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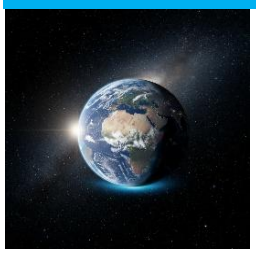

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Impact of smoking and alcohol consumption on the development and progression of valvular heart diseases – a review

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Abstract:

Introduction and aim: Valvular heart diseases (VHD) represent a growing problem in aging societies. The impact of modifiable lifestyle factors, such as substance use, plays a very important role in their pathogenesis. The aim of this study is to summarize current knowledge on the impact of tobacco smoking and alcohol consumption on the development and progression of valvular heart diseases.

Review methods: PubMed, Embase, and Google Scholar databases were searched. Keywords used included: valvular heart disease, aortic stenosis, smoking, alcohol, alcoholic cardiomyopathy. The analysis included publications from 2017-2025, while retaining selected older studies of fundamental importance for pathophysiology and anatomy.

State of knowledge: Tobacco smoking strongly promotes calcific aortic valve disease (CAVD) by inducing oxidative stress and promoting chronic inflammation within the myocardium. This process leads to biomineralization and, consequently, aortic stenosis. The impact of alcohol on the valvular apparatus is secondary. Chronic ethanol abuse is toxic to cardiomyocytes – it leads

to the development of so-called alcoholic cardiomyopathy. In its course, cardiac chamber dilation and stretching of the valve annuli occur, resulting in the development of symptomatic functional regurgitation.

Summary: Tobacco smoking favors structural valve degeneration (stenosis), whereas alcohol damages the myocardium, promoting secondary defects. The elimination of these factors is of key importance in the prevention of VHD.

Keywords: heart valve diseases; cigarette smoking; aortic valve stenosis; alcohol drinking; cardiomyopathies.

1. Introduction

1.1. Significance of cardiovascular diseases in modern medicine: Cardiovascular diseases remain the leading cause of death worldwide (1). In Europe, too, they are currently one of the major public health problems. According to 2021 data from the European Society of Cardiology (ESC), nearly 2.2 million deaths among women and 1.9 million among men were recorded in Europe, translating to 45% and 39% of all deaths in women and men in European countries, respectively. Although the most common causes of mortality are ischemic heart disease, followed by ischemic stroke, valvular heart diseases (VHD) have also proven to be a highly significant component, closely linked to the overall disease burden of cardiological patients (2). The presence of VHD is strictly associated with an increased risk of death in this patient group; therefore, the reduction of modifiable risk factors, early diagnosis, and appropriate treatment of these conditions should be a priority for modern medicine (3).

1.2. Epidemiology of valvular heart diseases: The recognition and burden of VHD are systematically increasing, which is mainly associated with the aging of the population (3). Among high-income countries, the leading cause is calcific aortic valve disease (CAVD), especially in the elderly group (65+), whereas in middle-income countries, rheumatic heart disease (RHD) plays a much greater role, resulting in defects of the mitral and aortic valves, respectively (2). The growing recognition of VHD in post-mortem examinations of patients with cardiac burden may suggest that global epidemiological statistics are still underestimated – the main cause being attributed to limited access to diagnostics (echocardiography) in developing countries (3,4).

Although valvular defects (mainly aortic stenosis - AS) are traditionally associated with the population over 64 years of age, recent studies draw attention to a significantly high prevalence of these defects already in middle-aged individuals, often in an asymptomatic form (5). A cohort study conducted on a Swedish population (n = 30,154, CAVD = 2,053) showed a prevalence of 3%, 7%, and 11% among the 50-54, 55-59, and 60-64 age groups, respectively (6). Additionally, it was demonstrated that this disease is strongly associated with a history of cardiovascular diseases and the presence of modifiable cardiovascular risk factors, where six of them - cigarette smoking, hypertension, hyperlipidemia, diabetes, BMI above normal, and eGFR <60 - accounted for approximately one-third of the cases in these age groups (6).

