Cardiologia Hungarica
2021; 51: 289–296.

The year in cardiovascular medicine 2020: epidemiology and prevention

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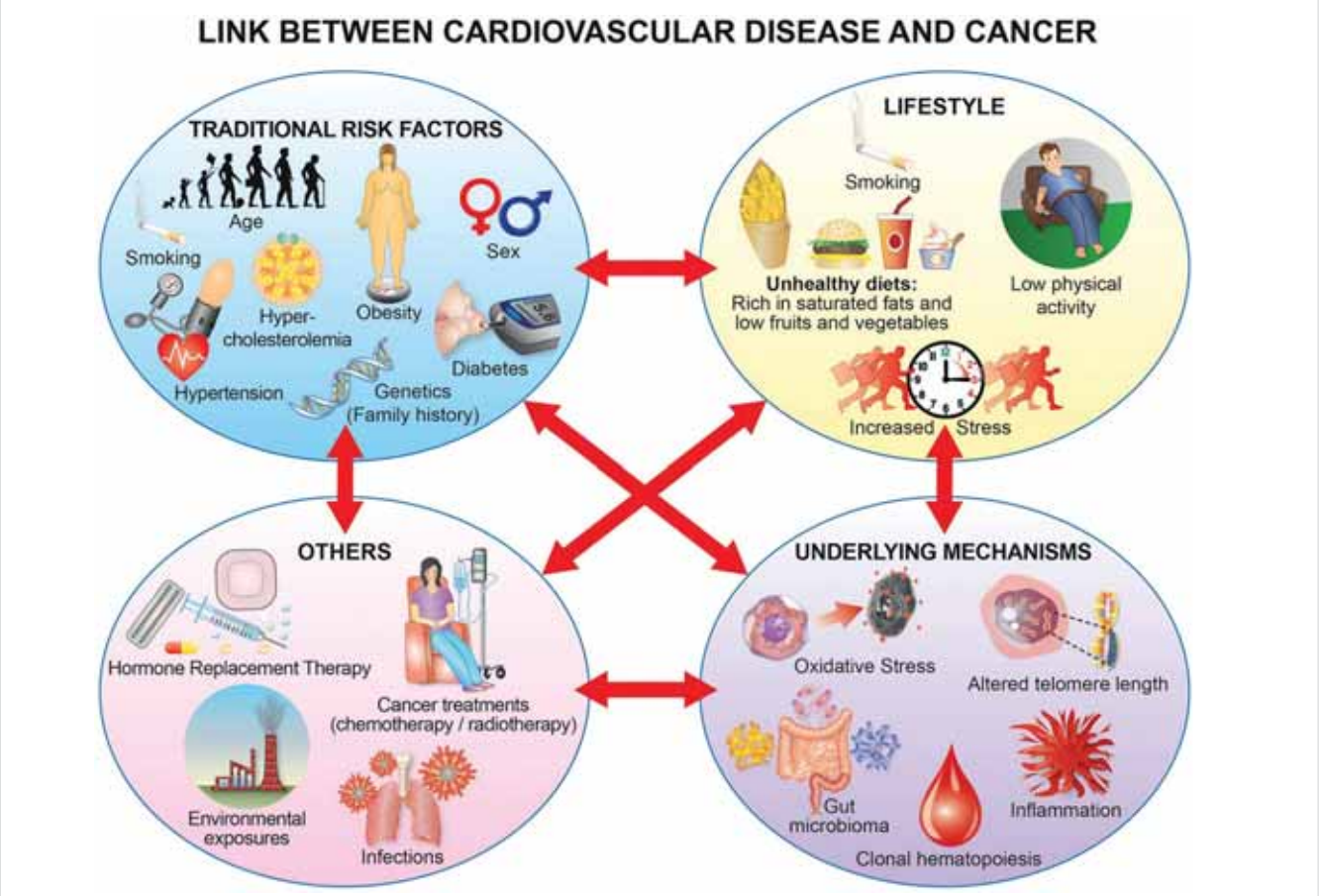
Received: 23 October 2020; Revision received: 01 December 2020; Editorial decision: 11 December 2020; Accepted: 12 December 2020



GRAPHICAL ABSTRACT. Cardiovascular disease and cancer continue to be the major causes of death worldwide and the two conditions have more in common than previously acknowledged. In fact, both diseases share many predisposing factors and mechanisms, with a common background of low-grade inflammation. Thus, both cardiologists and oncologists should score both cardiovascular and cancer risk factors and develop risk reduction strategies for their patients.

