ PAV	The progression of the atheroma volume was significantly slowed by Atorvastatin 80 mg
ASTEROID Nissen SE et al. /2006/Ref. [236]	Prospective, open-label blinded end-points	Rosuvastatin 40 mg/day	349/507 pts had evaluable serial IVUS examinations.	IVUS	Δ PAV, Δ atheroma volume, Δ TAV	significant reduction of mean change in PAV for the entire vessel, mean change in atheroma volume in the most diseased 10-mm subsegment and change in TAV
COSMOS Takayama T et al./2009/Ref. [237]	open-label	Rosuvastatin (2.5-20 mg/day)	126 pts 92 (72.2%) received the maximum dosage (20 mg/day)	IVUS	Δ TAV	Rosuvastatin induced significant regression of TAV
JAPAN-ACS Hiro T et al. /2009 Ref. [238]	prospective, randomized, open-label, parallel group study with blind end point evaluation	Pitavastin 4 mg/day vs Atorvastatin 20 mg/day	Among 307 patients with ACS undergoing IVUS-guided PCI, 252 patients had evaluable IVUS examinations at baseline and 8 to 12 months' follow-up	IVUS	Δ PV in NTL	Pitavastatin and atorvastatin induced an equivalent significant regression of coronary PV
SATURN Nicholls SJ/2011/ Ref. [239]	prospective, randomized, multicenter, double-blind clinical	Atorvastatin 80 mg vs Rosuvastatin 40 mg (for 104 weeks)	1039 CAD pts	IVUS	Δ PAV Δ TAV	The regression of PAV was similar in the two groups. A greater reduction in TAV occurred with rosuvastatin
Guo et al./2012 Ref. [240]	randomized, controlled	Placebo (54 pts) vs atorvastatin 10 mg (47 pts) vs atorvastatin 20 mg (45 pts) vs atorvastatin 50 mg (43 pts) vs atorvastatin 80 mg (39 pts)	228 stable CAD pts with CAG and IVUS	IVUS	Δ PAV Δ Plaque necrosis	The percentages of plaque necrosis increased in the placebo and atorvastatin 10 mg groups; remained stable in the atorvastatin 20, 40 and 80 mg groups. Plaque volumes did not change in the placebo, atorvastatin 10 and 20 mg groups; decreased in atorvastatin 40 and 80 mg groups,

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YELLOW Kini AS et al./2013/Ref. [241]	prospective, randomized, single center, single-blinded	Rosuvastatin 40 mg daily vs standard-of-care lipid-lowering therapy	87 patients with at least 2-vessel obstructive CAD (angiographic diameter stenosis >70%). TLs were treated with PCI, NTLs with>70% diameter stenosis and FFR ≤0.8 were evaluated for plaque composition	IVUS NIRS	change in lipid-core burden index at the 4-mm maximal segment ($LCBI_{4mm}$ max),	median reduction in $LCBI_{4mm}$ max was significantly greater in the intensive vs standard group
IBIS-4 Raber L et al/2015/ Ref. [242]	prospective cohort study nested in the COMFORTABLE-AMI trial	Rosuvastatin 40 mg daily	82 patients with 146 non-infarct-related arteries (non-IRA)	IVUS RF-IVUS	Δ PAV in the proximal segment of non-IRA after 13 months of therapy (IVUS) and reduction of necrotic core (RF-IVUS);	Rosuvastatin induced an atherosclerosis regression (measured by a change in PAV) in the non-IRA, but did not change RF-IVUS defined proportion of necrotic core;
IBIS-4 Raber L et al./2019/Ref. [243]				OCT	changes in coronary plaque composition	significant increase in minimum fibrous cap thickness and reduction in macrophage accumulation
PRECISE IVUS Tsujita K et al./2015 Ref. [244]	prospective, randomized, controlled, multicenter	Atorvastatin+ezetimibe vs Atorvastatin	246 CAD patients scheduled for PCI were enrolled; 202 patients available for IVUS after 9-12 months of treatment (100 in the atorvastatin-ezetimibe group and 102 in the atorvastatin group	IVUS	Δ PAV Δ TAV	The atorvastatin/ezetimibe group was noninferior to the atorvastatin group for the absolute change in percent atheroma volume (Δ PAV)
STABLE Park S et al./2016/Ref. [245]	prospective, single-center, double-blind, randomized	Rosuvastatin 40 mg vs Rosuvastatin 10 mg	225 patients with an IVUS-defined fibroatheroma-containing index lesion.	IVUS	Δ PAV	Rosuvastatin reduced necrotic core and plaque volume and decreased thin-cap fibroatheroma rate with no significant differences between the two dosages
Ahn J et al./2016/ Ref. [246]	prospective randomized placebo-controlled	ώ-3 PUFA vs placebo, All patients were taking statins	74 patients scheduled for PCI	IVUS	Δ PAV in a target lesion located more than 10 mm away from the stent	No differences
GLAGOV Nicholls SJ et al./2016/Ref. [247]	Multicenter, double-blind, placebo-controlled	Patients with angiographic CAD treated with statins	Subcutaneous Evolocumab 420 mg monthly for 76 weeks (484 patients) vs placebo (484 patients) in addition to statins	IVUS	Δ PAV(from baseline to week 76) Δ TAV Plaque regression	Evolocumab added to statin induced a significant reduction of PAV and TAV and plaque regression in a greater

