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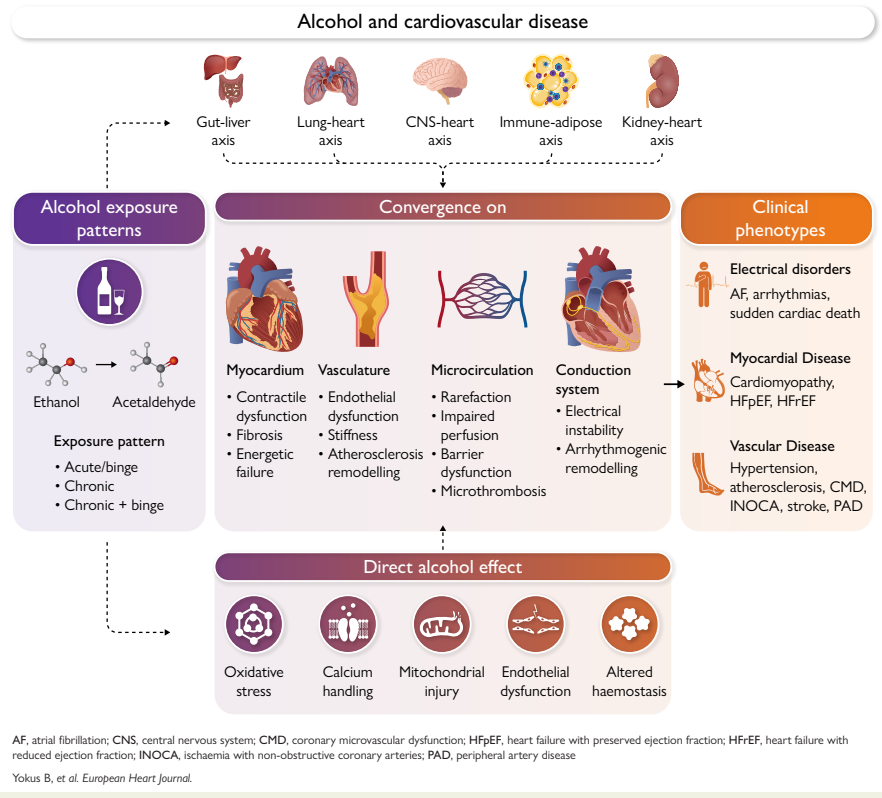
Alcohol and cardiovascular disease: inter-organ crosstalk, microvascular dysfunction, and cardiovascular ageing

Burhan Yokus[1], Zoltan Ungvari [2,3], György Haskó[4], Falk W. Lohoff [5], Thomas Thum [6], and Pal Pacher [1,*]

[1]Laboratory of Cardiovascular Physiology and Tissue Injury, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, 5625 Fishers Lane Rockville, Bethesda, MD 20852, USA; [2]Vascular Cognitive Impairment, Neurodegeneration, and Healthy Brain Aging Program, Department of Neurosurgery, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [3]International Training Program in Geroscience, Doctoral College, Health Sciences Division/Institute of Preventive Medicine and Public Health, Semmelweis University, Budapest, Hungary; [4]Department of Anesthesiology, Columbia University, New York, NY, USA; [5]Section on Clinical Genomics and Experimental Therapeutics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA; and [6]Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Carl-Neuberg-Straße 1, Hannover, Germany

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Graphical Abstract



* Corresponding author. Tel: 301-443-4830, Cell: 240-437-6193, Email: pacher@mail.nih.gov
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Alcohol and the heart: a systems perspective. Alcohol and its metabolite, acetaldehyde, directly injure the myocardium, vasculature, microcirculation, and conduction system. Alcohol also disrupts gut–liver, lung–heart, CNS–heart, immune-adipose, and kidney–heart axes, amplifying cardiovascular injury. Together, these direct and inter-organ mechanisms drive electrical, myocardial, and vascular phenotypes. AF, atrial fibrillation; CMD, coronary microvascular dysfunction; CNS, central nervous system; HFpEF and HFrEF, heart failure with preserved and reduced ejection fraction, respectively; INOCA, ischaemia with non-obstructive coronary arteries; PAD, peripheral artery disease.

Abstract

Alcohol-related cardiovascular risk is being fundamentally reappraised. Observational associations suggesting cardioprotection with light-to-moderate drinking have been challenged by contemporary cohort analyses, Mendelian-randomization studies, biomarker-informed investigations, and updated public-health guidance. Uncertainty nevertheless persists at very low exposure levels and for selected coronary or all-cause outcomes. Alcohol is therefore best viewed as a dose-, pattern-, and host-dependent cardiovascular stressor. Acute or binge drinking, sustained heavy intake, chronic intake with episodic binges, and withdrawal produce overlapping but distinct phenotypes, including hypertension, atrial fibrillation, ventricular arrhythmias, sudden death, alcohol-associated cardiomyopathy, heart failure, stroke, and vascular disease. A systems–cardiology framework is presented in which direct myocardial injury, electrical instability, haemodynamic and autonomic stress, vascular and microvascular dysfunction, and disrupted inter-organ signalling interact. Ethanol and acetaldehyde toxicity, redox imbalance, microbial and inflammatory mediators, neurohumoral activation, and metabolic or electrolyte disturbances can impair endothelial signalling, mitochondrial energetics, excitation–contraction coupling, electrical stability, and repair. Pathway dominance varies across exposure patterns and susceptible hosts; coronary microvascular dysfunction may represent a convergence pathway rather than an obligatory mediator. Cumulative injury can diminish perfusion, contractile, electrical, autonomic, and exercise reserve. Alcohol-related cardiovascular ageing is proposed as a unifying cumulative phenotype encompassing mitochondrial dysfunction, oxidative and nitrative stress, inflammageing, senescence, impaired repair, circadian and epigenetic dysregulation, fibrosis, and ventriculo-arterial uncoupling, although direct human evidence remains incomplete. Age, biological sex, genetics, comorbidities, sleep–circadian disruption, nutrition, medications, and polysubstance misuse may modify pathway dominance and reversibility. Structured exposure assessment and alcohol reduction or abstinence, when indicated, are actionable components of cardiovascular prevention and care.

Keywords Alcohol • Cardiovascular disease • Inter-organ crosstalk • Cardiovascular ageing • Microcirculation • Precision medicine

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Introduction: reframing alcohol-related cardiovascular risk

Alcohol use is a major contributor to global morbidity and mortality, with cardiovascular disease accounting for a substantial share of alcohol-attributable harm among adults older than 40 years.[1–3] The traditional view that light-to-moderate alcohol intake might protect the heart has become increasingly debated. Earlier J-shaped associations were vulnerable to reference-group misclassification, sick-quitter bias, residual confounding, exposure misreporting, and the difficulty of separating ethanol from diet, socioeconomic status, physical activity, and other behavioural correlates of drinking.[4–7] Comparisons with non-drinkers should distinguish lifetime abstainers from former or occasional drinkers and those who stopped because of illness, because self-reported lifetime abstention is unstable and frequently misclassified.[5,8] Apparent cardiovascular benefits of low alcohol intake are substantially attenuated when reference-group bias, exposure misclassification, residual confounding, and selective reporting are addressed.[6,7,9] Kaplan *et al.*[10] reported exceptionally low coronary calcification among the Tsimane; although alcohol exposure was not assessed, the findings illustrate that low lifetime atherosclerotic burden does not require an assumed cardioprotective effect of alcohol.

Contemporary pooled cohorts, Mendelian-randomization analyses, and biomarker-informed studies generally support a continuum-of-risk framework, although causal certainty varies by outcome and very low-dose associations with coronary and all-cause outcomes remain incompletely resolved.[11–18] Evidence is particularly consistent for hypertension and atrial fibrillation. Current cardiovascular guidelines recommend limiting alcohol exposure as part of lifestyle management, particularly for hypertension, atrial fibrillation, and chronic coronary syndromes[19–22] (see Supplementary data online, *Figure S1*).