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Introduction

Cardiovascular disease (CVD) prevention has been classically divided into primary (aimed to asymptomatic subjects) and secondary (aimed to patients who have already suffered a cardiovascular event), but currently this classification is considered arbitrary given the overlap observed, for example in diabetic patients. Thus, prevention measures may be better divided into "prevention at the population level" and "prevention strategies in subjects with high vascular risk" (1–3). *Figure 1* summarizes the role of different actors in the prevention of CVD.

Lifestyle, behaviour, and environmental factors

Genetics

Both sex and gender have significant impact on the incidence and severity of cardiovascular events (4). Compared to men, women disclose a higher incidence of some cardiovascular conditions such as heart failure with preserved ejection fraction (5) or *Takotsubo syndrome* (6), but they also suffer from relevant differences in presenting symptoms of acute coronary syndrome (ACS) (7, 8). Perhaps, different treatment protocols should be applied in men and women to avoid the differences observed.

New advances on precision nutrition occur every year. Although the relevance of dietary cholesterol on health has been questioned in the last years (9, 10), *Helgadottir et al.* (11). have found that sequence variants that decrease the function of ABC5/8 transporters increase the absorption of both dietary cholesterol and phytosterols, thereby increasing the risk of coronary artery disease (CAD).

Smoking and vaping

The use of electronic cigarettes (e-cigarettes) has dramatically increased, especially among young generations. Although e-cigarettes may be useful to save smokers or generate new addicts, the list of toxic compounds found in e-cigarette vapour is large, mainly nicotine, propylene glycol, and glycerine (12). In fact, daily e-cigarette use has been associated with increased CVD morbidity and mortality (12), and various forms of pneumonitis (13). *Kuntic et al.* (14) demonstrated that the e-cigarette use is associated with a marked impairment in endothelium-dependent flow-mediated vasodilatation and an increase in pulse wave velocity, a measurement of arterial stiffness. They also observed in mice that e-cigarette vapour raised blood pressure (BP) and increased superoxide production that reacts with nitric oxide in peripheral arteries and brain cortex. Thus, e-cigarettes are truly toxics and the recommendation should be to never start their use and for users to stop them (15).

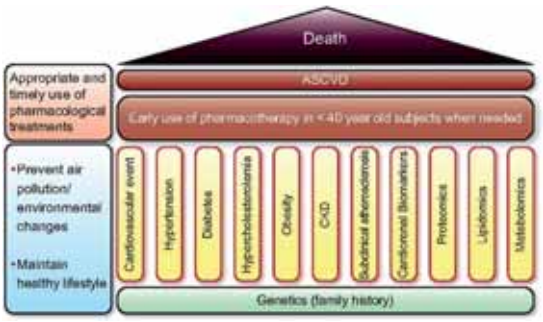

FIGURE 1. Different components involved in the lifetime genesis and evolution of cardiovascular risk. The three most important messages are: first, the need to prevent an unhealthy environment; second, the need to maintain an adequate lifestyle; and third, the use of appropriate pharmacotherapy when required. The first two have to be maintained for the lifetime, while pharmacological treatment should be started at an earlier age than was recommended a few years ago.

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Nutrition

The most important strategy for the prevention of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and atrial fibrillation (AF) is to promote a healthy lifestyle. Mediterranean diet is considered as one of the most cost-effective strategies to prevent CVD (16), but individual responsiveness to compliance with this dietary pattern may vary due to differences in metabolic responses. *Li et al.* (17) identified a metabolic signature comprised of 67 metabolites that correlated with the Mediterranean diet adherence screener and also predicted future CVD risk independent of traditional risk factors in a Spanish (PREDIMED) and three US cohorts (NHS, NHSII, and HPFSP). Metabolomics profiling may allow stratifying individuals based on dietary response and disease risk, thus facilitating individualized approaches to dietary interventions.