1.3. The role of environmental and lifestyle factors: Contemporary cohort studies unequivocally indicate that, alongside age, the key determinants of AS development – the dominant valvular disease in Europe – are modifiable

risk factors. The most important of these include smoking status and excessive alcohol consumption (7). Additionally, newer reports suggest the role of circadian rhythm disturbances, such as insomnia or frequent daytime napping, in the pathogenesis of AS, which expands the list of potential preventive targets (8,9). Furthermore, comprehensive health education and the promotion of physical activity are emphasized as foundational elements in mitigating cardiovascular risks overall (38).

Besides the above, non-modifiable factors, including genetic polymorphisms, also play an indisputable role in the etiopathogenesis of VHD. A strong correlation has been documented between variants of the lipoprotein A gene (LPA: rs10455872 and rs3798220) and an increased risk of developing aortic stenosis. In turn, in the case of rheumatic heart disease (RHD), significant importance is attributed to polymorphisms of the transforming growth factor gene TGF-β1 (C509T and T-869C) (10).

The crucial problem to solve remained the question of whether the increased risk in genetically burdened patients could be mitigated by environmental factors. The answer was provided by a large-scale study conducted on the British population (n = 499,341), which confirmed the modifiability of risk through lifestyle, regardless of the genetic profile. In the analysis accounting for polygenic risk, individuals maintaining a healthy lifestyle achieved a reduction in the risk of developing VHD by 15-23% and AS by 30-36% across all genetic risk groups (low, moderate, and high). A similar trend was observed in the analysis based on family history – a healthy lifestyle was associated with a 23% reduction in AS risk in individuals without family burdens and up to 32% in individuals with a positive family history of VHD (11).

These conclusions correlate with long-term observations of the American population (ARIC study 1987-2013), which demonstrated a relationship between maintaining an optimal cardiovascular health score (CVHS) and a reduced risk of AS. The definition of optimal CVHS included: BMI <25 kg/m², nicotine abstinence, physical activity, and normal metabolic parameters (BP <120/80 mm Hg, glucose <100 mg/dL, total cholesterol <200 mg/dL) without pharmacological support (12).

1.4. Aim and scope of the study: The aim of this study is to summarize current knowledge regarding the impact of two of the most common risk factors – tobacco smoking and alcohol consumption – on the development and progression of valvular heart diseases. The growing prevalence of VHD and numerous pieces of evidence indicating the role of modifiable risk factors in their prevention make the proper assessment of potential pathophysiological pathways and the strength of current clinical evidence of key importance in the prophylaxis of these diseases.

1.5. Review methods: In order to find appropriate literature, electronic databases were searched: PubMed, Embase, and Google Scholar. The following keywords were used in the search process: "valvular heart disease", "aortic stenosis", "mitral regurgitation", "smoking", "tobacco", "alcohol consumption", and "alcoholic cardiomyopathy", combining them with terms describing pathophysiology and epidemiology. According to the adopted strategy, the focus was on the latest publications from 2017–2025, which constitute the main axis of considerations. However, highly valued, older studies of fundamental importance for understanding pathophysiological mechanisms were not excluded from the review.

2. Structure and function of heart valves

2.1. Mitral and aortic valves: The mitral valve (MV) apparatus is a dynamic complex consisting of two leaflets, the subvalvular apparatus (papillary muscles and chordae tendineae), and the mitral annulus (13). The leaflets are divided into the anterior leaflet, with a trapezoidal shape occupying one-third of the valve circumference, and the broader posterior leaflet, occupying two-thirds of the circumference. From a clinical perspective, the leaflets are divided into segments (A1-A3, P1-P3) (14). A key role in structural integrity is played by the mitral annulus – an oval, saddle-shaped structure. It serves as an attachment site for the leaflets and connects the left atrium with the left ventricle. During systole, its size decreases by approximately 25%, which allows for optimal leaflet coaptation and prevents regurgitation (13).