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						percentage of patients compared to placebo
Alfaddagh et al. /2017/Ref. [248]	Randomized controlled	ώ-3 PUFA (1.86 g of EPA and 1.5 g of DHA daily) vs placebo for 30 months	285 subjects with stable CAD and on statin therapy	CCTA at baseline and after 30 months	Δ indexed volume of non-calcified coronary plaque	High-dose EPA and DHA+statin provided more benefit in preventing progression of fibrous coronary plaque compared to statins only. Omega-3 ethyl-ester supplementation prevented progression of fibrous plaque in those on LIS therapy, but not in those on HIS therapy
ESCORT/2018/Ref. [249]	prospective, randomized, active-controlled, single-center	Pitavastatin 4 mg/day from baseline (early statin group) vs pitavastatin 4 mg/day from 3 weeks after the baseline (late statin group)	53 patients with 1) successful PCI for ACS; 2) de novo, intermediate, NCL suitable for OCT examination; 3) scheduled coronary catheterization at 3 and 36 weeks after the index procedure and 4) untreated dyslipidemia (LDL-C level >100 mg/dl).	OCT in 53 patients (performed at baseline, 3-week and 36-week follow up)	Δ FCT	Early therapy with pitavastatin 4 mg/day for patients with ACS provided an increase in FCT in coronary plaques during the first 3 weeks of follow-up and a further increase during 36 weeks of follow-up. T
PARADIGM/2018 Ref. [250]	prospective, multinational	Statin naïve patients vs patients on statins (94% of patients on statins were taking moderate to high-intensity statins: atorvastatin or rosuvastatin)	consecutive patients without history of CAD who underwent serial coronary CTA at an interscan interval of ≥2 years. 1,079 coronary artery lesions were evaluated in statin naïve patients (n 474), and 2,496 coronary artery lesions were evaluated in statin-taking patients (n 781).	CCTA	Δ %DS, Δ PAV, plaque composition, and presence of high-risk plaque (presence of ≥2 features of low-attenuation plaque, positive arterial remodeling, or spotty calcifications).	Lesions in patients on statin therapy showed a slower rate of overall PAV progression but more rapid progression of calcified PAV Progression of noncalcified PAV and annual incidence of new HRP features were lower in lesions of patients on statin treatment.
ODYSSEY J-IVUS/2019 Ref. [251]	Randomized controlled	Alirocumab 75 -150 mg every 2 weeks vs Atorvastatin ≥10 mg/day OR Rosuvastatin ≥5 mg/day) for 36 weeks	206 patients with ACS and hypercholesterolemia (LDL-C not at target)	IVUS	Δ TAV :Normalized TAV (Week 36)− Normalized TAV (baseline)/Normalized TAV (baseline)×100	36 weeks of alirocumab treatment resulted in a numerically greater but not statistically

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					Δ PAV from baseline to week 36	significant percentage reduction in normalized TAV
Budoff MJ et al. (EVAPORATE)/2020 Ref. [252]	Randomized, double-blind, placebo-controlled	Statin+icosapent ethyl vs Statin+mineral oil placebo (18 month treatment)	80 patients with documented CAD and with persistent hypertriglyceridemia	MDCT	Δ low-attenuation plaque (LAP) volume	Significant reduction of LAP volume at 18 months
Nicholls SJ et al. (HUYGENS) /2022/Ref. [253]	Randomized, multicenter, double-blind, placebo controlled clinical	Evolocumab 420 mg /month for 52 weeks + statin vs placebo+statin	161 patients with a non–ST-segment MI and at least 1 NTL with coronary stenosis>20% 135 had evaluable imaging	OCT IVUS	Δ FCT Δ LA Δ TAV Δ PAV	Evolocumab added to the maximally tolerated statin induced greater increase in minimum FCT, larger decrease in maximum LA, greater regression of TAV and PAV
Raber L et al. (PACMAN-AMI)/2022 Ref. [254]	Double-blind,randomized placebo controlled	Biweekly subcutaneous Alirocumab 150 mg +Rosuvastatin 20 mg vs Placebo+Rosuvastatin 20 mg for 52 weeks	300 patients with AMI treated with PCI: 148 pts Alirocumab+rosuvastatin vs 152 pts Placebo+Rosuvastatin	IVUS, NIRS and OCT of NTLs	Δ PAV of NTLs (from baseline to week 52) Δ maximum lipid core burden index (MLCBI) Δ minimal FCT	Significant greater change in PAV with alirocumab (-2.13 vs -0.92%) Greater change in MLCBI Increase in minimal FCT
Nakano Y et al. (substudy of the CuVic trial)/2023/ Ref. [255]	Randomized controlled	Statin+ezetimibe (S+E) vs Statin monotherapy (S) (6-8 month- treatment)	79 CAD patients treated with PCI: S+E 39 pts; S 40 pts	IVUS of NTLs	Δ plaque burden Δ percent change in plaque burden	Greater plaque regression in the S+E group Lower values of Campesterol (a marker of cholesterol absorption), and oxysterols in the S+E group with a positive correlation with plaque regression

Abbreviations bid: twice a day; tid: three times a day; qid: four times a day; ASTEROID: A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; BECAIT: Bezafibrate Coronary Intervention Trial; CABG: CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CCT: coronary computed tomography; COMFORTABLE-AMI: Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction; %DS: percent diameter stenosis; ESCORT: Effect of PitavaStatin on Coronary Fibrous-cap Thickness–Assessment by Fourier-Domain Optical CoheRence Tomography; FCT: fibrous cap thickness; FFR: fractional flow reserve, HUYGENS (High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study); IBIS-4: Integrated biomarker imaging study; IVUS: intravascular ultrasound; MARS: Monitored Atherosclerosis Regression Study; LDL-C serum low density lipoprotein cholesterol; MDCT multidetector computed tomography; MV: multivessel; NIRS = near-infrared spectroscopy; NOCS: non-obstructive coronary stenosis; NTL: non target lesion; OCT: optical coherence tomography; PARADIGM: Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging; PAV: percentage change in the atheroma volume; PCI: percutaneous coronary intervention; PRECISE-IVUS: Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound; QCA: Quantitative Coronary angiography; REVERSAL: Reversal of Atherosclerosis with Aggressive Lipid Lowering; STABLE: Statin and Atheroma Vulnerability Evaluation; SATURN: Study of CoronaryAtheroma by InTravascular Ultrasound: effect of Rosuvastatin versus AtorvastatiN; STABLE: Statin and Atheroma Vulnerability Evaluation; TAV: total atheroma volume; TC: Total cholesterol; vs: versus; YELLOW: Reduction in Yellow Plaque by Intensive Lipid Lowering Therapy.

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(ii) **Metformin**, first introduced in the late 1950s and still widely used today, targets three key molecular pathways: complex 1 of the mitochondrial electron transport chain (ETC), adenosine monophosphate (AMP)-activated protein kinase (AMPK), and mechanistic target of rapamycin complex 1 (mTORC1). Inhibition of hepatic gluconeogenesis is linked to its effect on mitochondrial complex 1, which reduces ATP levels and increases the AMP/ATP ratio, activating AMPK and further inhibiting gluconeogenesis [258,259]. Metformin also stimulates the release of glucagon-like peptide 1 (GLP-1) from the intestine [260]. Additionally, AMPK can be activated via the serine-threonine liver kinase B1 (LKB1) and mitochondrial glycerol-3-phosphate dehydrogenase (mGPD), which increases the cytosolic redox state [261,262]. Activation of AMPK by metformin results in reduced blood sugar, improved inflammatory control, enhanced oxidative status, and activation of endothelial nitric oxide synthase, which may explain metformin's protective effect on endothelial function. Preclinical studies suggest that metformin stabilizes atherosclerotic plaques by inhibiting matrix metalloproteinase 9 (MMP-9), an enzyme responsible for degrading the extracellular matrix (ECM) of blood vessels [263,264]. A retrospective clinical study of 313 patients with type 2 diabetes and CAD found that metformin, particularly when not combined with insulin, reduced the prevalence of vulnerable plaque features based on optical coherence tomography (OCT) analysis of 409 non-culprit plaques [265].