In addition to CAD, diet may affect stroke risk. *Tong et al.* (18) examined the association between intake of major foods and fibre with risk of ischaemic and haemorrhagic stroke in 418 329 participants in the EPIC cohort. For ischaemic stroke, participants with high consumption of fruit and vegetables combined, dietary fibre, milk, yogurt, and cheese reduced risks by 13%, 23%, 5%, 9%, and 12%, respectively. Interestingly, for haemorrhagic stroke, higher risk was only associated with higher egg consumption, with a 25% increase per 20 g/day.

Notably, iron overload profoundly aggravated atherosclerotic damage in an APOE-deficient mouse model (19), but iron deficiency was associated with a worse outcome in a cohort of 2357 patients with HF studied by *van der Wal et al.* (20). Depending on the context,

iron excess and iron deficiency may both be harmful to cardiovascular health.
Excessive alcohol intake always affects the cardiovascular system, including induction of AF and adverse atrial remodelling. A randomized clinical trial (RCT) of continuous alcohol drinking vs. abstinence in patients with AF demonstrated reduced arrhythmia rates during a 6-month follow-up in the group assigned to abstinence (21), emphasizing the present recommendation to abstain from alcohol in patients with recurrent AF.

Exercise

Physical activity is associated with a dose-dependent reduction in all-cause and CVD mortality (22). This assertion was reconfirmed by a very large study of persons with and without CVD (23). Physical activity should be promoted in young ages, since low levels of cardiorespiratory fitness (and obesity) in 1 078 685 male adolescents were associated with later cardiovascular disabilities (24). Physical activity and cardiorespiratory fitness were also associated with lower long-term risk of CVD and all-cause mortality in patients with AF (HUNT study) (25). Likewise, incidence of AF and ventricular arrhythmias was lower among those who were physically active and remained relative stable over a broad range of activity levels (26).
Finally, sport may favour healthy aging (27). In this respect, a controlled trial (EXAMIN AGE) of high-intensity interval training in aged individuals reported restoration of retinal microvascular dysfunction, a clinical outcome associated with major adverse cardiovascular events (MACE), together with the reduction of other cardiovascular risk factors (28, 29).

Obesity

Association between obesity and all-cause and CVD mortality follows a J-shaped curve (30). Over two-thirds of deaths attributable to high body mass index (BMI) are due to CVD, mainly CAD (31), but the causal role of adiposity for other CVD outcomes remains unclear. In a Mendelian randomization study, *Larsson et al.* (32) assessed the association of BMI-related genetic variants with 14 cardiovascular conditions among 367 703 UK Biobank participants and reported that higher BMI was associated with increased risk of aortic valve stenosis, AF, ischaemic stroke and abdominal aortic aneurisms.
Among diets used to lose weight (30), intermittent fasting has gained increased popularity since it is purported to not only help reduce body weight, but also to reverse aging, increase lifespan, and improve several other chronic conditions, albeit most evidence is preclinical (33). Concerning weight loss effects, *Moussa et al.* (34) evaluated the long-term effect of bariatric surgery on CVD outcomes in a UK nationwide nested cohort study. Occurrence of MACE (mainly myocardial infarction) and new HF diagnoses were reduced by nearly 60% in obese individuals who underwent the procedure compared to a matched control group.

Other lifestyle factors

Emerging evidence has implicated sleep duration (35) and depression (36) as risk factors for CVD. Another study of 385 292 UK biobank participants (37) reported that ~10% CVD events could be attributed to disturbed sleep. By contrast, a healthy sleep pattern reduced risk of CAD and stroke by 34%. A position paper of the European Society of Cardiology (ESC) working group on coronary pathophysiology and microcirculation (38) concluded that depression is associated with a 30% increased risk for future CAD events.
Low education, low income, and work stress are also considered as risk factors for CVD (39). In an analysis of a prospective cohort of 1.6 million Danish employees, *Framke et al.* (40) reported that low education was associated with higher risk of incident CVD and CVD mortality.