Alcohol-related cardiovascular disease is often framed either as direct myocardial/vascular toxicity or as a collection of discrete clinical phenotypes. A more specific interpretation separates direct tissue injury from secondary physiological stress. Ethanol and its metabolites can directly impair cardiomyocyte energetics, calcium handling, sarcomeric integrity, electrophysiological stability, and endothelial function. Tachycardia, hypertension, altered loading, diuresis, electrolyte loss, and withdrawal add haemodynamic and autonomic stress. Ethanol metabolism and organ injury also generate redox, inflammatory, microbial, endocrine, and neurohumoral signals across multiple organs.[23,24] The gut, liver, kidney, lung, adipose tissue, immune system, and central nervous system communicate with the heart and vasculature.[25] Gut–liver injury generates microbial, inflammatory, and metabolic signals; renal, pulmonary, immune-adipose, and

CNS-autonomic responses add electrolyte, hypoxaemic, cytokine, and neurohumoral stress. These signals act on endothelium and myocardium and modify platelet, fibroblast, pericyte, and immune-cell responses.[23,24,26–29]

Accordingly, alcohol-related cardiovascular disease is best viewed as a systems disorder involving direct myocardial and electrical injury, haemodynamic and autonomic stress, vascular and microvascular dysfunction, and disrupted inter-organ communication (Graphical Abstract). These pathways converge on the myocardium, conduction system, vasculature, and coronary and systemic microcirculation. Cardiovascular reserve denotes the capacity to augment perfusion, contractile, diastolic, electrical, autonomic, and integrated function during stress. Cumulative injury may contribute to a proposed cardiovascular–ageing phenotype encompassing mitochondrial dysfunction, oxidative and nitrative stress, inflammageing, cellular senescence, impaired repair, circadian disruption, epigenetic age acceleration, fibrosis, and ventriculo-arterial uncoupling.[27,30,31] This is an organizing framework rather than a proven mechanism, and direct human evidence remains incomplete. Age, biological sex, genetic susceptibility, comorbidities, sleep–circadian disruption, nutrition, medication interactions, and polysubstance misuse may determine which pathways become clinically dominant and influence reversibility.

Exposure amount and pattern matter

The cardiovascular consequences of alcohol depend on dose, pattern, duration, and host susceptibility. However, cross-study interpretation of dose–risk relationships is complicated by inconsistent exposure definitions: standard-drink size varies internationally, and thresholds for moderate, heavy, and binge drinking differ across organizations and countries by up to 2.5-fold[9,32] (*Figure 1*).

Beverage type may modify biological exposure through ethanol concentration and delivery, volume, energy content, congeners, and other non-ethanol constituents; however, apparent benefits attributed to red wine remain difficult to disentangle from diet, socioeconomic factors, consumption with meals, and drinking pattern.[33–35] Four clinically relevant phenotypes are acute or binge intake, sustained heavy intake, chronic intake with episodic binges, and withdrawal after heavy use (*Table 1*).

The dominant cardiovascular biology differs by exposure pattern rather than representing co-equal pathways. This prioritization reflects the relative prominence of mechanisms within each exposure phenotype; the pathways are overlapping and interacting rather than isolated or strictly sequential. Acute or binge exposure primarily acts as an electrical, autonomic, and haemodynamic trigger, with human evidence for acute AF, autonomic destabilization, and endothelial dysfunction.[36–38] Sustained heavy intake promotes hypertension, endothelial dysfunction, myocardial injury, and structural remodelling.[19,51] Chronic intake with episodic binges combines a chronic myocardial, vascular, and electrical substrate with acute autonomic and electrophysiological triggers.[44,45] Withdrawal is a high-risk transition characterized by catecholamine excess, hypertension, QT prolongation, electrolyte depletion, and susceptibility to atrial and ventricular arrhythmias.[49,50] Total weekly consumption alone does not capture pattern-dependent cardiovascular risk.[46,47] *Table 1* prioritizes the dominant mechanisms, clinical manifestations, evidence strength, reversibility, and current actionability of these exposure and cessation phenotypes. The categories identify dominant, overlapping mechanisms and do not imply a fixed sequence.

Clinical cardiovascular phenotypes

Alcohol exposure is associated with hypertension, atrial and ventricular arrhythmias, sudden cardiac death, alcohol-associated cardiomyopathy, heart failure, coronary and cerebrovascular disease, and peripheral vascular disease (see Supplementary data online, *Figure S1*). Magnitude and dominant mechanisms vary by dose, pattern, and susceptibility: acute exposure may trigger electrical or haemodynamic events, whereas chronic intake promotes myocardial, vascular, and fibrotic remodelling. No single relative-risk estimate applies across outcomes.

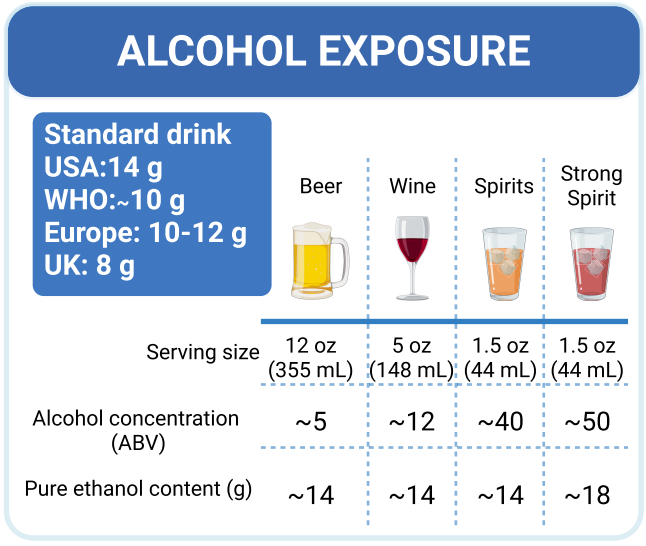
Effect size varies by phenotype and exposure pattern. In more than one million adults without hypertension, habitual alcohol consumption was associated with a 10% higher adjusted risk of incident hypertension, compared with 35% for obesity, 23% for smoking, and 22% for diabetes; the corresponding population-attributable fractions were 2.10%, 6.36%, 3.39%, and 1.55%.[52] Larger relative effects may occur for acute, dose-sensitive phenotypes: one drink per day is associated with an approximately 16% higher risk of incident AF, while alcohol consumed within hours of an event may transiently increase AF risk two- to three-fold.[36,39]

Hypertension is the most consistently demonstrated alcohol-related cardiovascular phenotype. Prospective cohorts support a near-linear association without a clear protective threshold,[40] and longitudinal data show parallel changes in light-to-moderate alcohol intake and blood pressure in both sexes.[53] Mechanisms include sympathetic and renin-angiotensin-aldosterone activation, vascular oxidative stress, impaired nitric-oxide bioavailability, and vascular stiffening. Blood pressure may fall within weeks of substantial reduction or abstinence, supporting reversibility, and alcohol reduction is endorsed in contemporary hypertension guideline.[21,41] Although the individual effect is generally smaller than that of severe hypertension, its population relevance is substantial because exposure is common and modifiable.

Atrial fibrillation has one of the clearest dose-sensitive relationships with alcohol. In pooled European cohorts, one drink per day was associated with an approximately 16% higher risk of incident AF,[39] while abstinence reduces recurrence and burden in regular drinkers with established AF.[54] Acute alcohol exposure promotes autonomic imbalance, atrial ectopy, QTc prolongation, and triggered activity, whereas chronic exposure promotes atrial enlargement, fibrosis, slow conduction, and electrical remodelling.[38,45] Sleep disruption, withdrawal, electrolyte depletion, cardiomyopathy, and stimulant or sedative co-use further amplify risk.

Life-threatening ventricular arrhythmias and sudden cardiac death are less well characterized than AF. Chronic heavy intake may create an arrhythmogenic substrate through ventricular dilation, fibrosis, mitochondrial and calcium-handling abnormalities, connexin and ion-channel remodelling, and acquired QT prolongation. Binge exposure, withdrawal, catecholamine excess, electrolyte depletion, hypoxaemia, or stimulant co-use may then provide the trigger.[45,49] Sudden death is therefore

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Core Definitions by Major Organizations