(iii) Preclinical studies in animal models have demonstrated that **sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors)** have favourable effects on plaque size, composition, and inflammatory pathways [266,267]. However, there are limited data on these effects in humans [268–270], they are summarized in Table 2.

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Table 2. SGLT2-Inhibitors and their effects on the atherosclerotic plaque.

Study/year/Reference	Type of study	Lipid – lowering therapy	Population	Imaging	Endpoints	Results
SGLT2-Is and FCT. Ref. [268]	observational, randomized, multicenter study	SGLT2-Is vs Non-SGLT2-Is	369 T2DM Patients with MV NO-CS: 111 SGLT2-I users vs 258 non-SLGT2-I users	OCT	Δ FCT (from baseline to a 12 month follow up control)	SGLT2-Is increased FCT and reduced the values of lipid arc degree
SGLT2-Is Stabilize Coronary Plaques in Acute Coronary Syndrome With Diabetes Mellitus. Ref. [269]	Retrospective study	SGLT2-Is vs Non-SGLT2-Is	109 patients in the total cohort: 69 non-SGLT2-I users and 40 SGLT2-I users; 29 patients in the OCT cohort: 15 non-SGLT2-I users and 14 SGLT2-I users	OCT images of unstable plaques in nonstented lesions during ACS catheterization and at the 6-month follow-up.	Δ FCT	SGLT2-Is improved plaque stability through a significantly thicker fibrous cap and a reduced lipid arc
Evaluation of the effect of tofogliflozin on the tissue characteristics of the carotid wall—a sub-analysis of the UTOPIA trial. Ref. [270]	Sub-analysis of the UTOPIA trial	Tofogliflozin	168 and 169 patients in the tofogliflozin and conventional treatment groups were included in the full analysis set, respectively	B-mode US carotid arteries	longitudinal change in the ultrasonic tissue characteristics of the carotid wall using gray-scale median (GSM),	Reduction of IMT, but no change in plaque composition

Abbreviations ACS: acute coronary syndrome; FCT: fibrous cap thickness; IMT: intima-media-thickness; OCT: optical coherence tomography; SGLT2-Is: sodium-glucose co-transporter-2 inhibitors.

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2.2.2. Cardiometabolic Therapies and Their Potential Effect in Cardioncology

The shared mechanisms between CVD and cancer explain the unexpected anticancer effects of many cardiometabolic drugs. These effects are largely due to metabolic remodelling in cancer cells.

(i) **Statins.** Statins reduce low-density lipoprotein cholesterol (LDL-C) in a dose-dependent manner, lower triglycerides (TG) by 10-20% (with greater reductions from high-intensity statins), and have a minimal effect on lipoprotein(a) [Lp(a)] [271]. Their beneficial impact on CV morbidity and mortality is well-documented [272–275]. Statins can be safely and effectively used in elderly patients, including those over 75 years of age [276]. The ESC Guidelines on CVD prevention (Class I A) recommend high-intensity statins at the highest tolerated dose to achieve LDL-C targets based on specific risk groups [6]. Statins may have anticancer properties due to their cholesterol-lowering effects [277,278] and ability to enhance efficacy of ICIs [279,280]. Preclinical studies have shown statins' direct antiproliferative and immunomodulatory effects, promoting immunogenic cell death in KRAS (Kirsten rat sarcoma viral oncogene homolog) - mutated cancer cells. This occurs through increased expression of "eat me" signals and damage-associated molecular patterns, while reducing proteins that suppress T cell antitumor responses [281].

(ii) **Ezetimibe.** In a meta-analysis of eight randomized, double-blind, placebo-controlled trials (12-week duration), Ezetimibe showed a significant reduction in LDL-C compared to placebo [282]. When combined with statins, it provided an additional 21-27% reduction in LDL-C [283]. The IMPROVE-IT trial, involving over 18,000 patients with acute coronary syndrome (ACS), demonstrated a modest but significant CV benefit from adding ezetimibe to simvastatin, with encouraging safety data [284]. These findings support the use of ezetimibe as second-line therapy alongside statins when LDL-C targets are unmet, or statins are not viable options.

(iii) **Bempedoic acid** inhibits ATP citrate lyase, a cytosolic enzyme upstream of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, and reduces LDL-C levels. It has a low incidence of muscle-related side effects, making it suitable for patients who are statin-intolerant. The CLEAR OUTCOMES trial, a double-blind, placebo-controlled study that included high-risk CVD patients who could not tolerate statins, has documented a significantly lower risk of major adverse CV events (MACE), including CV death, nonfatal MI, stroke, or coronary revascularization in patients treated with bempedoic acid [285]. The 2024 ESC Guidelines on chronic coronary disease (CCD) recommend bempedoic acid in combination therapy for statin-intolerant patients or those not reaching LDL-C goals on maximum tolerated statin and ezetimibe therapy [286].

(iv) **PCSK9 inhibitors** (PCSK9Is). PCSK9Is target the PCSK9 protein, which regulates LDL receptors (LDLRs). These inhibitors work through monoclonal antibodies (mAbs) that lower plasma PCSK9 levels by reducing its binding to LDLRs, and through a small interfering RNA (siRNA), Inclisiran, that inhibits PCSK9 synthesis. The result is a significant reduction in plasma LDL-C levels. Alirocumab and evolocumab effectively lower LDL-C in high or very high CV risk patients, including those with T2DM, and reduce CVD events [287,288]. Statins increase circulating PCSK9 levels, enhancing the benefits of the mAbs. These drugs are recommended for secondary prevention in patients who do not achieve LDL-C targets with statins and ezetimibe [6,286]. The long-term benefits of PCSK9 inhibitors (PCSK9Is) were evaluated in the FOURIER-Open Label Extension (FOURIER-OLE) study, which followed individuals originally randomized to evolocumab in the FOURIER trial [288]. The study confirmed both the efficacy and safety of extended PCSK9I use [289], which Shapiro described as "the gift that keeps giving" [290]. The efficacy in lowering LDL-C of Inclisiran was demonstrated in the ORION trials in patients with familial hypercholesterolemia, atherosclerosis, and high CV risk [291,292]. Beyond LDL-C lowering, PCSK9Is have pleiotropic effects, such as reducing platelet reactivity, decreasing smooth muscle cell proliferation, limiting macrophage accumulation, and promoting plaque regression and stabilization [293]. Emerging data suggest a link between PCSK9 and cancer: PCSK9 gain-of-function variants are associated with higher LDL-C and an increased risk

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of BC, while loss-of-function variants show the opposite effect [294]. PCSK9Is may also enhance the anticancer efficacy of immune checkpoint inhibitors (ICIs), as seen in colorectal cancer, where PCSK9 inhibition boosts the effectiveness of PD-1 blockade by reducing LDL-R and transforming growth factor-β (TGF-β) levels [295].