The aortic valve apparatus is composed of: the left ventricular outflow tract (LVOT), the aortic annulus, three semilunar cusps, three sinuses of Valsalva, and the sinotubular junction (STJ). The aortic annulus, described as a virtual ring, is a functional structure determined by the lowest attachment points of the cusps to the aortic wall (15,16). The cusps are symmetrical structures forming an extension of the sinuses of Valsalva, which give rise to the left and right coronary arteries and serve the function of unloading the cusps and reducing the forces acting upon them (16).

2.2. Tricuspid and pulmonary valves: The tricuspid valve (TV) apparatus consists of three leaflets of varying sizes (anterior, septal, and posterior). Similar to the mitral valve, the leaflets are stabilized by papillary muscles and chordae tendineae, which connect to the wall of the right ventricle and the interventricular septum (17). From a clinical standpoint, it is worth mentioning that the tricuspid valve annulus is structurally weaker compared to the mitral valve annulus, which is due to a reduced amount of fibrous tissue and collagen in this area. This vulnerability makes the TV functionally particularly susceptible to secondary structural changes occurring in this region of the myocardium (17).

The pulmonary valve consists of three semilunar cusps, similar to the aortic valve. Due to the significantly lower pressures prevailing in the pulmonary circulation, its acquired defects are marginally present in the literature and constitute a negligible percentage of the VHD burden.

3. Pathophysiology of valvular diseases

3.1. Mechanisms of degeneration (calcification, inflammation, mechanical stress): Calcific aortic valve disease (CAVD) is the primary cause of aortic stenosis (AS) and affects a significant percentage of elderly patients. Until recently, this phenomenon was treated as a passive process of degeneration and wear-and-tear occurring with age; however, this has been redefined by new research in this field. It turned out to be an active inflammatory and fibrotic process, in which oxidative stress, lipid disorders, and chronic inflammation play a major role (18,19).

This process begins with endothelial damage and the accumulation of oxidized lipoproteins (ox-LDL), which serves as the primary inflammatory signal (18). Subsequently, local inflammation develops, accompanied by

macrophage migration and the expression of cytokines (e.g., TNF-α), which accelerate tissue damage. A crucial role here is played by the aforementioned oxidative stress, which stimulates the inflammatory cascade through an increased amount of oxidized phospholipids and LDL, being the mechanism linking CAVD with tobacco smoking and dyslipidemia. Furthermore, an important aspect is the action of omega-3 fatty acids, which, by inhibiting the lipid oxidation process, also inhibit the calcification process (18).

The mechanism leading to the above-described process is biomineralization, which acts similarly to osteogenesis (18). Oxidative stress, through various metabolic pathways, stimulates osteoblast synthesis – this results in the mineralization of the extracellular matrix and, ultimately, the development of symptomatic CAVD (18,19).

Besides metabolic factors, genetic factors also play an important role here. It has been shown that polymorphisms within lipoprotein A (LPA: rs10455872 and rs3798220), as well as mutations in the NOTCH1 gene, are associated with an increased risk and rate of calcification (19).

3.2. Regurgitation – structural and functional determinants: In the context of modifiable risk factors, mitral and tricuspid valve regurgitation are of the greatest significance. Aortic valve regurgitation will not be discussed in detail because its etiology (aortic dilation, congenital defects) has fewer connections with the aforementioned factors, which are the subject of this study.

Valvular regurgitation is divided into two types: primary (organic), caused by changes within the valve leaflets, and secondary (functional), caused by changes in paravalvular structures (20).

The etiology of primary mitral regurgitation includes myxomatous degeneration of the leaflets, post-inflammatory changes (rheumatic fever, infective endocarditis), or drug-induced damage (20,21). Secondary regurgitation arises as a result of ischemic processes of the heart or other conditions disrupting the optimal function of the myocardium. In such cases, leaflet coaptation is impaired despite the absence of pathology in their structure (22).

Secondary/functional regurgitation predominates within the tricuspid valve (23). Its most common mechanism involves disturbances within the pulmonary circulation, causing pulmonary hypertension. Consequently, remodeling of the right ventricle and dilation of the tricuspid valve annulus occur (24).

3.3. The role of comorbidities in the pathophysiology of VHD: Among the previously discussed risk factors for VHD (25), it is also necessary to mention comorbidities that exacerbate the calcification process.