Organizations	Standard Drink	Moderate / Low-Risk Drinking	Heavy Drinking	Binge Drinking
National Institute on Alcohol Abuse and Alcoholism	14 g	Men: ≤2/day; Women: ≤1/day	Men: ≥5/day or ≥15/week; Women: ≥4/day or ≥8/week	≥5 (men) / ≥4 (women) in ~2h (BAC ≥0.08%)
Centers for Disease Control and Prevention	~14 g	Men ≤2/day; Women ≤1/day	Men ≥15/week; Women ≥8/week	≥5 (men) / ≥4 (women) per occasion
Dietary Guidelines for Americans	~14 g	Men ≤2/day; Women ≤1/day	Above moderate = increased risk	Uses NIAAA/CDC definition
World Health Organization	~10 g	No fixed "safe" level; lowest risk = minimal intake	"Harmful use" defined by health impact	Not standardized globally (risk-based approach)
UK Chief Medical Officers	8 g (Unit)	≤14 units/week (men & women)	>14 units/week = increasing risk	>8 units (men) / >6 units (women) per occasion
European Union (consensus / country-based)	~10–12 g	Men: 20–40 g/day; Women: 10–20 g/day	>40 g/day (men); >20 g/day (women)	~60 g per occasion (varies by country)
Canadian Centre on Substance Use and Addiction (CCSA)	13.6 g	0 drinks → no risk 1–2/week → low risk 3–6/week → moderate risk	≥7/week → increasingly high risk	Previously ≥4–5 drinks/occasion
National Health and Medical Research Council (Australian NHMRC)	10 g	≤10 drinks/week; ≤4/day	>10/week or >4/day	≥4 drinks/occasion
Ministry of Health, Labour and Welfare (Japan)	~20 g	≤20 g/day	≥40–60 g/day	Not formally standardized
Chinese Dietary Guidelines	~10 g	≤25 g/day (men); ≤15 g/day (women)	>25–40 g/day (men); >15–20 g/day (women)	Not standardized

Figure 1 Core definitions of alcohol exposure used by major organizations/countries. Summary of selected organizational definitions for standard drink size, heavy drinking, binge drinking, and moderate or lower-risk drinking. Thresholds are not directly interchangeable because standard drink size, units of measurement, risk framing, and sex-specific cut points differ across jurisdictions. US definitions generally use a 14 g standard drink; UK guidance uses an 8 g unit; Australian guidance uses a 10 g standard drink; and European and international definitions vary by country or context. Where organizations do not define a single threshold, the table reports the prevailing risk-based guidance or indicates that no standardized definition is available. ABV, alcohol by volume; BAC, blood alcohol concentration; CCSA, Canadian Centre on Substance Use and Addiction; CDC, Centers for Disease Control and Prevention; CMO, Chief Medical Officer; EU, European Union; NHS, National Health Service; NHMRC, National Health and Medical Research Council; NIAAA, National Institute on Alcohol Abuse and Alcoholism; WHO, World Health Organization

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Table 1 Prioritized cardiovascular biology according to alcohol exposure and cessation phenotype

Exposure or cessation phenotype	Dominant biology and pathway priority	Principal cardiovascular manifestations	Strength of evidence	Potential reversibility	Current clinical actionability
Acute or binge exposure[36–38]	Primary: sympathetic activation, vagal withdrawal, atrial electrophysiological instability, tachycardia and haemodynamic variability. Secondary: endothelial dysfunction, vasodilatation, diuresis and electrolyte loss.	Acute AF, atrial or ventricular ectopy, transient blood-pressure elevation or variability, endothelial dysfunction, ventricular arrhythmias mainly in susceptible individuals.	High for acute AF, autonomic dysfunction and endothelial impairment in humans; moderate for ventricular arrhythmias and sudden death.	Functional abnormalities generally resolve over hours to days after clearance, although recurrent exposure may promote longer-term remodelling.	Identify binge pattern; advise avoidance in AF or arrhythmia-prone patients; assess blood pressure, rhythm, sleep and electrolytes when clinically indicated.
Sustained heavy intake[39–43]	Primary: hypertension, sympathetic and RAAS activation, endothelial dysfunction, mitochondrial injury and myocardial remodelling. Secondary: inflammation, lipotoxicity, fibrosis, vascular stiffness and impaired repair.	Hypertension, AF, alcohol-associated cardiomyopathy, HFrEF or HFpEF-like phenotypes, stroke and vascular disease.	High for hypertension and AF; moderate-to-high for cardiomyopathy; detailed cellular and microvascular mechanisms are supported mainly by translational and preclinical studies.	Blood pressure and arrhythmia burden may improve within weeks to months; ventricular function may recover over months after abstinence if fixed fibrosis is limited.	Alcohol reduction or abstinence; guideline-directed treatment of hypertension, AF and heart failure; targeted echocardiography or CMR in suspected myocardial disease.
Chronic intake with episodic binges[44–48]	Primary: chronic myocardial, vascular and electrical substrate combined with acute autonomic, haemodynamic and electrophysiological triggers. Secondary: amplified mitochondrial dysfunction, oxidative and nitrative stress, steatosis and electrolyte-sensitive triggered activity.	Coronary and ischaemic-stroke risk; adverse post-MI prognosis; AF, long-QT and ventricular arrhythmias; myocardial injury and acute heart-failure decompensation.	Moderate human evidence for pattern-dependent coronary, stroke and post-MI risk; strong preclinical evidence for synergistic myocardial injury; mechanistic mediation in humans remains incomplete.	Acute triggers are potentially reversible, but chronic fibrosis, chamber remodelling and electrical substrate may persist.	Assess clustering and timing of intake rather than weekly volume alone; prevent recurrent binges and relapse; consider ECG, rhythm monitoring and electrolyte assessment in high-risk patients.
Withdrawal after heavy use or recurrent withdrawal cycles[45,49,50]	Primary: catecholamine surge, sympathetic activation, vagal withdrawal, QT prolongation and electrolyte depletion. Secondary: hypertension, sleep deprivation, hypoxaemia and increased myocardial oxygen demand.	AF, ventricular tachyarrhythmias, hypertensive crises, decompensated heart failure and withdrawal-associated takotsubo syndrome.	Moderate human evidence from hospital cohorts and clinical series; mechanistic pathways are biologically coherent but incompletely quantified prospectively.	Acute abnormalities often improve over days with appropriately managed withdrawal; repeated cycles may progressively reduce electrical and cardiovascular reserve.	Patients with physiological dependence should undergo medically supervised withdrawal; monitor rhythm, blood pressure and potassium/magnesium in high-risk presentations.

Primary and secondary pathways indicate their relative prominence within each exposure phenotype and do not imply mutually exclusive or sequential mechanisms. Evidence strength was assessed qualitatively. High indicates consistent findings from multiple human studies; moderate indicates supportive but limited or heterogeneous human evidence; and moderate-to-high indicates substantial human evidence with some remaining uncertainty. Strong preclinical evidence refers to consistent experimental findings that require further validation in humans. These categories do not represent a formal GRADE assessment.
AF, atrial fibrillation; CMR, cardiovascular magnetic resonance; ECG, electrocardiogram; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; QT, QT interval; RAAS, renin-angiotensin-aldosterone system.

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better understood through a substrate-trigger model than as a uniform dose-dependent effect.

Mendelian-randomization analyses link genetically predicted alcohol intake to coronary artery disease, ischaemic stroke, and intracerebral haemorrhage.[13,14] Binge patterns are associated with ischaemic stroke; heavy intake increases intracerebral-haemorrhage risk.[48,55] Associations between very low intake and ischaemic stroke or coronary outcomes remain less certain because of residual confounding, reference-group misclassification, and exposure error. Alcohol is also linked to cerebral small-vessel disease, white-matter injury, microbleeds, vascular cognitive impairment, disability, coronary vasospasm, aortic aneurysm, and dissection.[56–61] Experimental and imaging studies suggest blood–brain barrier dysfunction and impaired neurovascular reserve, but these mechanisms are less firmly established in humans than overt stroke associations.[56,62–66]

Alcohol-associated cardiomyopathy is a heterogeneous dilated cardiomyopathy in which cumulative exposure interacts with genetic susceptibility. Rare protein-altering variants in dilated-cardiomyopathy genes, especially titin-truncating variants, are enriched in alcohol-associated cardiomyopathy, supporting a double-hit model in which inherited vulnerability and ethanol exposure interact.[42,43,67] Mechanistically, alcohol-associated cardiomyopathy reflects direct and indirect injury, including mitochondrial dysfunction, oxidative/nitrative stress, acetaldehyde-mediated sarcomeric injury, neurohumoral activation, lipid accumulation, inflammation, and interstitial fibrosis. Women may develop myocardial injury at lower cumulative exposure, although contemporary sex-stratified thresholds remain insufficiently defined. Sustained abstinence, particularly before irreversible fibrotic remodelling, is associated with recovery of left-ventricular function and improved survival, making alcohol cessation the cornerstone disease-modifying intervention.[43]