(v) **Fibrates** (bezafibrate and fenofibrate) are used to lower triglyceride levels, but their limited impact on CV outcomes has led to a Class IIb recommendation in the 2021 ESC Guidelines on CVD prevention. They are suggested for patients on statins who have reached LDL-C targets but still have triglyceride levels >2.3 mmol/L (200 mg/dL) [6]. A recent meta-analysis of 12 trials involving over 50,000 patients found that fibrate therapy was associated with a reduced risk of major adverse CV events (MACE); however, this benefit was attributed to LDL-C reduction rather than changes in triglyceride levels [296].

(vi) **Metformin.** Untreated patients with type 2 diabetes (T2DM) have an increased risk of cancer, likely due to the growth-promoting effects of chronically elevated glucose and insulin levels. This heightened risk is most pronounced for cancers of the liver, pancreas, endometrium, colon, breast, and bladder [297]. The anticancer potential of metformin has been widely studied, but its preventive role remains debated. A review and meta-analysis of 27 trials involving over 10,000 patients found no significant reduction in cancer incidence with metformin use [298]. However, another meta-analysis of 166 studies indicated a decreased risk of T2DM-associated cancers (gastrointestinal, urologic, and hematologic), suggesting metformin may reduce cancer risk indirectly by improving diabetes control [299]. A recent review by Galal et al. [300] highlights metformin influence on cancer cell biology through its effects on energy metabolism, cellular growth, angiogenesis, and programmed cell death. Metformin exerts both direct (insulin-independent) and indirect (insulin-dependent) effects on cancer cells, which may interact with each other. However, in recent clinical trials, metformin failed to improve the clinical course of prostate cancer [301,302] and BC [303]. Metformin has also been proposed as an immuno-metabolic adjuvant for cancer therapy. Preclinical studies suggest it can alter the tumor immune microenvironment [304,305] and reduce programmed death ligand 1 (PD-L1) expression, enhancing its degradation [306,307]. However, the "boosting" effect of metformin on cancer immunotherapy has been questioned due to confounding factors [308]. A meta-analysis of 22 studies involving over 9,000 patients revealed a significant association between metformin use and poorer overall survival, suggesting an adverse prognosis when combined with immune checkpoint inhibitors (ICIs) [309]. Further research is needed to fully assess metformin's clinical and immunomodulatory potential in cancer treatment.

(vii) **Glucagon-like peptide 1 Receptor Agonists** Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are incretin-based therapies that enhance insulin secretion in response to meals [310]. In addition to their role in glucose regulation, they promote weight loss, reduce chylomicron secretion, and lower blood pressure [311,312]. GLP-1 RAs, such as Liraglutide, Semaglutide, Exenatide, Albiglutide, and Dulaglutide, are approved for treating type 2 diabetes mellitus (T2DM) and have shown CV benefits in several trials [313–319]. A meta-analysis of 40 randomized controlled trials demonstrated that GLP-1 RAs significantly reduce inflammatory markers such as CRP, tumor necrosis factor-alpha (TNF-α), and malondialdehyde (MDA) [320]. Notably, the effects of Liraglutide and Semaglutide on CV outcomes are independent of baseline blood pressure [321], BMI [322], glycated hemoglobin A_{1c} (HbA_{1c}) levels [323], and triglycerides [324]. The 2023 ESC Guidelines for the management of CVD inpatients with diabetes recommend GLP-1 RAs with proven CV benefits (Liraglutide, Semaglutide, Dulaglutide, Efpeglenatide) for patients with T2DM and ASCVD to reduce CV events, irrespective of baseline HbA1c or other glucose-lowering treatments [325]. Liraglutide and Semaglutide have also been approved for obesity treatment. Liraglutide approval for weight loss followed the SCALE program [326], while Semaglutide approval was based on the STEP program, which included four key trials [327–330]. A recent trial demonstrated a significant reduction in death from CV causes, nonfatal MI, and nonfatal stroke with weekly Semaglutide (2.4 mg) in overweight or obese patients with preexisting CV disease but without diabetes, over a 39.8-month follow-up

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[331]. The 2024 ESC Guidelines for CCD recommend Semaglutide for patients without diabetes but with overweight or obesity (BMI >27 kg/m²) to reduce CV mortality, MI, or stroke (class IIa, B) [286]. GLP-1 receptor agonists (GLP-1 RAs) may have a potential role in reducing obesity-related cancer risk [332]. A recent study involving over 1.6 million patients with type 2 diabetes (T2DM) compared the incidence of 13 obesity-associated cancers among those treated with GLP-1 RAs, insulin, or metformin. GLP-1 RA treatment was associated with a significant reduction in the risk of 10 cancers, including esophageal, colorectal, endometrial, gallbladder, kidney, liver, ovarian, and pancreatic cancers, as well as meningioma and multiple myeloma, compared to insulin-treated patients. When compared to metformin, GLP-1 RAs showed a beneficial effect in reducing the risk of colorectal and gallbladder cancer [333]. In preclinical studies liraglutide has shown potential to enhance the anti-tumor efficacy of immune checkpoint inhibitors (ICIs) in lung and liver cancers [334]. However, conflicting data exist regarding the effects of GLP-1 RAs on cancer initiation and progression. The expression of the GLP-1 receptor (GLP-1R) varies across different tumor types, as well as between healthy and diseased tissues [335]. GLP-1R is highly expressed in endocrine tumors and has also been detected in embryonic cancers, nervous system tumors, and certain carcinomas. It is also expressed in various healthy tissues, including the pancreas, digestive tract, heart, skeletal muscle, liver, central nervous system, and immune cells, where it can be activated [336]. The effects of GLP-1 RAs appear to be tumor-specific. Notably, Semaglutide carries a boxed warning from the Food and Drug Administration (FDA) regarding the potential risk of thyroid C-cell cancer, specifically medullary thyroid carcinoma; [337]; this increased risk has not been observed with liraglutide A recent French multicenter registry reported an association between GLP-1 RA use for 1-3 years and an increased risk of thyroid cancers (adjusted hazard ratio [HR] 1.58, 95% CI 1.27-1.95) [338], a finding supported by a systematic review of 64 randomized controlled trials [339].