Diabetes

Over the last decade, large CVD outcome trials in patients with type-2 diabetes (T2D) have provided data on the efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium glucose cotransporter 2 inhibitors (SGLT2i) to reduce cardio-renal events. Today's awareness of the CVD continuum as a chain of pathophysiological events makes difficult to define risk in a binary manner using only primary and secondary prevention to drive management. Thus, the recent ESC guidelines on diabetes/prediabetes and CVD (2) recommend that patients with diabetes should be classified according to three levels of cardiovascular risk, into those at very high, high, or moderate risk *(Figure 2)*.
The four available SGLT2 inhibitors have demonstrated to favourably affect a spectrum of CVD and kidney outcomes. Most recently, canagliflozin in the CREDENCE trial significantly reduced 3-point-MACE in a diabetes population with chronic kidney disease (CKD) (41). In DECLARE TIMI-58 trial, dapagliflozin vs. placebo did not significantly affect 3-point-MACE, possibly due to the lower-risk cohort recruited with ~60% of participants with only multiple risk factors without established ASCVD (42). The VERTIS CV trial with ertugliflozin also did not show a reduction in MACE, despite the fact that people with established ASCVD were studied (43). On the other hand, all the SGLT2 inhibitors investigated in the different trials showed a significant reduction in HF hospitalization. Most interestingly, dapagliflozin in DAPA-HF (44) and empagliflozin in EMPEROR-Reduced (45) showed a reduction in the combined endpoint of HF or CV death in patients with HFrEF with or without diabetes. A very recent meta-analysis representing the totality of CVD outcomes trial data for the four SGLT2 inhibitors available shows that reduction in risk for HF