Alcohol may also contribute to HFpEF through overlapping pathways that include endothelial dysfunction, vascular stiffness, metabolic inflammation, mitochondrial energetic failure, fibrosis, diastolic dysfunction, and ventriculo-arterial uncoupling. Coronary microvascular dysfunction is a plausible contributor, but direct evidence that it mediates alcohol-related HFpEF remains limited. Integrated cardiac magnetic resonance and ^{11}C-acetate PET imaging in asymptomatic chronic male drinkers demonstrates myocardial tissue abnormalities and reduced oxidative metabolism before overt structural disease.[68] In alcohol-associated liver disease, subclinical diastolic dysfunction and elevated NT-proBNP and high-sensitivity troponin suggest a continuum of cardiac involvement rather than a binary cirrhosis-only phenotype.[69] Thiamine-deficiency wet beriberi and withdrawal-triggered takotsubo syndrome remain clinically important phenotypes within the broader alcohol–heart failure spectrum.[50,70,71]

Alcohol-related vascular injury extends beyond the heart and brain. In peripheral artery disease, heavy alcohol use may exacerbate skeletal myopathy through mitochondrial dysfunction, capillary rarefaction, and fibre-type shifts, contributing to weakness, frailty, exercise intolerance, and reduced cardiorespiratory reserve, particularly in older adults.[72] Severe alcohol-associated rhabdomyolysis further illustrates skeletal muscle–cardiorenal coupling, as myocyte injury may precipitate acute kidney injury, electrolyte-mediated arrhythmias, and haemodynamic instability.[73]

Across phenotypes, alcohol acts both as an acute trigger and a cumulative stressor; clinical expression depends on whether electrical, myocardial, vascular, or systemic injury exceeds host reserve.

Inter-organ crosstalk, microvascular dysfunction, and myocardial injury

Alcohol-related cardiovascular disease cannot be explained by direct myocardial toxicity alone. Ethanol and its metabolites can directly injure cardiomyocytes, the conduction system, endothelium, and larger vessels. Gut–liver, renal, pulmonary, immune-metabolic, and autonomic responses provide additional circulating or physiological stress.[23,24,26,74,75] *Figure 2* depicts interacting rather than hierarchical routes whose importance varies by exposure and host. Human evidence is strongest for gut–liver, autonomic, haemodynamic, and electrolyte pathways; pulmonary, renal–endocrine, microbiome–metabolite, and several microvascular links remain predominantly experimental or inferential.

Gut–liver–heart axis: microbial, hepatic inflammatory and lipid signals

Chronic ethanol disrupts intestinal barrier integrity, allowing microbial products into portal and systemic circulation.[76–78] In healthy adults, a single binge rapidly increases circulating endotoxin and bacterial 16S rDNA[79]; experimental models link microbial translocation to transient myocardial and haemodynamic dysfunction.[80,81] Lipopolysaccharide activates TLR4 signalling in hepatic, immune, endothelial, and myocardial cells, amplifying inflammation.[82] Alcohol-induced dysbiosis also modifies microbial metabolites with cardiovascular activity, including phenylacetylglutamine, TMAO, secondary bile acids, and imidazole propionate.[83–87] The alcohol-injured liver contributes to inflammatory, endocrine, and vesicular mediators, including extracellular-vesicle miR-122 and miR-155 and FGF21-related metabolic signals.[28,88,89] In MASLD and MetALD, hepatic, adipose, inflammatory, and vascular stressors likely interact to amplify microvascular dysfunction, myocardial injury, and cardiovascular risk.[29,90–92] Chronic alcohol consumption also dysregulates hepatic lipid metabolism,[93] contributing to elevated circulating triglycerides and LDL cholesterol.[27] Human evidence is strongest for barrier dysfunction, dysbiosis, liver injury, and systemic inflammation; causal mediation of coronary microvascular dysfunction remains less directly established.

Kidney–heart axis: neurohumoral, electrolyte, and uraemic mediators

Alcohol links the kidney–heart axis to cardiovascular disease through acute electrolyte and water shifts, chronic neurohumoral activation, and renal injury. Acutely, ethanol suppresses vasopressin, causing diuresis, free-water loss, and hypokalaemia or hypomagnesaemia, thereby increasing arrhythmic vulnerability. In advanced alcohol-associated liver disease, splanchnic vasodilation reverses this pattern by driving non-osmotic vasopressin release, dilutional hyponatraemia, and water retention.[94] Chronically, alcohol activates sympathetic and renin–angiotensin–aldosterone signalling, promoting vasoconstriction,

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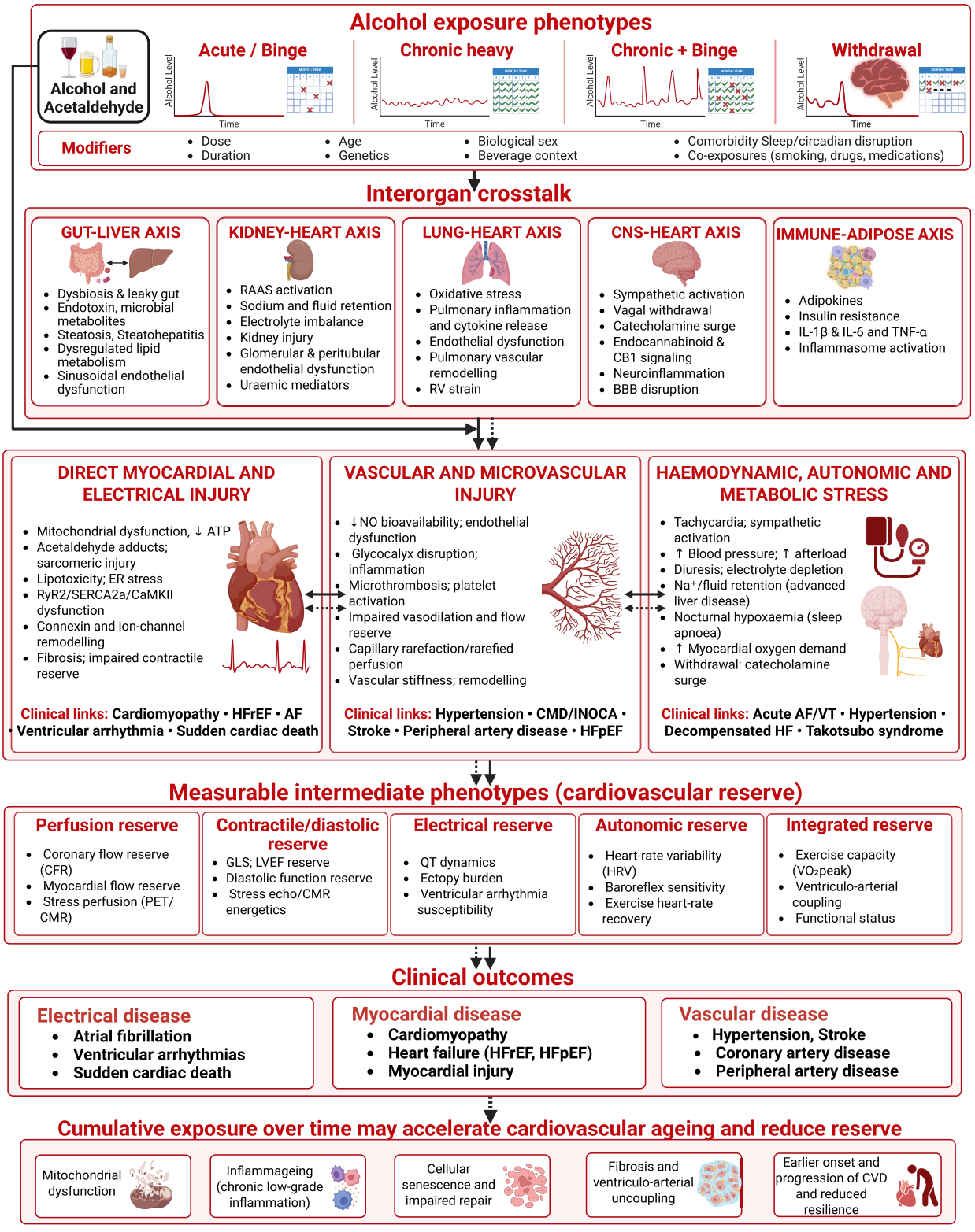


Figure 2 Inter-organ crosstalk and parallel pathways linking alcohol exposure to cardiovascular injury, cardiovascular ageing, and loss of reserve. Alcohol-related cardiovascular injury is shaped by distinct exposure phenotypes-including acute or binge drinking, chronic heavy consumption, chronic-plus-binge exposure and withdrawal-and is modified by dose, duration, age, biological sex, genetics, beverage context, comorbidities, sleep or circadian disruption and co-exposures. Alcohol and its metabolites exert direct systemic molecular effects while also disrupting the gut-liver, kidney-heart, lung-heart, central nervous system-heart and immune-adipose axes. These pathways generate inflammatory, oxidative, metabolic, endothelial, autonomic and neurohumoral stress that converge through three parallel