(viii) SGLT2 Inhibitors Numerous trials have evaluated the effects of SGLT2 Inhibitors (Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin) on CV morbidity and mortality, as well as the effects of Canagliflozin and Sotagliflozin on reducing the risk of kidney failure and CV events [340–349]. According to the 2023 ESC Guidelines for managing CVD in patients with diabetes, empagliflozin, canagliflozin, dapagliflozin, and sotagliflozin are recommended for patients with T2DM and ASCVD to reduce CV events, regardless of baseline or target HbA1c levels and independent of other glucose-lowering treatments [325]. In T2DM patients without ASCVD or severe target organ damage (TOD), but with a 10-year CV risk of ≥10% according to the SCORE2-Diabetes algorithm, SGLT2 inhibitors may also be considered to lower CV risk, a benefit that appears to be independent of their glucose-lowering effects [350,351]. Empagliflozin and dapagliflozin have shown impressive results in improving outcomes for patients with symptomatic heart failure (HF), regardless of ejection fraction [352]. SGLT2 inhibitors have demonstrated antiproliferative effects against certain tumor types. Cancer cells often exhibit high glucose uptake and glycolysis, and the antineoplastic activity of SGLT2 Inhibitors is partially attributed to their ability to block glucose uptake in metabolically reprogrammed cancer cells expressing SGLT2 receptors. However, preclinical studies suggest that the anticancer effects of SGLT2 Inhibitors are multifactorial, involving several metabolic pathways [353]. Beyond their potential direct anticancer effects, SGLT2 Inhibitors may offer protective benefits against cancer therapy-induced CV toxicity. Preclinical studies have shown significant cardioprotective effects against anthracycline exposure [354,355] and ponatinib-induced cardiac toxicity [356]. Clinical studies have also reported favorable outcomes in patients with cancer and T2DM treated with anthracyclines [357], as well as improved outcomes in patients with cancer therapy-related cardiac dysfunction or heart failure [358].

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2.2.4. Anti-Inflammatory Agents in CVD and Cancer

In atherosclerosis, the NLRP3 inflammasome (nucleotide oligomerization domain-like receptor protein 3) detects environmental danger signals—such as cholesterol, disturbed blood flow, and dead cells—and activates caspase-mediated processing of pro-IL-1β into its active form, IL-1β. This promotes an inflammatory response in endothelial cells, triggering the activation of adhesion molecules such as intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1); and chemokines like monocyte chemoattractant protein-1 (MCP-1), which recruit leukocytes to the site [359]. Cells in atherosclerotic plaques can also produce IL-1 in response to inflammatory stimuli [360]. The association of inflammatory biomarkers, such as hsCRP and interleukin-6 (IL-6), with CV risk—independent of cholesterol levels—has been well established [361–363]. Numerous studies have shown improved outcomes with reductions in both LDL-C and CRP [364–368]. A recent meta-analysis of 53 randomized controlled trials involving 171,668 subjects found that statins, bempedoic acid, ezetimibe, and omega-3 fatty acids significantly reduced CRP levels, independent of LDL-C reduction [369]. Notably, in high-risk, statin-intolerant patients, inflammation (assessed by hsCRP) was a stronger predictor of future CV events than hyperlipidaemia (assessed by LDL-C) [370]. The critical role of inflammation in atherosclerosis has sparked interest in clinical trials investigating anti-inflammatory therapies, such as the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) with the IL-1 inhibitor canakinumab [371], and colchicine studies [372–374] with potential interest in cardioncology.

(i) **Interleukin inhibitors -** The CANTOS trial was the first to test the inflammatory hypothesis of atherosclerosis by selectively inhibiting interleukin-1β with canakinumab in 10,061 patients with a history of MI and hsCRP levels of 2 mg/L or higher. Treatment with canakinumab (150 mg every 3 months) significantly reduced the incidence of the primary endpoint (nonfatal MI, nonfatal stroke, or CV death) and the secondary endpoint (including urgent revascularization), independent of lipid lowering [371]. Interestingly, CANTOS also observed a reduced incidence of lung cancer in the canakinumab group [375]. However, later trials failed to demonstrate a survival benefit in patients with resected or advanced non–small-cell lung cancer (NSCLC) [376–378]. These contradictory findings highlight the complex, pleiotropic role of IL-1 signalling [379]. Elevated IL-1 levels are associated with poor prognosis in various cancers [380] and promotes carcinogenesis by driving chronic inflammation and establishing a protumor cytokine network [381]. Furthermore, IL-1 exert paradoxical effects on antitumor immunity. While it enhances the activation of natural killer- and T- cells, promoting antitumor activity [382], it also contributes to immunosuppression by facilitating the expansion and mobilization of immune cells such as myeloid-derived suppressor cells (MDSCs) [383]. As a result, therapeutic strategies targeting IL-1 require further clinical studies to determine the efficacy and optimal use of anti-IL-1 therapies in specific clinical contexts. The phase II RESCUE trial showed that Ziltivekimab, a monoclonal antibody targeting the IL-6 ligand, significantly reduced inflammation and thrombosis biomarkers linked to atherosclerosis [384]. The results of this small study with Ziltivekimab are particularly intriguing from a cardio-oncology perspective. IL-6 plays a key role in tumorigenesis, cancer progression, and treatment resistance [385]. In preclinical studies, IL-6 inhibition combined with immune checkpoint blockade (ICB) enhanced antitumor immunity and slowed tumor progression across various cancer models [386–388]. IL-6 is also implicated in the development of immune-related adverse events (irAEs) associated with ICB, as shown by the effectiveness of tocilizumab, an IL-6 receptor inhibitor in managing these events in clinical practice. Thus, combining IL-6 inhibitors with ICB holds promise for improving cancer immunotherapy while reducing the risk of adverse events [389,390], including atherosclerosis [391]. More definitive data are expected from the ongoing ZEUS trial, which is investigating the effects of Ziltivekimab on CV outcomes (CV death, nonfatal MI, and nonfatal stroke) in 6,000 patients with CVD, CKD and systemic inflammation [392].