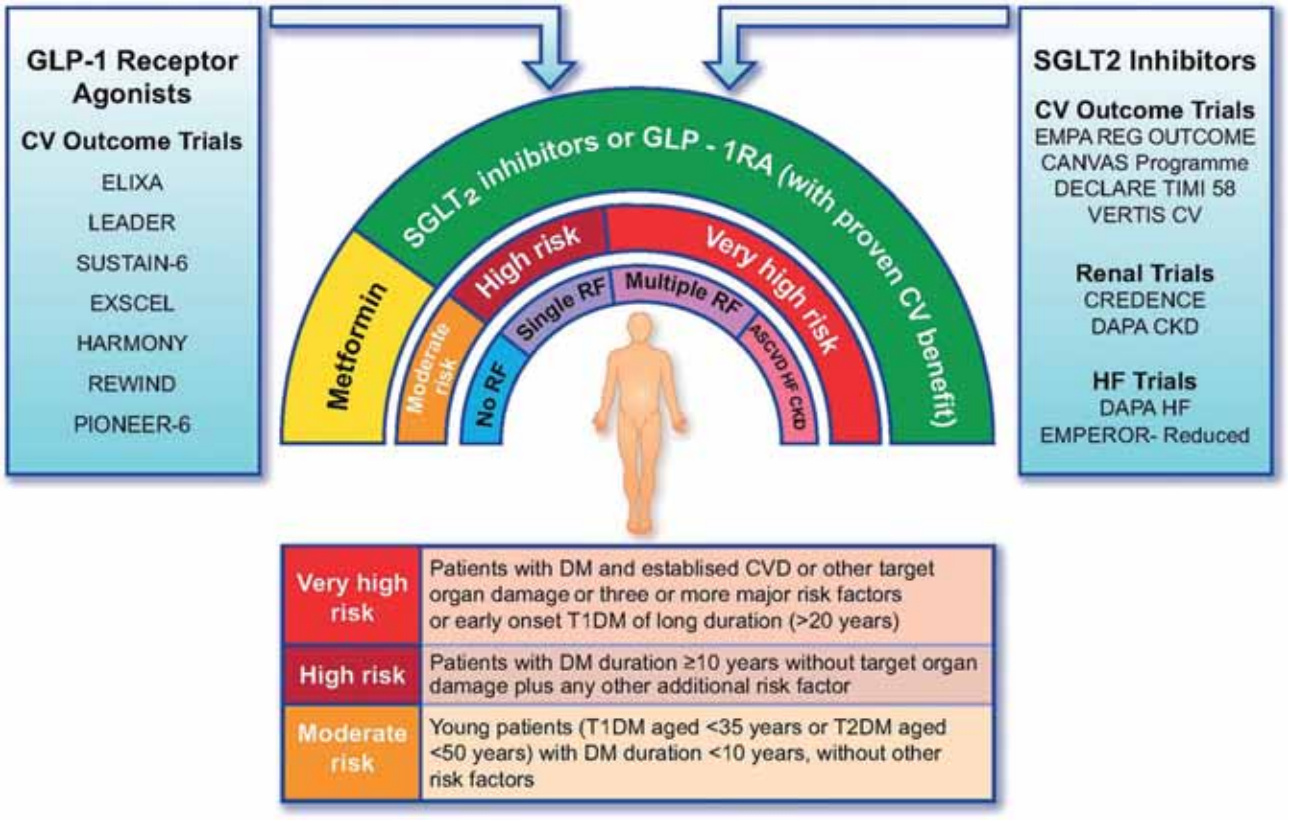

FIGURE 2. Cardiovascular risk classification and treatment recommendation to reduce cardiovascular outcomes in patients with T2D according to the 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure; green, Class I/A recommendation; RF, risk factor; yellow, Class IIa/C recommendation (modified from Marx N, Eur Heart J 2020. doi:10.1093/eurheartj/ehaa174).

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and CKD progression is the most consistent observation across the trials (46).

Despite using different definitions of renal endpoints, all SGLT2-inhibitor RCTs also showed protection against progression of diabetic kidney disease. In most trials, these findings were secondary endpoints, but CREDENCE demonstrated a significant 30% reduction in the primary composite endpoint of CKD, doubling of serum creatinine, death from kidney causes or CV death in people with diabetes and CKD (41).

A recent meta-analysis of RCTs concluded that also GLP-1 RAs lead to a significant reduction in the 3P-MACE as well as the risk of CV mortality, all-cause mortality, fatal and nonfatal stroke and heart failure hospitalization (47). Moreover, based on data from five GLP-1 RA CVD outcome trials, which enrolled patients both with and without ASCVD, there were no between-group differences in GLP-1 RAs benefit on 3P-MACE, indicating consistent protective effects in patients with established ASCVD, as well as in those with multiple risk factors. The results of these RCTs and meta-analyses support the ESC guidelines to prioritize the use of SGLT2i and GLP-1 RAs in patients with T2D at high/very high risk to prevent CVD and kidney complications *(Figure 2).*

Of note, an analysis of the ORIGIN trial data assessing the relationship between body weight and CVD outcomes reported findings that contradict conventional wisdom on body weight and health outcomes (48). In patients with DM/prediabetes, overweight/mild obesity was associated with lower all-cause and CV mortality compared to those with normal weight. Also, loss of weight related to higher all-cause and CV mortality compared to no weight loss, while weight gain was neutral. Further research is needed to clarify if recommendations on weight management should differentiate more clearly between moderate risk and patients with established ASCVD or elevated cardiovascular risk profiles.

Hypertension

The ESC in its 2020 publication on CVD statistics (49) described that in Europe the prevalence of major risk factors was higher in middle-income countries compared to high-income countries. In middle-income coun-

tries, the prevalence of hypertension was 23.8% compared with 15.7% in high-income countries. Prevention and control of arterial hypertension has then to be particularly intensive in middle-income countries. However, within the high-income countries after the improvement in hypertension awareness since the 1980s and 1990s, we have assisted to control figure rates with a plateau in the past decade (50). This finding is probably due to an inadequate accomplishment of guidelines leading to an improper management of elevated BP that could depend on a delayed start of BP management.

How can we improve the control of BP and cardiovascular risk? Probably, risk assessment should start before age 40 (51) due to the importance of early life exposure to risk factors and development of future CVD. The age of onset of hypertension correlates with CVD and mortality (52) and the BP trajectories exhibit sex differences that begin early and persist with aging, allowing the setting for later CVD (53). Thus, an early control of BP and other cardiovascular risk factors, particularly cholesterol, has to be performed to obtain an adequate prevention of CVD and renal disease.

A recent publication has opened a new door to delimitate the definition of normal BP to start intervention. Performed with data from the Multi-Ethnic Study of Atherosclerosis (54), the study (55) shows that beginning at a systolic BP (SBP) of 90 mmHg there is a progressive increase in coronary artery calcium and in ASCVD with progressing SBP. Hence, primordial prevention of BP elevation and other risk factors is necessary to improve cardiovascular prevention in subjects at risk of developing hypertension.