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sodium retention, afterload, oxidative stress, fibrosis, and myocardial workload.[44]

Alcohol-related renal injury further increases cardiovascular risk through microvascular and tubular toxicity, oxidative stress, glomerular endothelial dysfunction, and impaired sodium handling.[95] Altered renal endocrine and clearance functions (including FGF23, erythropoietin, uraemic toxins, TMAO, and phenylacetylglutamine) may contribute to hypertrophy, vascular stiffness, endothelial dysfunction, and reduced myocardial reserve, although alcohol-specific human evidence remains limited. In advanced liver disease, these pathways converge as hepato–cardio–renal syndrome, with cirrhotic vasodilation, renal hypoperfusion, sodium-water retention, and impaired cardiac reserve reinforcing one another.[96,97]

Lung–heart axis: pulmonary vascular and inflammatory coupling

Chronic alcohol exposure can impair pulmonary antioxidant defence, alveolar macrophage function, surfactant, and epithelial/endothelial barrier integrity, increasing susceptibility to pneumonia, sepsis, and acute respiratory distress syndrome.[98] Pulmonary inflammation, oxidant stress, and hypoxaemia may secondarily impair vascular and myocardial function. Experimental studies also report pulmonary-pressure elevation, vascular remodelling, right-ventricular hypertrophy, and altered endothelin-1, cytokine, and BMPR2 signalling,[99] but clinical validation remains limited. Alcohol can further worsen sleep-disordered breathing and nocturnal hypoxaemia, thereby amplifying sympathetic activation, hypertension, atrial fibrillation, pulmonary vascular stress, and right-heart strain.

Immune–adipose–metabolic axis: inflammatory amplification of vascular and myocardial injury

Alcohol-induced immune and metabolic remodelling amplifies vascular and myocardial injury. Chronic alcohol activates NF-κB/NLRP3 signalling, reprogrammes monocyte-macrophage responses, and increases IL-1β, IL-6, and TNF-α, promoting endothelial activation, senescence, vascular stiffness, myocardial inflammation, and remodelling.[29,100–102] These cytokine pathways may also favour arrhythmogenesis through IL-6-mediated conduction slowing, connexin remodelling, and NLRP3/IL-1β-driven atrial fibrosis. CHIP may further amplify this inflammatory axis, although direct alcohol-CHIP evidence remains limited.[103]

Adipose dysfunction provides a complementary metabolic input. Alcohol lowers adiponectin and leptin, increases lipolysis and ectopic fatty-acid flux, and induces pro-inflammatory adipokines, including TNF-α, IL-6, MCP-1, and resistin.[100] Through portal fatty-acid and cytokine delivery, visceral adipose tissue links alcohol exposure to the gut–liver–heart axis, worsening insulin resistance, ectopic lipid accumulation, vascular inflammation, cardiomyocyte lipotoxicity, and HFpEF-like microvascular dysfunction, particularly in obesity, diabetes, dyslipidaemia, MASLD, and MetALD. Together, immune and metabolic signals may amplify endothelial dysfunction, myocardial fibrosis, and HFpEF-like biology; direct causal evidence for alcohol-specific HFpEF remains limited.

CNS–autonomic axis

The CNS–autonomic axis rapidly converts alcohol exposure into haemodynamic and arrhythmic risk.[104] Alcohol shifts autonomic balance towards sympathetic activation and vagal withdrawal, reflected by reduced heart-rate variability, impaired respiratory sinus arrhythmia, QTc prolongation, and increased arrhythmia burden.[38,105] Chronic heavy use may produce persistent vagal impairment, baroreflex dysfunction, neuroinflammation, and hypothalamic–pituitary–adrenal activation.[106,107] The endocannabinoid–CB1 receptor pathway provides a gut-brain–heart link: acute binge exposure increases cardiac anandamide and depresses contractility, whereas depletion of Gram-negative gut bacteria attenuates both anandamide elevation and cardiovascular dysfunction.[80,81]

Collectively, these inter-organ signals interact with direct ethanol- and acetaldehyde-mediated injury to affect the microcirculation, myocardium, conduction system, and systemic vasculature. Endothelial dysfunction, impaired vasodilation,

Figure 2 Continued
but interacting injury domains: direct myocardial and electrical injury; vascular and microvascular injury; and haemodynamic, autonomic and metabolic stress. The resulting abnormalities reduce cardiovascular reserve across perfusion, contractile and diastolic, electrical, autonomic and integrated functional domains. These intermediate phenotypes can be assessed using coronary or myocardial flow reserve, stress perfusion imaging, ventricular functional reserve, electrocardiographic dynamics, heart-rate variability, baroreflex sensitivity, exercise recovery and cardiopulmonary exercise capacity. Progressive loss of reserve contributes to electrical, myocardial and vascular disease, including atrial and ventricular arrhythmias, sudden cardiac death, cardiomyopathy, heart failure, myocardial injury, hypertension, coronary artery disease, stroke and peripheral artery disease. Cumulative exposure may further accelerate cardiovascular ageing through mitochondrial dysfunction, oxidative stress, inflammageing, cellular senescence, impaired repair, fibrosis and ventriculo-arterial uncoupling, thereby promoting earlier cardiovascular disease and reduced resilience. Solid arrows denote relationships supported by established clinical evidence, whereas dashed arrows denote relationships that are predominantly inferential, preclinical or hypothesis-generating. AF, atrial fibrillation; ATP, adenosine triphosphate; BBB, blood–brain barrier; CaMKII, calcium/calmodulin-dependent protein kinase II; CB1, cannabinoid receptor type 1; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiovascular magnetic resonance; CNS, central nervous system; CVD, cardiovascular disease; ER, endoplasmic reticulum; GLS, global longitudinal strain; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HRV, heart-rate variability; IL, interleukin; INOCA, ischaemia with non-obstructive coronary arteries; LVEF, left ventricular ejection fraction; Na^+, sodium ion; NO, nitric oxide; PET, positron emission tomography; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; RV, right ventricular; RyR2, ryanodine receptor 2; SERCA2a, sarcoplasmic/endoplasmic reticulum calcium ATPase 2a; TNF-α, tumour necrosis factor-α; VO_2peak, peak oxygen uptake; VT, ventricular tachycardia

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inflammation, microthrombosis, capillary loss, mitochondrial dysfunction, abnormal calcium handling, and fibrosis provide overlapping-not obligatory-routes to disease. *Figure 2* shows vascular and microvascular injury as a candidate convergence pathway alongside direct myocardial and electrical injury extending the Camici-Crea framework.[108,109]

Shared cellular injury programmes and cardiovascular ageing

Alcohol-derived and inter-organ signals activate shared cellular injury programmes in the endothelium, myocardium, conduction system, and vasculature (*Figure 3*). Redox and mitochondrial injury impair energetics and perfusion; inflammatory and thrombo-inflammatory signalling promotes endothelial activation and remodelling; impaired repair and fibrosis reduce tissue adaptability. These processes affect perfusion, myocardial, electrical, and autonomic reserve in parallel rather than in a fixed sequence.

The effects of ethanol and acetaldehyde are not uniformly injurious. In isolated-heart and *in vivo* models, brief exposure to either compound reduced ischaemia-reperfusion injury through preconditioning-related signalling.[110–112] These effects varied with dose, timing, genotype, and experimental context; low acetaldehyde concentrations were protective, whereas accumulation was deleterious.[110–114] Translation to humans remains uncertain, and these findings should not be extrapolated to habitual drinking, which entails fundamentally different exposure patterns and may promote hypertension, binge-withdrawal stress, arrhythmogenic remodelling, and cumulative myocardial injury.

Acute binge and chronic heavy exposure impair endothelial function in humans.[37,115] In experimental systems, ethanol and acetaldehyde activate NADPH oxidases, increase superoxide generation. This lowers nitric-oxide bioavailability, promotes peroxynitrite formation, and may uncouple eNOS.[44,100,116–118] The resulting vasodilator impairment, endothelial activation, and leukocyte adhesion reduce perfusion reserve. Evidence supports systemic endothelial dysfunction, whereas universal mediation by coronary microvascular dysfunction remains unproven.