A study conducted on the Spanish NEFRONA population (26) demonstrated a strong correlation between the progression of valve calcification and the occurrence of chronic kidney disease. Over two years of observation, the percentage of patients with calcification increased from 30% to 43.1% (27). The most probable mechanism is a secondary disturbance of calcium-phosphate metabolism, which directly promotes the mineralization of soft tissues.

Despite the declining importance of rheumatic fever in developed countries, it remains a significant problem in lower-GDP nations – especially in Africa. In Ethiopia, as many as 86% of valvular heart disease cases are triggered by this clinical entity. This is attributed to high population density and limited access to antibiotics (28).

4. The impact of tobacco smoking on valvular heart diseases

4.1. Mechanisms of action of tobacco smoke on the cardiovascular system: The impact of tobacco smoking on heart valves is a multifaceted process. It is closely linked to the mechanisms of degeneration described in the previous section. Two key phenomena leading to calcification remain: an increase in systemic oxidative stress and progressive endothelial dysfunction (18,29).

In the course of chronic exposure to tobacco smoke, an imbalance occurs, resulting in a rapid increase in the level of reactive oxygen species. This results in an increased amount of oxidized phospholipids (OxPL) and oxidized LDL (oxLDL) in the body. The subsequent stage is their accumulation within the valve structures, where they act as potent pro-inflammatory signals, initiating inflammation and the structural remodeling of the leaflets (18,29).

4.2. Associations of smoking with inflammatory and calcific processes: Progressive endothelial dysfunction results directly from a systemic deficiency of nitric oxide (NO) in smokers. This triggers a complex signaling cascade, leading to the activation of the nuclear transcription factor NF-κB. In addition, there is increased expression of dipeptidyl peptidase-4 (DPP-4), an enzyme that inhibits the protective signaling of insulin-like growth factor 1 (IGF-1). In combination, these phenomena result in the promotion of osteogenic differentiation of valve cells – the calcification process (18,29) (Figure 1).