Intervention on BP at young ages is then needed and it must be considered that BP values will stay within the range of normalcy (SBP 90–129 mmHg) preventing the development of arterial hypertension in individuals with good cardiovascular health estimated as Life's Simple 7 metrics (adequate values and performance of BMI, diet, smoking, physical activity, BP, cholesterol, and glucose) (56).

Treatment and control of hypertension in 2020 requires a substantial improvement and one of the ways to accomplish it and thus diminish the burden of disease consists in ensuring an adequate control of BP and the other main cardiovascular risk factors since the early stages of life.

Dyslipidaemia

New guidelines for the management of dyslipidemias from the ESC and the European Atherosclerosis Society have been published in 2020 (10). The treatment targets and goals for cardiovascular prevention defined in these guidelines are depicted in *Table 1.* The intensity of lipid-lowering treatment to accomplish approximate LDL-C targets relies on the use of moderate-intensity statin to reduce LDL-C by 30%, high-intensity statin (50% reduction), high-intensity statin plus ezetimibe (65% reduction), PCSK9 inhibitors (60% reduction), PCSK9 inhibitors plus high-intensity statin (75% reduction), and PCSK9 plus high-intensity statin plus ezetimibe (85% reduction).

TABLE 1 Lipid treatment targets for cardiovascular disease prevention (54)

LDL-C. In patients with very high risk in primary or secondary prevention
A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline and an LDL-C goal of 1.4 mmol/L (<55 mg/dL)
No current statin use: this is likely to require high-intensity LDL-lowering therapy
Current LDL-lowering treatment: an increased treatment intensity is required
High risk
A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline and an LDL-C goal of 1.8 mmol/L (<70 mg/dL)
Moderate risk
A goal of <2.6 mmol/L (<100 mg/dL)
Low risk
A goal of <3.0 mmol/L (<116 mg/dL)
Non-HDL-C
Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively
ApoB
ApoB secondary goals are <65, 80, and 100 mg/dL, for very-high-, high-, and moderate-risk people, respectively
Triglycerides
No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors

The REDUCE-IT trial (57) has demonstrated profound reductions in first and total CVD events in patients treated with statins and well-controlled LDL-C presenting with elevated triglyceride levels with the administration of 4 g daily of icosapent ethyl. These findings should substantially change the management of patients with diabetes and/or metabolic syndrome presenting with hypertriglyceridemia whose lipid phenotype needs treatment beyond isolated LDL-C (58).

Recently, a class of lipids termed ceramides has been demonstrated to be indices of cardiometabolic health (59). The ceramide-based scores are simple and practical to be used in clinical practice to identify at-risk patients. In addition, new drugs to treat elevated LDL-C have been described (60, 61) and soon will become part of the armamentarium. One of them is inclisiran, an inhibitor of hepatic synthesis of proprotein convertase subtilisin type 9 that reduces LDL-C by ~50% with subcutaneous administration every 6 months. Another is evinacumab, a monoclonal antibody against ANGPTL3 (Angiopoietin-like 3) that has been tested in homozygous familial hypercholesterolaemia with good results.

Cardio-renal syndrome

There is a clear linkage between cardiovascular and renal diseases characterized by an elevated prevalence of CVD in patients with CKD, and vice versa. Accordingly, RCTs addressing new therapies with the capacity to improve CVD outcomes in patients with CKD are needed (62). Acute kidney injury, defined as an abrupt increase in serum creatinine, a fall in urinary volume, or both, is also a situation with relevant cardiovascular consequences mediated by cardiac inflammation and cellular apoptosis and necrosis rapidly developing and followed by cardiac fibrosis leading to CVD events, in particular HF (63). Like in the case of CKD trials new studies aimed to find therapies improving CVD and renal outcomes in acute kidney injury are required.

Usually patients are diagnosed as having CKD when they present with albuminuria and/or an estimated Glomerular filtration rate [GFR (eGFR)] <60 mL/min/1.73 m^2. Detection of patients developing CKD before albuminuria develops or eGFR falls (early renal damage) actually is not clearly defined albeit some data indicate that certain interventions like control of adolescent hypertension can impede the future development of kidney failure (64).