(ii) **Colchicine** is a potent anti-inflammatory agent that works by inhibiting microtubule polymerization, neutrophil extracellular trap (NET) release, platelet activation, and the NLRP3 inflammasome [393,394]. Its effects on the NLRP3 inflammasome limit the activation of

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inflammatory cytokines, such as interleukin-1 and interleukin-18, in response to danger signals. Preclinical studies have shown that low-dose colchicine exerts anti-atherosclerotic and plaque-stabilizing effects, strongly inhibiting foam cell formation and cholesterol crystal-induced inflammation [395]. In 2013, Nidorf et al. reported a significant reduction in the primary outcome (a composite of ACS, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke) after a 3-year follow-up in patients with stable coronary disease treated with colchicine in addition to aspirin (and/or clopidogrel) and statins, compared to those who did not receive colchicine [372]. These findings were confirmed in 2019 by a larger study on patients within 30 days of AMI [373]. Low-dose colchicine also showed benefits in chronic coronary disease, as demonstrated in the LoDoCo2 RCT, where colchicine-treated patients had a significantly lower incidence of CV events (CV death, non-procedural MI, ischemic stroke, or ischemia-driven coronary revascularization) after a 28.6-month follow-up compared to placebo [374]. Colchicine reduces hsCRP levels and may decrease coronary artery plaque volume [396]. A low-dose regimen (0.5 mg daily) has been approved by the FDA for secondary prevention in patients with CAD [397]. The drug's role in oncogenicity remains unclear. In the LoDoCo2 trial, non-cardiovascular deaths were more frequent in colchicine-treated patients than in the placebo group (hazard ratio, 1.51), although cancer diagnosis rates were similar [374]. However, a study of 85,374 Israeli patients with Familial Mediterranean Fever (FMF) showed a significantly lower incidence of cancer compared to the general population, potentially due to colchicine treatment [398]. Shared risk factors between gout and cancer (e.g. obesity and alcohol) have suggested a potential cancer susceptibility in gout patients, as demonstrated in a study of 8,408 male gout patients [399]. A further analysis of 24,050 gout patients found that those diagnosed with cancer were older and had a lower rate of colchicine prescriptions than those without cancer [400]. Interestingly, preclinical studies have shown a cardioprotective effect of low-dose colchicine in doxorubicin-induced cardiotoxicity, likely through the restoration of autophagy [401]. A recent study has documented, in mice and humans carrying CHIP (clonal hematopoiesis of indeterminated potential)-mutations, that colchicine can blunt the higher risk of ASCVD associated with somatic *TET2* mutation-driven CHIP by suppressing IL-1β overproduction [402].

Conclusions

The evolving landscape of atherosclerosis—shaped by emerging exposomes, cardiometabolic, socioeconomic and psychological factors, and the complex role of immunity with a growing interest in complement (the so-called immuno-atherosclerosis) [403,404]—has heightened the complexity of cardiac patient management. The exposome concept, which contextualizes patients within their environment and lifestyle, encompasses biochemical and metabolic changes resulting from various lifelong exposures; these components, as identified by Münzel [229], play crucial roles in the development of both CVD and cancer. Moreover, the interaction between exposomes and metabolic disorders is not merely additive but represents a "syndemic," a term introduced in 1996 to describe an "interrelated complex of health and social crises" [405]. In this scenario, cardio-oncology patients present unique challenges due to the overlap of CVD and cancer, compounded by the cardiotoxic effects of cancer treatments. Prevention is therefore essential and it has to start at baseline, with a comprehensive evaluation of all the complexities: the modifiable risk factors (the essential 8), the unmodifiable risk factors (e.g. age), the psychological determinants of health and the socioeconomic background. As illustrated in Figure 1 all the risk factors in the inner circle (the CVH components) may interact with the components of the other circles and all the interactions have a syndemic nuance. The patient may be the target of all these syndemic effects and only a proactive multidisciplinary intervention can prevent the dangerous "swiss cheese effect"[406].

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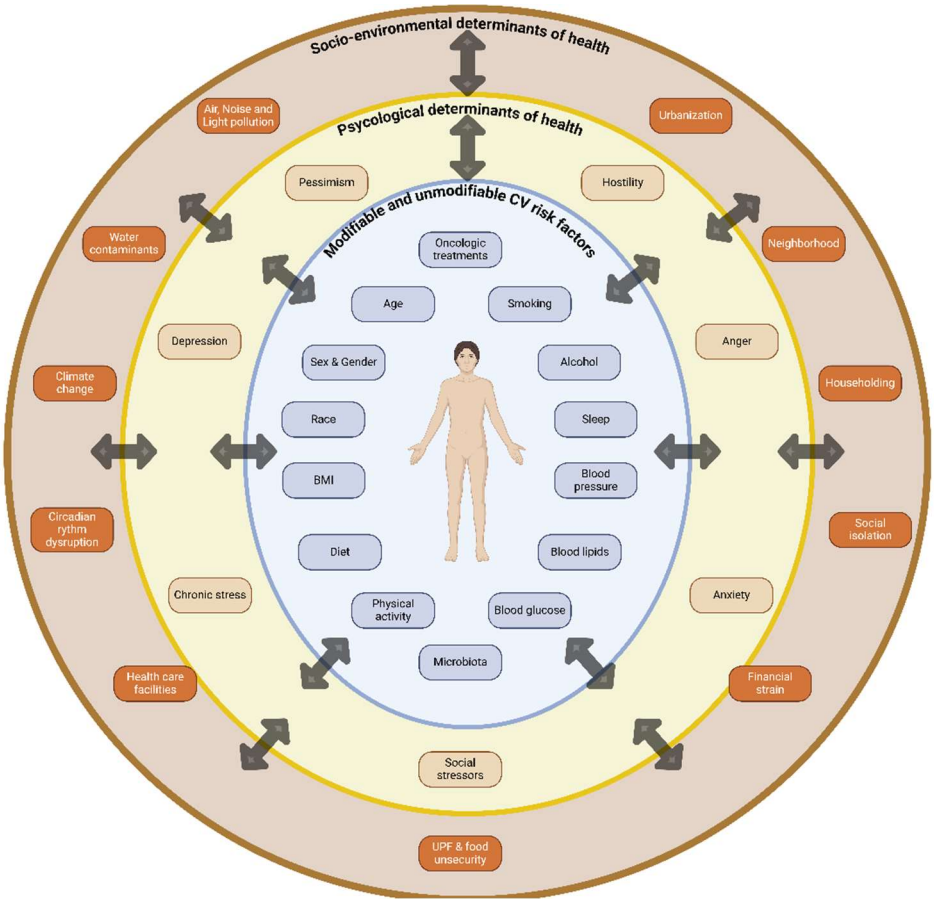

Figure 1. The figure illustrates the cardio-oncology patient as a target of many syndemics: in the inner circle the clustering of cardiovascular risk factors and the effects of the oncologic treatments, in the first outer circle the psychological determinant of health, and in the external circle the social determinants of health including environmental exposomes. The arrows illustrate how the various health conditions cluster and interact and how harmful alignments can lead to dangerous conditions mimicking the "Swiss Cheese" effect (Ref. [406]).