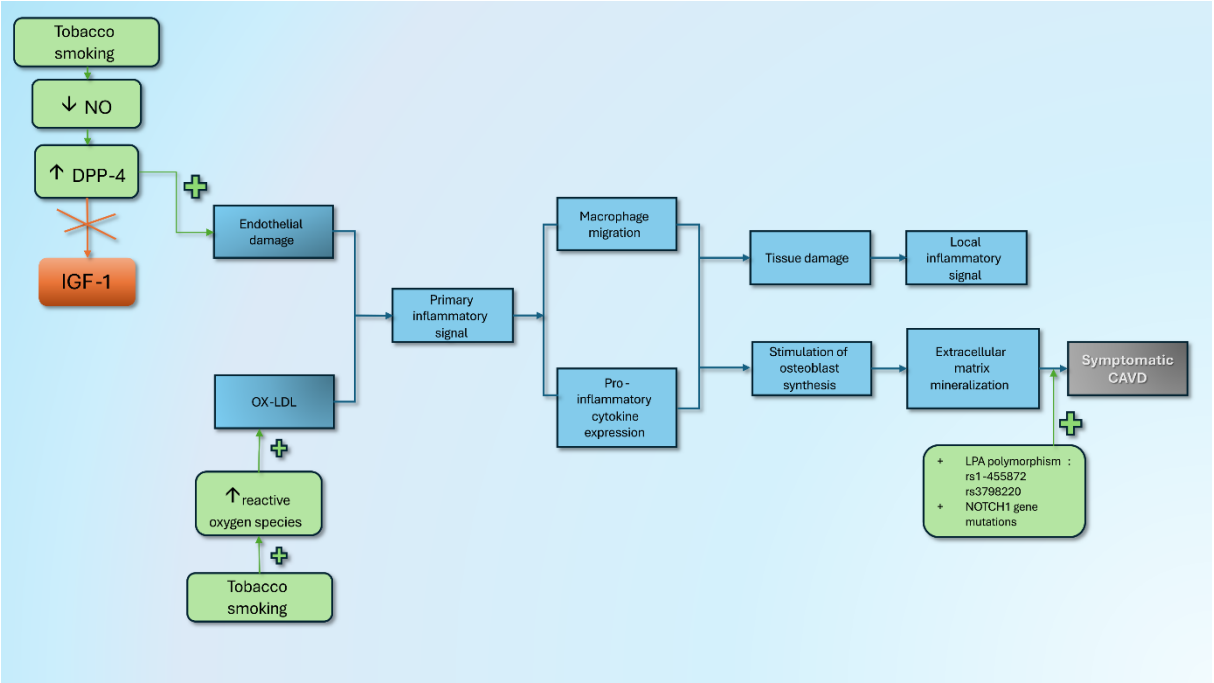

Figure 1. Pathomechanism of tobacco smoking-induced calcific aortic valve disease (CAVD), including molecular pathways and modifying genetic factors.

4.3. Smoking as a factor in the progression of aortic stenosis: In assessing the impact of smoking on the progression of AS, considering coexisting factors and research methodology remains a highly important issue for the drawn conclusions. Very interesting data is provided by a prospective study on a northern Swedish population, which evaluated patients years before the need for cardiac surgical intervention (30).

A multivariate model demonstrated that active smoking was associated with a significant increase in the risk of AS (HR 1.44; 95% CI 1.04 – 1.99). Importantly, after excluding patients operated on within the first 5 years from the start of observation (to eliminate the impact of pre-existing disease), this risk increased even further – reaching an HR of 1.73 (30).

It should be noted, however, that after excluding patients who were found to have concomitant coronary artery disease (CAD) on angiography, the association between smoking and AS lost statistical significance. This suggests that traditional risk factors, including smoking, have a high predictive value primarily in the group of patients with accompanying coronary atherosclerosis (30).

These conclusions are supported by a genetic study using Mendelian randomization (MR) on a population of over 360,000 Europeans. It did not show a direct association between a genetic predisposition to smoking and AS. The researchers suggest that the increased risk observed in clinical studies may result from confounding factors, such as an unhealthy lifestyle, which are statistically more prevalent among smokers (31).

4.4. Data from clinical and epidemiological studies: Despite the complexity of molecular mechanisms, epidemiological studies unequivocally position smoking as one of the most important modifiable risk factors for CAVD from a population perspective:

- SCAPIS study (Sweden): In a large cohort of middle-aged individuals (50-64 years), smokers had a 37% higher risk of developing CAVD compared to non-smokers (OR 1.37; 95% CI 1.25–1.51; $p < 0.001$) (6).
- Asian population: Studies on a southern Chinese population (aged 65+) confirm this trend, indicating a 34.1% higher risk of valve degeneration in smokers (OR 1.341; 95% CI 1.132–1.589; $p < 0.001$) (32,33).
- Global analysis: The Global Burden of Disease Study 2019 report analyzed data from 204 countries, demonstrating a strong correlation ($R = 0.75$; $p < 0.001$) between the prevalence of smoking in the population and the standardized incidence rate of CAVD. In the analysis of modifiable risk factors, smoking ranked at the very top, second only to alcohol consumption ($R = 0.79$) (34).

4.5. Summary and conclusions: Tobacco smoking constitutes a highly significant risk factor for the development of VHD. Although its impact on isolated aortic stenosis may be partially masked by coexisting coronary artery disease, strong epidemiological evidence justifies the absolute necessity of smoking cessation as a key element in the prevention of VHD.

5. The impact of alcohol on the development and progression of valvular heart diseases

5.1. The impact of alcohol on the myocardium (background for valvular changes): The impact of the toxic effect of alcohol on the myocardium manifests clinically as alcoholic cardiomyopathy (ACM). It is defined as

myocardial damage in individuals consuming at least 80 g of ethanol daily for a period longer than 5 years, in whom other causes of dilated cardiomyopathy have been excluded (35,36).