On the other hand, the clinical diagnosis of progressive CKD is usually based on the evolution of eGFR and the variation in albuminuria and it is accepted that actual management for cardiovascular protection translates into renal protection (65), albeit CVD events, in particular HF, requiring hospitalization are associated with kidney failure independent of kidney risk factors (66).

The use of new antidiabetic drugs sodium glucose cotransporter 2 and inhibitors of glucagon-like peptide-1 in patients with diabetes and CKD has provided evidence of simultaneous cardio-renal protection (67). The results of similar trials using finerenone, a non-steroidal mineralocorticoid receptor antagonist, will be published soon (68).

COVID-19 and cardiovascular disease

The novel coronavirus disease (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) initiated at the end of 2019. COVID-19 was shown initially to affect the lungs, causing interstitial pneumonitis and severe acute respiratory distress syndrome. Later it was observed that it also affects multiple organs, including the cardiovascular system. Advanced age and male sex are accompanied by severe infection and mortality that is promoted by accompanying comorbidities, particularly CVD, hypertension, diabetes, obesity, CKD, chronic pulmonary disease, and cancer (69, 70). Ultimately, a severe prognosis is the consequence of endothelial dysfunction and COVID-19 is finally considered an endotheliopathy (71).

While waiting for adequate vaccines to prevent COVID-19 and specific medications counteracting the SARS-CoV-2, an array of medications, amply reviewed by *Guzik et al.* (72), has been considered for the treatment of COVID-19 patients with variable effects. It has been established that the use of renin–angiotensin–aldosterone antagonists for the treatment of hypertension and/or heart diseases could be beneficial for COVID-19 (73) as well as the use of anticoagulant therapy needed to diminish the risk of pulmonary embolism (74).

Cancer and cardiovascular disease

CVD and cancer continue to be the leading causes of death worldwide. Interestingly, CVD and cancer share common pathways (75, 76) and, in addition, an increasing number of cancer patients – successfully treated – show an increasing incidence of CVD mortality (77) and CVD events such as HF (78), ACS (79), and arrhythmia (80).

Future perspectives in preventive cardiology

Probably in the next years, new advances on precision medicine will appear with the help of more useful genetic tests and better characterization patients according to their metabolomics profile.

Summary and conclusions

The current article summarizes relevant advances on CVD prevention in 2020.

We have highlighted the need for different protocols for men and women because of differences in presenting symptoms of ACS among sex, the truly toxic effects of e-cigarettes, and the usefulness of intermittent fasting to reduce body weight, improve several chronic conditions and reverse aging. Four available SGLT2 inhibitors have demonstrated favourable effects on CVD and kidney outcomes. We have also underlined that CVD risk assessment should be started before age 40 given the importance of early life exposure to risk factors and development of future CVD events and that new treatment targets and goals have been defined in the new guidelines for the management of dyslipidemias.

Finally, despite the striking consequences of COVID-19 pandemic, prevention of most prevalent and relevant chronic diseases worldwide, CVD and cancer, should continue to be promoted by all actors (governments, scientific societies and mass media) at both population and individual levels. In this setting, an adequate and joint prevention program should be useful to fight both CVD and cancer. Let us get going!

Conflict of interest

R.E. reports grants from Cerveza y Salud, Spain, and Fundacion Dieta Mediterranea, Spain; also, personal fees for given lectures from Brewers of Europe, Belgium,

Fundacion Cerveza y Salud, Spain, Pernaud-Ricard, Mexico, Instituto Cervantes, Alburquerque, USA; Instituto Cervantes, Milan, Italy; Instituto Cervantes, Tokyo, Japan; Lilly Laboratories, Spain; and Wine and Culinary International Forum, Spain, and non-financial support to organize a National Congress on Nutrition; and also, feeding trials with product from Grand Fountain and Uriach Laboratories, Spain. L.R. has been speaker and advisor for Astra-Zeneca, Bayer, Novartis, Medtronic, Pfizer, Vifor and Menarini. F.C. reports personal fees from AstraZeneca, personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Bristol-Myers Squibb, personal fees from Merck Sharp & Dohme, personal fees from Mundipharma, personal fees from Novo Nordisk, personal fees from Pfizer, grants from King Gustav V and Queen Victoria Foundation, grants from Swedish Research Council, and grants from Swedish Heart & Lung Foundation, outside the submitted work. L.M.R. has nothing to declare.

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