At baseline, cardiovascular health (CVH) should be optimized, risk factors must be actively searched for and managed earlier, more intensively, and with greater precision adopting the principles widely used in cardiology: "the earlier, the better" and "strike early, strike strong"[407]. Machine learning-based recalibration of CV risk models, as proposed by Zinzuwadia et al. [408], may further improve risk stratification within local healthcare systems. An oncology-like screening approach for CVD may be particularly effective, aiming to detect preclinical signs of atherosclerosis, or "the lump in our artery," [131] and this can be done with meticulous evaluation of routine tests used in cancer patients such as computed tomography (CT) and blood testing to detect indicators of CAD, such as vascular calcification or inflammatory and cardiometabolic markers. Emerging technologies, especially if artificial intelligence-assisted, enhance the potential of this preventive approach: advanced vascular imaging offers near-histologic evaluation of plaque composition and progression; Positron emission tomography (PET) imaging can reveal molecular and cellular events before structural changes arise; cardiac CT provides a complete assessment of fractional flow reserve, perfusion, peri-coronary adipose tissue, plaque characterization, and cardiac abnormalities; and hybrid PET-CT imaging allows simultaneous evaluation of cardiac perfusion and coronary anatomy in a single scan. This vigilant approach should be sustained during and after cancer treatment to detect early signs of cardiotoxicity, allowing for timely interventions to prevent clinical events. Effective management of cardio-oncology patients requires a multidisciplinary team—cardiologists, oncologists, haematologists, radiotherapists, and specialized nurses—collaborating to address cancer and cardiac issues. Allied professionals, including primary care physicians, cancer surgeons,

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pathologists, palliative care providers, pharmacists, psychologists, social workers, and data managers, contribute critical support. Fostering effective and productive communication among members of the multidisciplinary team is essential; moreover, equitable and accessible cardio-oncology services, tailored to regional needs, must be prioritized. Addressing the current complexity of NCDs requires a paradigm shift towards promoting "chronic health" instead of merely managing "chronic disease." This preventive shift is embodied in the concept of the "Preventome"—an integrated, multifactorial approach that identifies individual and environmental factors influencing health from before birth and throughout life [52,409]. Achieving this goal demands commitment from communities, researchers, healthcare providers, and public health workers to quantify and monitor cumulative exposures as illustrated in Table 3. Tackling the root social and environmental causes of metabolic disorders should be a priority. Seen from this perspective, cardio-oncology serves as a valuable tool for identifying novel disease mechanisms, following a unique pathway from clinical observations through preclinical functional studies to clinical validation and drug development, as highlighted by Moslehi [410]. Addressing inequity in preventive measures is also urgent; policymakers and communities must support cardio-oncology teams in expanding equitable access to essential healthcare resources.

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Table 3. The PREVENTOME: How to manage CV and cancer risk factors, who is in charge, the pathways, the desirable targets.

	Risk factors	Committed subjects	Non-pharmacological management	Pharmacological Management	Involved Pathways	Targets
Lifestyle	**Obesity**	Patient, GP, caregiver	Healthy diet, exercise	GLP1-Ras	CRP, TNF-α, MDA (Ref. [320])	Optimal BMI (Ref. [2])
	Hypertension	Patient, GP, caregiver	Diet (Restriction of sodium to ~ 2 g per day, MD, DASH, moderate or no alcohol), exercise	ACE-Is, ARBs, CCBs,	Impaired NO production, Oxidative stress. Endothelial dysfunction	Tailored to CV risk, comorbidities and risk modifiers (Ref. [6])
	Diabetes	Patient, GP, caregiver	Diet, exercise	Metformin, GLP1-RAs, SGLT2-I	AMPK, IGFR, Mtor, ETC, β-Catenin Action, EGFR (Ref. [353])	Tailored to CV risk, comorbidities and risk modifiers (Ref. [6])
	Smoking	Patient, GP, caregiver	QUIT smoking	Drug support for smoking cessation (e.g. NRT)	ED, thrombosis, insulin resistance and dyslipidemia (Ref. [201])	No smoking
	Dyslipidemia	Patient, GP, caregiver	Diet, exercise	LLT: statins, bempedoic acid, ezetimibe, PCSK9-Is, fibrates	Cholesterol pathway, PCSK9 iperexpression in cancer	LLT tailored to CV risk (Ref. [6]) and cancer prevention (Ref. [164])
	sedentary behaviour	Patient, GP, policymakers (for population-based interventions and the promotion of healthy environments)	exercise	n/a	Regulation of cardiometabolic and immune function. Oxidative stress, genomic instability and myokines (Ref. [6]); reduction of obesity-related cancer (Ref [163])	Recommended for adults of all ages at least 150-300 min/week of moderate intensity or 75-150min/w of vigorous intensity aerobic PA. Adults who cannot perform 150 min of moderate-intensity PA/week should stay as active as their abilities and health condition allow (Ref. [6])
	unhealthy diet	Patient, GP, caregiver, institutions	Healthy diet (e.g.mediterranean diet, DASH).	n/a.	Oxidative stress	Optimal BMI (Ref. [2]) No alcohol (Ref [6,163])

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alcohol abuse	(e.g. schools, workplaces etc), policymakers	Moderate (<100 g/week) or No alcohol (Ref. [6], Ref. [163])			

Psycho

Risk enhancers	**Committed subjects**	**Non-pharmacological management**	**pharmacological management**	**Pathways**	**Targets**
Anxiety	Patient, Psychological support, caregiver	Healthy lifestyle; Psychotherapy; Care management approach, group-based cognitive behavioral therapy (Ref [2,411]	Antidepressants (SSRI)	Accelerated development of CV risk factors (Ref. [212])	Improvement of symptoms, some beneficial effects on CVH
Anger & hostility	Patient, Psychological support, caregiver	Healthy lifestyle		Accelerated development of CV Risk factors (Ref. [212])	Improvement of symptoms, some beneficial effects on CVH
Pessimism	Patient, Psychological support, caregiver	Healthy lifestyle	Psychopharmaco-therapy	Accelerated development of CV Risk factors (Ref. [212])	Optimistic behaviour, beneficial effects on CVH
Depression	Patient, Psychological support, caregiver	Healthy lifestyle; psychotherapy; care management approach (Ref. [2],	Antidepressnts (SSRI); psychotherapy; care management approach (Ref [2,410])	Acceleretad development of CV Risk factors (Ref. [212]), endothelial dysfunction (Ref. [215])	Resolution of symptoms of depression, some beneficial effects on CVH
Social determinants of health	**Committed subjects**	**Non-pharmacological management**	**Pharmacological management**	Involved pathways	Targets
Environmental conditions: Air, Noise and Light pollution	Policymaker, health-care practice	Interventions to improve air quality	n/a	Syndemic effect with CV risk factors	Mitigation strategies for air pollution (e.g. transition from fossil fuels to renewable energy sources and transportation reforms); for noise pollution (e.g. implementation of noise reduction protocols,