Mitochondrial injury is documented across several alcohol-exposed tissues, but the most direct cardiovascular evidence concerns myocardium and endothelium. In chronic-plus-binge models, ethanol reduces myocardial respiratory-chain activity, ATP generation, membrane potential, and mitochondrial DNA integrity.[44] Age can amplify this response: chronic exposure produces more severe respiratory-chain dysfunction and ventriculo-arterial uncoupling in aged than young hearts.[27] In endothelial cells, mitochondrial reactive oxygen species activate NF-κB, JNK/p38 MAPK, and NLRP3 pathways, linking bioenergetic failure to inflammation, senescence, and barrier disruption.[101,102] In cardiomyocytes, extrahepatic CYP2E1, fatty-acid ethyl esters, and acetaldehyde adducts further impair mitochondrial function, calcium handling, and sarcomeric integrity.[119–121] Alcohol-derived acetate may also influence transcription through ACSS2-dependent histone acetylation, providing a plausible epigenetic route by which exposure reshapes cardiovascular stress responses.[122] These detailed mechanisms derive mainly from experimental models; human imaging and biomarker studies support early energetic and structural abnormalities before overt cardiomyopathy.

Metabolic injury further couples vascular and myocardial dysfunction. Alcohol promotes cardiac and vascular lipid accumulation through hepatic triglyceride spillover, impaired fatty-acid β-oxidation, adipose lipolysis, and fatty-acid delivery to non-adipose tissues.[100] In chronic-plus-binge models, myocardial steatosis coexists with oxidative stress and contractile dysfunction.[44] Lipotoxic intermediates impair insulin signalling, mitochondrial function, and cardiomyocyte viability, linking alcohol-related steatosis to metabolic cardiac injury. This is clinically relevant in MASLD/MetALD, where even modest alcohol exposure may worsen fibrosis and cardiovascular risk.[123,124] These metabolic effects may be especially important in obesity, diabetes, and liver disease, where host factors determine whether vascular, myocardial, or HFpEF-like phenotypes predominate.

Inflammation and thrombo-inflammation can amplify cardiovascular injury. In experimental models, endotoxin and alcohol-derived damage signals activate NF-κB/NLRP3, leading to IL-1β/IL-18 release and pyroptotic signalling. This programme can activate endothelium and fibroblasts and alter atrial conduction. Ethanol-induced endothelial senescence is NLRP3 dependent, and colchicine attenuates the senescence-associated inflammatory response *in vitro*.[102] Colchicine is recommended for selected patients with chronic coronary syndromes and residual inflammatory risk, but no randomized trial has tested it specifically in alcohol-exposed cardiovascular populations.[22,125] Separately, endothelial and platelet activation, tissue factor expression, and impaired fibrinolysis can favour a prothrombotic microvascular phenotype. These observations identify trialable mechanisms, not current alcohol-specific anti-inflammatory therapy.

Cellular senescence and impaired repair may contribute to, but are not synonymous with, cardiovascular ageing. Ethanol induces endothelial and cardiomyocyte apoptosis, necroptosis, pyroptosis, autophagy impairment, and mitophagy failure.[126] Endothelial cells exposed to alcohol show p21 and p16 induction, telomere shortening, SA-β-galactosidase activity, impaired angiogenic capacity, and a senescence-associated secretory phenotype characterized by IL-6, IL-8, and matrix metalloproteinases.[101,102] *In vivo*, chronic alcohol consumption increases vascular and cardiac senescence and caspase activity, especially in aged animals.[27] Glycocalyx loss, pericyte dysfunction, and impaired endothelial repair may convert functional endothelial dysfunction into structural capillary rarefaction.[127–130] Its proposed clinical consequences include impaired perfusion reserve, HFpEF-like physiology, cerebral and peripheral microvascular disease, and reduced exercise capacity, but much of this linkage remains experimental or inferential.

Myocardial and electrical remodelling develop in parallel. Alcohol and acetaldehyde impair excitation–contraction coupling through RyR2, SERCA2a, L-type calcium-channel dysfunction, CaMKII activation, and calcium leak.[131–133] They also promote connexin remodelling, conduction slowing, atrial fibrosis, ventricular dilation, interstitial fibrosis, sarcomeric injury, and blunted contractile reserve.[133–136] These direct myocardial and electrophysiological effects provide substrates for alcohol-associated cardiomyopathy, atrial and ventricular arrhythmias, and sudden cardiac death, independent of (or amplified by) microvascular dysfunction.[36,43,54]

Within this review, alcohol-related cardiovascular ageing is therefore considered an organising cumulative phenotype rather than a single mechanism. It reflects the combined effects

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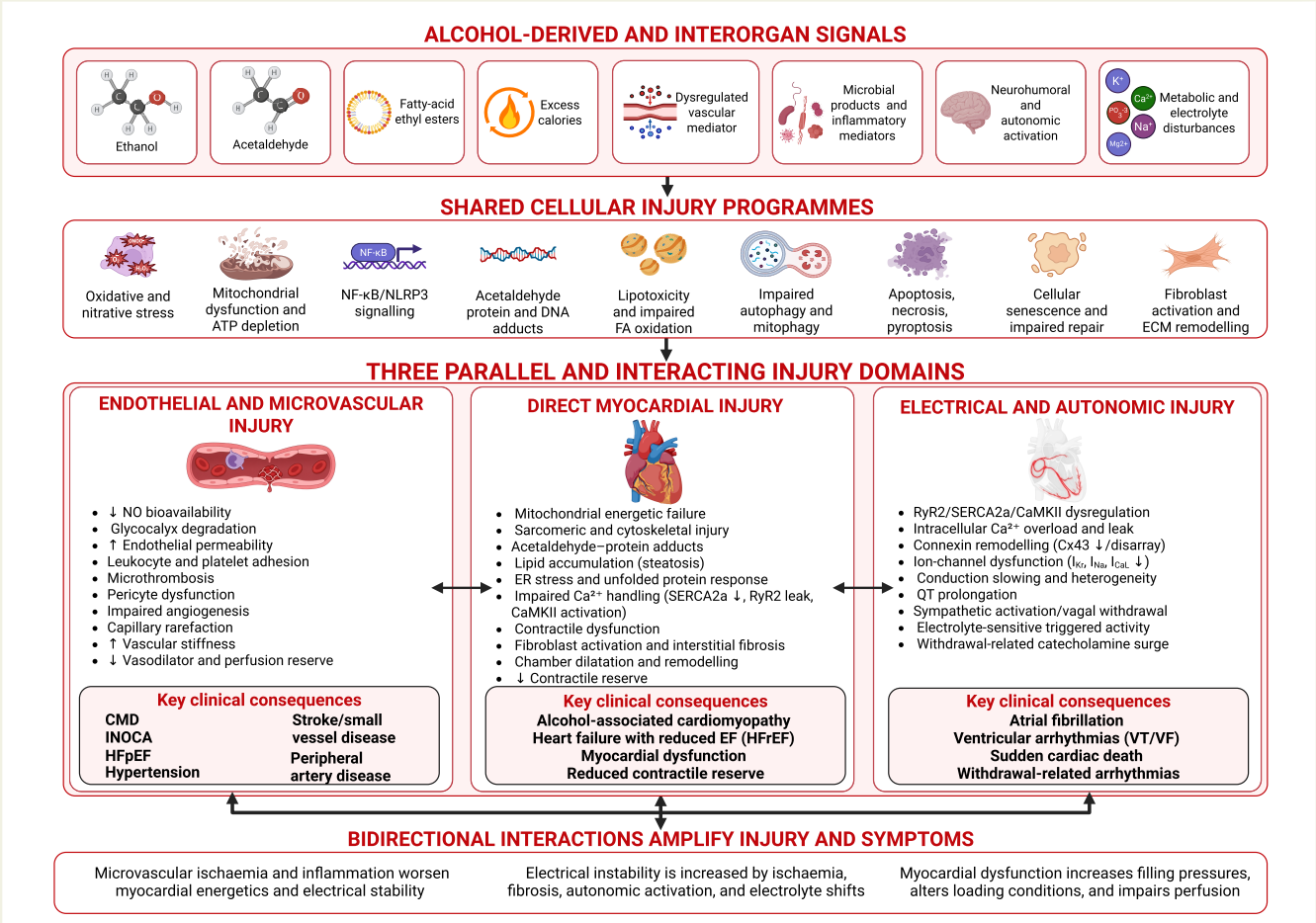