The direct toxic effect of ethanol and its main metabolite – acetaldehyde – leads to impaired contractility of the left or both cardiac ventricles. At the cellular level, exacerbated apoptosis of cardiomyocytes occurs, along with their replacement by connective tissue. A key pathophysiological mechanism in the context of systolic dysfunction involves disturbances in calcium homeostasis. As a result of abnormal calcium flow in the cytosol, the sensitivity of myofilaments to calcium ions changes, and the activity of L-type calcium channels is impaired. This results in the disruption of electromechanical coupling, i.e., the process by which an electrical impulse translates into a mechanical contraction (35).

Additionally, alcohol induces an energy deficit, deregulation of protein synthesis, and oxidative stress (through the activation of the NOX2 enzyme). The sum of these phenomena leads to thinning of the heart walls, contractility disorders, and ultimately ventricular dilation (36).

The genetic component also plays a significant role in the pathogenesis of ACM. In patients who are carriers of titin-truncating variants (TTNtv), the left ventricular ejection fraction was reduced by an additional 8.7% compared to individuals without this predisposition (37).

5.2. Alcoholic cardiomyopathy – secondary valvular changes: In the context of valvular heart diseases, alcohol rarely affects the structure of the leaflets. Its effect is secondary – through the promotion of ventricular dilation, the stretching of the valve annuli (mainly mitral and tricuspid) occurs. This leads to impaired leaflet coaptation and the development of functional (secondary) regurgitation (Figure 2). These changes remain potentially reversible – introducing total alcohol abstinence in the early stages of the disease may lead to an improvement in ventricular function and the resolution of regurgitation (35).

5.3. The relationship between alcohol consumption and the progression of stenosis/regurgitation: Epidemiological studies indicate a complex relationship between alcohol and valvular heart diseases. A study on a Swedish population (7) analyzing the risk of AS demonstrated a correlation – light alcohol consumption (1–6 drinks/week) was associated with a reduced risk of aortic stenosis, and moderate consumption (up to 14 drinks/week) was neutral compared to abstainers (1 drink = 12 g of ethanol). However, consumption exceeding these amounts did not result in an increased risk of developing stenosis. The authors emphasize that although alcohol does not directly induce AS, its abuse leads to the aforementioned ACM, which is a cause of severe secondary regurgitation (7).