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Exposome					promotion of green spaces as natural sound buffers) and for light pollution (energy conservation and light pollution regulations (Ref. [229])
	Socio-economic status	Policymakers, Health professionals	Improvement of social conditions	n/a	Stress-associated neural activity), bone marrow activity, and arterial inflammation (Ref. [211])	Reduction of stressors-induced inflammation, increase of resilience
	Social isolation	Policymakers, health professionals	Tailored interventions	n/a	Increased arterial stiffness (Ref. [216])	Reduction of loneliness feeling

Abbreviations ACE-Is Angiotensin converting enzyme-Inhibitors; AMPK: adenosine monophosphate (AMP)-activated protein kinase; ARBs: Angiotensin Receptor Blockers; BMI: body mass index; CCBs: calcium channel blockers; CRP: C reactive protein; CV: cardiovascular; CVH: cardiovascular health; DASH: Dietary Approaches to Stop Hypertension; ED: endothelial dysfunction; EGFR: epidermal growth factor receptor; ETC: electron transport chain; GLP-1 RAs: Glucagon-like peptide-1 receptor agonists; GPs general practitioners; IGFR: : insulin like growth factor receptor LLT: lipid lowering therapy; MD: Mediterranean diet; MDA: malondialdehyde ; mTORC1: mechanistic target of rapamycin complex 1; n/a not applicable; NO: nitric oxide NRT: Nicotine Replacement Therapy; PCSK9-Is: proprotein convertase subtilisin/kexin type 9 Inhibitors; SGLT2-Is: sodium-glucose co-transporter-2 inhibitors; SSRI: selective serotonin reuptake inhibitors.

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Abbreviations

ACE-Is	Angiotensin converting enzyme-Inhibitors;
ACS	acute coronary syndrome
ADT	androgen deprivation therapy
AHA	American Heart Association
AMI	acute myocardial infarction
AMP	adenosine monophosphate
AMPK	adenosine monophosphate (AMP)-activated protein kinase
ARBs	angiotensin receptor blockers
ASCVD	atherosclerotic cardiovascular disease
ATP	adenosine triphosphate
AYA	adolescent young adult
BMI	body mass index
CAC	coronary artery calcium
CAD	coronary artery disease
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcome Study
CCB	calcium channel blockers
CCD	chronic coronary disease
CCTA	coronary computed tomography angiography
CHIP	clonal hematopoiesis of indeterminate potential
CKD	chronic kidney disease
CKM	cardiovascular-kidney-metabolic
CKMH	cardiovascular-kidney-metabolic health
CORALS	Childhood Obesity Risk Assessment Longitudinal Study
CRP	C reactive protein
CT	computed tomography
CV	cardiovascular;
CVD	cardiovascular disease
CVH	cardiovascular health;
DASH	dietary approaches to Stop Hypertension
DEXA	dual-energy X-ray absorptiometry
ECM	extracellular matrix
ESMO	European society of medical oncology
EVOO	extra virgin olive oil
ETC	electron transport chain;
FAI	Fat Attenuation Index
FDA	Food and Drug Administration
FI	Food insecurity
FMF	Familial Mediterranean Fever
GLP-1	glucagon-like peptide 1
GLP-1 RAs	Glucagon-like peptide-1 receptor agonists;

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HbA_{1c}	hemoglobin A_{1c}
HF	heart failure
HMG-CoA	3-hydroxy-3-methylglutaryl-CoA
hs	high-sensitivity
ICAM-1	intercellular cell adhesion molecule-1
ICB	immune checkpoint blockade
ICIs	immune checkpoint inhibitors
IGFR	
IL	interleukin
IOM	Institute of Medicine
irAEs	immune-related adverse events
LDL-C	low-density lipoprotein cholesterol
LDLRs	LDL receptors
LLT	lipid lowering therapy
LKB1	liver kinase B1
Lp(a)	lipoprotein(a)
LPS	lipopolysaccharide
MACE	major adverse cardiovascular events
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemoattractant protein-1
MDA	malondialdehyde
MDSCs	myeloid-derived suppressor cells
MESA	Multi-Ethnic Study of Atherosclerosis
MetS	metabolic syndrome
mGPD	mitochondrial glycerol-3-phosphate dehydrogenase
MI	myocardial infarction
MMP-9	matrix metalloproteinase 9
mTORC1	mechanistic target of rapamycin complex 1;
NCDs	non-communicable diseases
NET	neutrophil extracellular trap
NF-Kb	nuclear factor-kB
NLRP3	nucleotide oligomerization domain-like receptor protein 3
NLR	neutrophil-lymphocyte ratio
NO	nitric oxide
Non-HDL-C	non–high-density lipoprotein cholesterol
NRT	Nicotine Replacement Therapy
NSCLC	non–small-cell lung cancer
OCT	optical coherence tomography
PA	Physical activity
PCa	prostate cancer
PCEs	Pooled Cohort Equations
PCSK9-Is	proprotein convertase subtilisin/kexin type 9 Inhibitors
PD-L1	programmed death ligand 1
PESA	Progression of Early Subclinical Atherosclerosis
PET	Positron emission tomography
PUFA	polyunsaturated fatty acids
PVAT	perivascular adipose tissue
RCT	randomized controlled trial
SCFAs	short-chain fatty acids
SCORE2	Systematic Coronary Risk Estimation 2
SCORE2-OP	SCORE2-Older Persons
SDOH	social determinants of health

SGLT2-Is	sodium-glucose co-transporter-2 inhibitors
T2DM	type 2 diabetes mellitus
TMAO	trimethylamine N-oxide
TNF-α	tumor necrosis factor-alpha
TG	triglycerides
TGF-β	transforming growth factor-β
TyG index	logarithmized semi-product of fasting levels of triglycerides and glucose {ln [triglycerides (mg/dl) x blood glucose (mg/dl)/2]}
UPF	ultra-processed foods
VCAM-1	vascular cell adhesion molecule-1

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