Figure 3 Cellular and tissue-level mechanisms linking alcohol exposure to microvascular, myocardial and electrical injury. Ethanol and acetaldehyde, fatty-acid ethyl esters, redox imbalance, microbial and inflammatory mediators, neurohumoral activation, and metabolic or electrolyte disturbances engage shared cellular injury programmes, including oxidative and nitrative stress, mitochondrial dysfunction, NADPH oxidase and NF-κB/NLRP3 activation, adduct formation, lipotoxicity, impaired autophagy and mitophagy, regulated cell death, cellular senescence, impaired repair, and extracellular-matrix remodelling. These mechanisms act through three parallel and interacting domains: endothelial and microvascular injury, including impaired NO signalling, glycocalyx disruption, increased permeability, leukocyte and platelet adhesion, microthrombosis, pericyte dysfunction, capillary rarefaction, vascular stiffening, and reduced perfusion reserve; direct myocardial injury, including energetic failure, sarcomeric injury, lipid accumulation, endoplasmic-reticulum stress, abnormal calcium handling, contractile dysfunction, fibrosis, and chamber remodelling; and electrical and autonomic injury, including RyR2/SERCA2a/CaMKII dysregulation, connexin and ion-channel remodelling, conduction slowing, QT prolongation, sympathetic activation, vagal withdrawal, and electrolyte-sensitive triggered activity. Bidirectional interactions between these domains amplify ischaemia, inflammation, myocardial dysfunction, and electrical instability. The resulting loss of perfusion, myocardial, electrical, autonomic, and integrated reserve contributes to electrical, myocardial, and vascular disease. With cumulative exposure, mitochondrial dysfunction, inflammageing, cellular senescence, impaired repair, fibrosis, and ventriculo-arterial uncoupling may accelerate cardiovascular ageing and favour earlier disease expression. AF, atrial fibrillation; ATP, adenosine triphosphate; CaMKII, calcium/calmodulin-dependent protein kinase II; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; Cx43, connexin 43; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; FAEE, fatty-acid ethyl ester; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HPA, hypothalamic–pituitary–adrenal; HRV, heart-rate variability; IL, interleukin; INOCA, ischaemia with non-obstructive coronary arteries; LPS, lipopolysaccharide; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; NLRP3, NOD-like receptor family pyrin domain-containing 3; NO, nitric oxide; PET, positron emission tomography; RNS, reactive nitrogen species; ROS, reactive oxygen species; RyR2, ryanodine receptor 2; SERCA2a, sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a; SNS, sympathetic nervous system; TIA, transient ischaemic attack; TNF-α, tumour necrosis factor-α; VO_2peak, peak oxygen uptake; VF, ventricular fibrillation; VT, ventricular tachycardia

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of mitochondrial dysfunction, oxidative and nitrative stress, inflammageing, senescence and impaired repair, epigenetic dysregulation, capillary loss, fibrosis, and ventriculo-arterial uncoupling. These changes may reduce measurable perfusion, contractile, electrical, autonomic, and exercise reserve and favour earlier clinical expression of cardiovascular disease.

Susceptibility modifiers: biological exposure, ageing, sex, genetics, circadian disruption, and co-exposures

Alcohol-related cardiovascular risk is heterogeneous because biological exposure is not equivalent to grams consumed. Age, sex, body composition, genetic background, epigenetic state, comorbidity, circadian alignment, nutritional status, medication exposure, and polysubstance use determine the threshold at which alcohol-induced vascular and myocardial injury becomes clinically apparent. These factors do not merely modify overall risk; they may determine whether electrical, myocardial, vascular, or systemic injury becomes dominant.

Ageing should be considered both a susceptibility factor and a biological consequence of alcohol exposure, because chronic or recurrent intake engages mitochondrial dysfunction, oxidative/nitrative stress, inflammageing, endothelial senescence, fibrosis, circadian disruption, epigenetic age acceleration, and ventriculo-arterial uncoupling, thereby reducing cardiovascular reserve.[27] Experimental data support this interaction: chronic alcohol exposure causes greater respiratory-chain dysfunction, impaired energetics, ventriculo-arterial uncoupling, and molecular cardiovascular injury in aged than young animals.[27] In humans, age-related baroreflex impairment, vascular stiffness, mitochondrial vulnerability, and reduced physiological reserve may render alcohol an age-amplifying insult, further compounded by ageing of the gut–liver axis.[31,137] Direct human evidence that alcohol accelerates cardiovascular ageing as a unified phenotype remains incomplete; the construct is best regarded as an organizing framework supported by convergent molecular, imaging, and epidemiological observations.

Biological sex may modify ethanol pharmacokinetics and cardiovascular susceptibility, whereas gender influences drinking behaviour, reporting, co-exposures, and access to care. Historical studies suggested lower cumulative exposure among women with alcohol-associated cardiomyopathy, but contemporary sex-specific thresholds remain poorly defined.[43,138,139] Recent data show alcohol-related blood-pressure changes in both sexes and frequent or high intake associated with AF in both women and men.[40,53,140] Current evidence therefore supports sex-stratified assessment but not a universally lower cardiovascular-risk threshold in women.

Genetic factors influence both exposure biology and tissue vulnerability. The ALDH2 rs671 loss-of-function variant increases acetaldehyde exposure and has been linked to coronary artery disease, alcohol-associated cardiomyopathy, pulmonary arterial hypertension, and anthracycline cardiotoxicity; its flushing effect may also reduce cumulative intake and modify hypertension risk.[141,142] Because ALDH2 bioactivates organic nitrates, carriers may have impaired nitroglycerin responses.[143] ADH1B rs1229984 modifies ethanol oxidation and supports Mendelian-randomization evidence linking alcohol intake to blood pressure and cardiovascular outcomes.[12] APOE may modify alcohol-related vascular, lipoprotein, and neurocognitive effects.[144,145] In alcohol-associated cardiomyopathy, TTN truncating variants support a double-hit model of inherited myocardial vulnerability and alcohol exposure.[42,43,146] Thus, ADH1B and ALDH2 primarily influence exposure biology, whereas TTN and other cardiomyopathy genes influence tissue vulnerability.

Epigenetic age acceleration may integrate cumulative alcohol-related stress. DNA-methylation clocks, including GrimAge and PhenoAge, partly mediate associations between long-term alcohol use and cardiovascular disease[147]; in Framingham, greater intake was associated with PhenoAge acceleration that partly mediated the alcohol–hypertension association.[148] DunedinPACE and GrimAge V2 also link alcohol use disorder to accelerated biological ageing,[149] while inflammatory-epigenetic signatures may indicate vulnerability.[150] These measures remain research tools rather than validated cardiovascular risk markers.

Clonal haematopoiesis of indeterminate potential (CHIP) may represent an age-related inflammatory amplifier. CHIP may amplify alcohol-related inflammation through IL-1β, IL-6, and NLRP3 signalling, but direct evidence for an alcohol-CHIP interaction remains limited.[103]

Late-evening drinking, binge episodes, withdrawal-related insomnia, shift work, and sleep-disordered breathing may disrupt central and peripheral clocks[151] governing vascular tone, thrombosis, metabolism, and autonomic recovery. Alcohol-related circadian misalignment may therefore amplify blood-pressure variability, endothelial dysfunction, and arrhythmia susceptibility, although its independent long-term contribution remains uncertain.

Cardiometabolic, renal, hepatic, respiratory, and psychiatric comorbidities lower cardiovascular reserve and may amplify alcohol-related injury. Medication interactions also matter clinically, including anticoagulant-associated bleeding, QT-prolonging drugs, antihypertensive hypotension, diuretic-related electrolyte depletion, and hepatotoxicity concerns during lipid-lowering or antiarrhythmic therapy.

Polysubstance misuse is an under-measured risk amplifier. Tobacco adds oxidative and thrombotic stress; stimulants add sympathetic, vasospastic, and myocardial oxygen-demand stress[152]; cannabinoids may alter autonomic tone and exert direct cardiodepressive effects[153]; and opioids or sedatives increase hypoxaemia and cardiorespiratory instability. Alcohol–cocaine co-use generates cocaethylene, which is associated with myocardial injury and sudden death[154] and alcohol–cannabinoid administration exacerbates cardiac dysfunction in an experimental model.[155] Co-use with opioids, including methadone, can compound QT and hypoxaemic risk.[156] These exposures should be assessed in patients with arrhythmia, myocardial injury, or sudden-death risk.

Translational phenotyping and therapeutic opportunities

A systems-cardiology framework requires objective exposure assessment, targeted multiorgan and cardiovascular phenotyping, and interventions addressing both alcohol use and downstream disease. These approaches should be separated by clinical readiness.