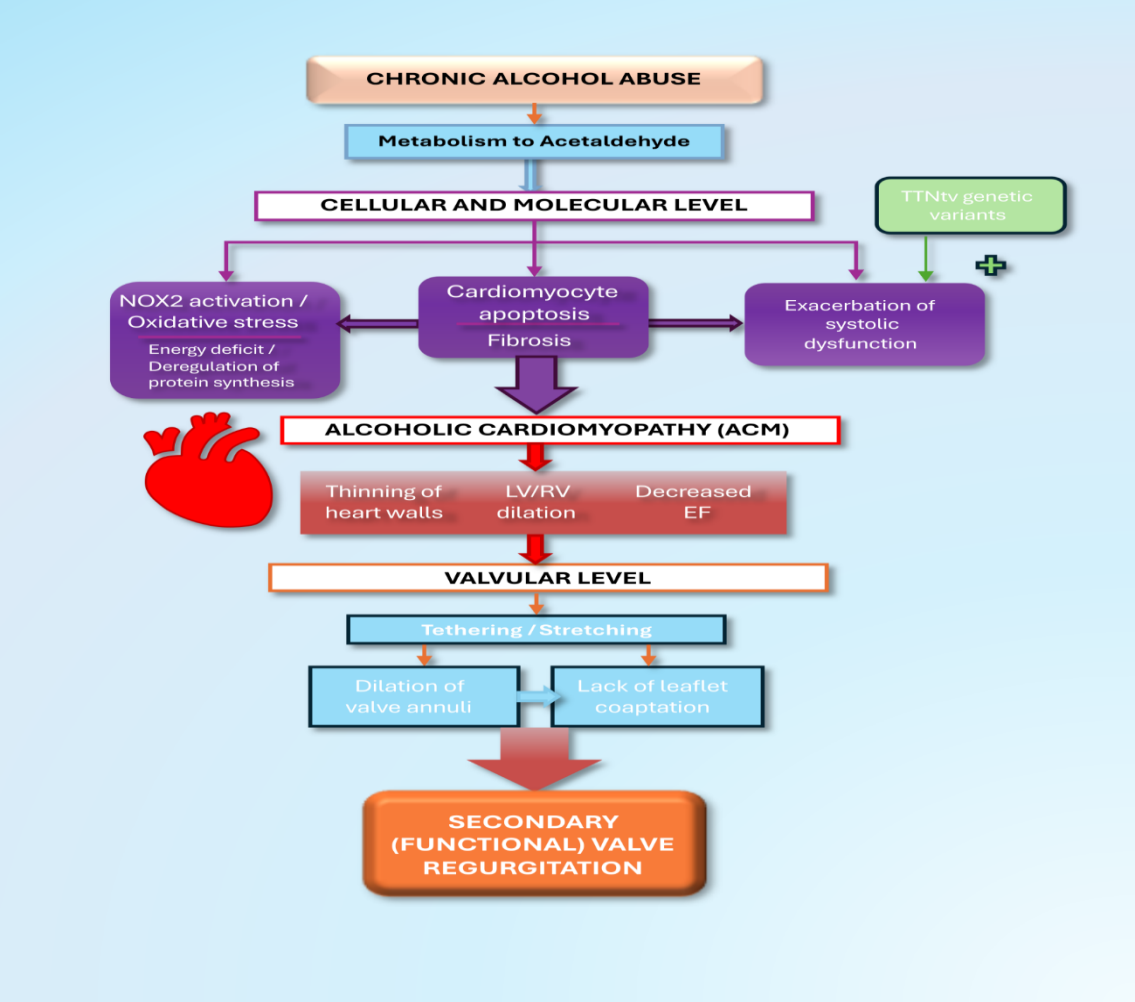

Figure 2. Schematic of the pathophysiological cascade leading to the development of secondary (functional) atrioventricular valve regurgitation in the course of alcoholic cardiomyopathy (ACM).

5.3. The relationship between alcohol consumption and the progression of stenosis/regurgitation: Epidemiological studies indicate a complex relationship between alcohol and valvular heart diseases. A study on a Swedish population (7) analyzing the risk of AS demonstrated a correlation – light alcohol consumption (1–6 drinks/week) was associated with a reduced risk of aortic stenosis, and moderate consumption (up to 14 drinks/week) was neutral compared to abstainers (1 drink = 12 g of ethanol). However, consumption exceeding these amounts did not result in an increased risk of developing stenosis. The authors emphasize that although alcohol does not directly induce AS, its abuse leads to the aforementioned ACM, which is a cause of severe secondary regurgitation (7).

5.4. Overview of clinical data and population studies: Globally, alcohol remains one of the most significant risk factors. The Global Burden of Disease 2019 report showed that alcohol consumption exhibits the strongest correlation with the standardized incidence rate of CAVD among all lifestyle factors ($R = 0.79$; $p < 0.001$), even surpassing the impact of tobacco smoking ($R = 0.75$) (34).

5.5. Summary and conclusions: Excessive alcohol consumption leads to the development of dilated cardiomyopathy, which is the main cause of secondary atrioventricular valve regurgitation. Although moderate consumption does not appear to increase the risk of aortic stenosis, the strong global correlation between alcohol consumption and CAVD, as well as the toxic effect of ethanol on the myocardium, make the reduction of alcohol intake a key element in the prevention of VHD.

6. Discussion

6.1. Comparison of the strength of evidence for tobacco smoking and alcohol: An analysis of the available literature indicates significant differences in the mechanisms and the strength of evidence linking the discussed risk factors with VHD. In the case of tobacco smoking, epidemiological evidence is strong and consistent across observational studies, indicating a 34-37% increase in the risk of aortic stenosis (6,32). This mechanism is directly associated with degenerative processes (calcification) and oxidative stress. An important aspect also involves genetic studies, which suggest that this association may be partially modified by coexisting factors, such as obesity or coronary artery disease (31).

In the case of alcohol, the situation is different. Although global data indicate a significant correlation between alcohol consumption and CAVD (R = 0.79) (34), the pathophysiological mechanism is more complex. On the one hand, alcohol exerts a toxic effect on the myocardium, leading to cardiomyopathy and severe secondary regurgitation (35); on the other hand, moderate consumption does not show a linear increase in the risk for aortic stenosis itself (7).

6.2. Possible common pathophysiological pathways: Despite differences in the clinical picture (stenosis in the case of smoking, regurgitation in the course of alcoholism – as summarized in Table 1), oxidative stress appears to be a common denominator for both factors. Both tobacco smoke (through oxidized lipids, ox-LDL) and ethanol metabolites (activation of the NOX2 enzyme) lead to a disruption of the oxidative balance in heart tissues (18,36). This suggests that reducing oxidative stress through lifestyle modifications may be a universal preventive strategy for valvular heart diseases – inhibiting both degenerative processes and adverse ventricular remodeling.

Feature / Risk factor	Tobacco smoking	Chronic alcohol abuse
Main pathomechanism	Oxidative stress, chronic inflammation, ox-LDL	Direct toxicity to cardiomyocytes (ethanol/acetaldehyde)
Type of valve damage	Primary (organic leaflet damage)	Secondary (functional, without structural changes in leaflets)
Dominant defect	Aortic valve stenosis	Atrioventricular valve regurgitation (mitral, tricuspid)
Target process	Biomineralization (calcification, CAVD)	Dilation of valve annuli (due to cardiomyopathy)
Potential for reversibility	Calcific changes are largely irreversible	Early secondary regurgitation may be reversible after abstinence

Table 1. Comparison of tobacco smoking and chronic alcohol abuse in the context of the pathomechanisms of valvular heart diseases.

6.3. Limitations of available studies: A significant limitation of the current state of knowledge is the methodological heterogeneity of the studies. Many analyses regarding tobacco smoking do not differentiate patients with isolated aortic stenosis from those with concomitant coronary artery disease, which may overestimate the calculated risk (30). In the case of alcohol, most data come from observational studies, which may be burdened by bias resulting from the underestimation of consumption by these patients. Additionally, there is a lack of large, prospective studies evaluating the potential reversibility of early valvular changes following the cessation of the discussed substances.

7. Conclusions: Valvular heart diseases represent a growing health problem, and their development is closely linked to modifiable lifestyle factors. Among them, tobacco smoking and alcohol consumption play a key role. Smoking is a strong promoter of aortic valve calcification in the course of chronic inflammation, oxidative stress, and the promotion of osteogenic processes. Alcoholism affects the valvular apparatus primarily through a secondary mechanism. Toxic myocardial damage (alcoholic cardiomyopathy) leads to the dilation of valve annuli

and the development of functional regurgitation. Despite genetic predispositions, a healthy lifestyle (including nicotine and alcohol abstinence) significantly reduces the risk of valvular defects and prolongs the lives of patients with already diagnosed disease.

Disclosure Section

Abbreviations: VHD - valvular heart diseases, ESC - European Society of Cardiology, CAVD - calcific aortic valve disease, RHD - rheumatic heart disease, AS - aortic stenosis, BMI - body mass index, eGFR - estimated glomerular filtration rate, LPA - lipoprotein A, TGF-β1 - transforming growth factor beta 1, CVHS - cardiovascular health score, BP - blood pressure, MV - mitral valve, LVOT - left ventricular outflow tract, STJ - sinotubular junction, TV - tricuspid valve, ox-LDL - oxidized low-density lipoprotein, TNF-α - tumor necrosis factor alpha, OxPL - oxidized phospholipids, NO - nitric oxide, NF-κB - nuclear factor kappa B, DPP-4 - dipeptidyl peptidase-4, IGF-1 - insulin-like growth factor 1, HR - hazard ratio, CI - confidence interval, CAD - coronary artery disease, MR - Mendelian randomization, OR - odds ratio, ACM - alcoholic cardiomyopathy, NOX2 - NADPH oxidase 2, TTNtv - titin-truncating variants.

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