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Current clinical practice

Self-reported drinking remains vulnerable to under-reporting, social desirability bias, and poor capture of binge or relapse patterns. Phosphatidylethanol (PEth), a direct ethanol-derived phospholipid, is among the most useful biomarkers of recent moderate-to-heavy exposure, generally reflecting intake over the preceding 2–3 weeks.[157] Urinary ethyl glucuronide and ethyl sulphate provide shorter-window evidence over days, whereas indirect markers, such as γ-glutamyl transferase, carbohydrate-deficient transferrin, mean corpuscular volume, and AST:ALT ratio are less specific and more confounded by liver disease, medications, and metabolic comorbidity. In routine cardiovascular practice, screening means structured assessment of amount, pattern, binge episodes, withdrawal, beverage context, and co-exposures. Biomarkers are reserved for uncertain or clinically consequential exposure; advanced imaging, omics, and wearables are not routine screening tools.

When alcohol is contributing to cardiovascular risk, reduction or abstinence is the principal exposure-directed intervention, particularly before fixed fibrosis or advanced remodelling develops. Reduction lowers blood pressure and arrhythmogenic triggers; abstinence reduces AF recurrence and burden[54] and may permit left-ventricular recovery in alcohol-associated cardiomyopathy.[43] Standard cardiovascular therapies should be used according to established indications.

Selected high-risk phenotypes

In selected patients with unexplained hypertension, AF, cardiomyopathy, heart failure, liver disease, or recurrent relapse, exposure biomarkers may be combined with cardiac biomarkers (NT-proBNP, high-sensitivity troponin), rhythm monitoring, renal and liver indices, and targeted imaging. Broader inflammatory, microbial, or extracellular-vesicle panels remain research-grade.[83,88,89]

Imaging should move beyond resting ejection fraction when clinically indicated. Global longitudinal strain and stress echocardiography can detect subclinical myocardial dysfunction and impaired contractile or diastolic reserve. PET-derived myocardial blood flow and myocardial flow reserve quantify coronary microvascular dysfunction, whereas cardiac magnetic resonance can detect fibrosis, extracellular-volume expansion, stress-perfusion defects, and altered energetics. Integrated liver-heart imaging, coronary CT angiography, and vascular-inflammation imaging may refine assessment in selected patients with liver disease, INOCA, HFpEF-like presentations, alcohol-associated cardiomyopathy, or unexplained exercise intolerance.[158–161] These approaches may identify subclinical myocardial or microvascular dysfunction but should not be used as routine screening in all drinkers.[158–161]

Research and trial enrichment

Multi-omics phenotyping can integrate ALDH2, ADH1B, and TTN variation with proteomic, metabolomic, transcriptomic, and DNA-methylation signatures of inflammation, fibrosis, myocardial injury, and biological ageing.[26] Inter-organ crosstalk and multi-organ imaging frameworks provide methodological infrastructure, but dedicated alcohol–cardiovascular atlases remain lacking.[75,159] Digital phenotyping using continuous ECG, heart-rate variability, photoplethysmography, transdermal alcohol sensing, and continuous glucose monitoring can link exposure timing to arrhythmia, autonomic, metabolic, and sleep responses. These technologies are best regarded as research tools or trial-enrichment strategies rather than established clinical pathways.

Mechanism-based therapies remain largely untested in alcohol-exposed cardiovascular populations. Peripheral CB1 receptor antagonists,[80] microbiome-targeted approaches,[81] ALDH2 activators,[162,163] colchicine,[125] SGLT2 inhibitors, PCSK9 inhibitors,[93] GLP-1 receptor agonists,[164,165] NAD^+-restoring approaches, and senescence-targeting interventions are biologically plausible but require exposure-stratified testing. GLP-1 receptor agonists are of particular interest because they combine established cardiometabolic benefits with emerging evidence for reduced alcohol craving or consumption.[164,165] None should currently be regarded as alcohol-specific cardiovascular therapy.

Clinical and public health implications

Alcohol exposure should be considered in cardiovascular prevention as a modifiable, pattern-dependent risk factor. Current risk calculators, including SCORE2 and the AHA PREVENT equations, do not capture binge exposure, withdrawal cycles, objective alcohol biomarkers, genetic susceptibility, polysubstance use, or microvascular phenotype.[166,167] Future tools should first establish whether drinking pattern and objective exposure measures improve prediction beyond conventional risk factors. Structured alcohol-exposure assessment should be routine in patients with hypertension, AF, heart failure, cardiomyopathy, coronary disease, stroke, or unexplained exercise intolerance; this does not imply routine biomarker, advanced-imaging, or omics screening. AUDIT-C is feasible in cardiology practice, and brief interventions reduce consumption by approximately 10%–20%.[168,169] When behavioural intervention is insufficient, pharmacotherapy for alcohol use disorder should be considered with attention to renal, hepatic, and cardiovascular comorbidity.

Public-health messaging is shifting from a presumed cardioprotective threshold towards a continuum-of-risk model. WHO 2023, Canada 2023, Australia 2020, and 2024 ESC guidance increasingly emphasize lower-risk drinking and alcohol reduction rather than a clearly safe cardiovascular dose.[21,22,170–172] Causal certainty remains outcome-specific: evidence is strongest for hypertension and AF and for stroke with heavy or binge drinking, whereas very-low-dose coronary and all-cause associations remain less certain. For clinical cardiology, the actionable message is narrower: structured exposure assessment and alcohol reduction, when indicated, should be integrated into risk assessment and secondary prevention, particularly for hypertension, AF, stroke, and alcohol-associated cardiomyopathy. Supplementary data online, *Table S1* summarizes the principal clinical, genetic, and experimental evidence.

Future directions and conclusion

Prospective studies should combine objective exposure biomarkers with repeated assessment of drinking pattern, withdrawal, sleep, comorbidity, and cardiovascular outcomes. Priorities include determining whether alcohol reduction reverses subclinical myocardial or vascular injury, whether exposure biomarkers improve risk prediction, and which patients benefit from targeted imaging or rhythm monitoring. Sex-stratified studies are needed

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to define risk thresholds in women and men, particularly for hypertension, AF, HFpEF, alcohol-associated cardiomyopathy, and microvascular dysfunction. Existing cohorts should distinguish genes that modify exposure biology, such as ALDH2 and ADH1B, from genes that modify myocardial vulnerability, such as TTN. Studies of cardiovascular ageing should incorporate prespecified, measurable phenotypes, such as myocardial flow reserve, contractile or diastolic reserve, repolarization reserve, autonomic function, exercise capacity, and ventriculo-arterial coupling, rather than relying on ageing terminology alone.

High-priority trials include biomarker-verified alcohol reduction in AF, hypertension, and cardiomyopathy; wearable studies of binge- and withdrawal-triggered arrhythmia; and exposure-stratified testing of cardiometabolic or anti-inflammatory therapies. Mechanism-targeted treatments should be tested as hypotheses rather than extrapolated from non-alcohol-specific populations.

Alcohol-related cardiovascular disease can be conceptualized as a modifiable, dose-, pattern-, and host-dependent systems disorder. Ethanol and acetaldehyde exert direct myocardial, endothelial, and electrophysiological effects. Gut–liver, kidney–heart, lung–heart, immune-metabolic, and CNS–autonomic responses provide additional inflammatory, metabolic, neurohumoral, haemodynamic, and electrolyte stress. These pathways interact across the myocardium, conduction system, vasculature, and coronary and systemic microcirculation (Graphical Abstract).

Acute binge exposure may act as a trigger, chronic heavy intake as a remodelling stimulus, and recurrent binge-withdrawal cycles as repeated autonomic, haemodynamic, metabolic, and electrical stressors. Microvascular dysfunction is a plausible convergence pathway, but direct myocardial and electrical injury remain parallel determinants of disease. Cumulative injury may contribute to a proposed cardiovascular–ageing phenotype and reduce measurable perfusion, myocardial, electrical, autonomic, and exercise reserve. Direct human validation remains incomplete. Clinical expression depends on age, biological sex, genetic susceptibility, comorbidity, sleep–circadian disruption, medications, nutrition, and polysubstance misuse. Current practice centres on structured exposure assessment, reduction or abstinence when indicated, and guideline-directed cardiovascular care.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Nothing to declare.

Data Availability

No data were generated or analysed for or in support of this paper.

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AI use

ChatGPT 5.5 was used solely for English language editing, Oxford-style grammar, and stylistic refinement. All content was critically reviewed, edited, and approved by the authors, who take full responsibility for the accuracy and integrity of the manuscript. Figures were created with BioRender.com under an NIH institutional license.

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