



Review Article

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Silent but Synergistic: The Convergence of Hypertension and Atherogenic Cholesterol in Lifetime Cardiovascular Risk and Integrated Prevention: A Review

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To Cite This article: Loso Judijanto*, Silent but Synergistic: The Convergence of Hypertension and Atherogenic Cholesterol in Lifetime Cardiovascular Risk and Integrated Prevention: A Review. *Am J Biomed Sci & Res.* 2026 32(4) AJBSR.MS.ID.004181,

DOI: [10.34297/AJBSR.2026.32.004181](https://doi.org/10.34297/AJBSR.2026.32.004181)

Received: 📅 September 07, 2026 Published: 📅 October 21, 2026

Abstract

Hypertension and elevated atherogenic cholesterol are among the most important modifiable determinants of cardiovascular disease, yet they are often detected and managed as separate conditions. This qualitative literature review synthesises contemporary evidence published from 2020 to 2026 on their epidemiological coexistence, converging vascular mechanisms, cumulative exposure, cardiovascular consequences and opportunities for integrated prevention. Blood-pressure-related haemodynamic stress and prolonged exposure to Low-Density Lipoprotein Cholesterol (LDL-C) and other apolipoprotein-B-containing particles converge through endothelial dysfunction, lipid retention, oxidative stress, inflammation, vascular remodelling, arterial stiffness and accelerated atherosclerosis. Cardiovascular risk reflects not only the magnitude of blood pressure and LDL-C at a single examination but also the duration and timing of exposure across the life course. Dietary improvement, sodium reduction, physical activity, weight management, smoking cessation, moderation of alcohol intake and adequate sleep can influence multiple risk pathways simultaneously. Pharmacological blood-pressure lowering and intensive lipid-lowering therapies provide complementary opportunities for risk reduction, while single-pill and polypill strategies may improve adherence in selected populations. Evidence from Indonesia and other Asian settings nevertheless shows important gaps in screening, diagnosis, treatment, adherence and risk-factor control. An integrated prevention architecture combining early detection, validated measurement, total-risk assessment, lifestyle intervention, appropriate pharmacotherapy, adherence support and health-system strengthening may provide greater cardiovascular benefit than fragmented management of individual risk factors.

Keywords: Hypertension, LDL cholesterol, Dyslipidaemia, Atherosclerosis, Apolipoprotein B, Cardiovascular disease, Cumulative exposure, Vascular ageing, Integrated prevention, Indonesia

JEL Classification: I10, I12, I14, I15, I18

Introduction

Cardiovascular Disease (CVD) remains a major cause of premature mortality, disability and health-system expenditure worldwide. Although the clinical endpoints of cardiovascular disease—myocardial infarction, stroke, heart failure, peripheral arterial disease and cardiovascular death—often emerge in middle or later life, their biological foundations accumulate over decades. Among the modifiable exposures contributing to this process, elevated blood pressure and atherogenic lipoproteins occupy particularly important positions because both are common, frequently asymptomatic, biologically causal or strongly implicated in cardiovascular injury, and amenable to prevention and treatment. Global analyses demonstrate that the number of adults living with hypertension has increased substantially, while treatment and control remain highly heterogeneous among countries, with particularly important gaps in many low- and middle-income settings [18,37]. Hypertension and dyslipidaemia should not be understood merely as two abnormal laboratory or clinical measurements. Persistently elevated blood pressure imposes mechanical and haemodynamic stress on arteries, the heart, kidneys, brain and microcirculation, whereas circulating LDL and other apolipoprotein-B-containing particles can penetrate and become retained within susceptible arterial regions, initiating and sustaining atherosclerotic plaque formation. Contemporary prevention guidelines therefore increasingly place both blood pressure and lipid exposure within a broader model of absolute cardiovascular risk rather than treating either variable in isolation [33,34,51].

The importance of considering these conditions together is reinforced by their frequent coexistence. Obesity, insulin resistance, unhealthy dietary patterns, physical inactivity, ageing, smoking and other cardiometabolic determinants can simultaneously increase blood pressure and worsen lipid profiles. Population studies in Asia have documented substantial prevalence of both conditions, and a prospective Chinese cohort found that combinations of hypertension, diabetes and dyslipidaemia were associated with progressively greater cardiovascular risk than the absence of these cardiometabolic abnormalities [52]. In Indonesia and other Southeast Asian populations, hypertension, high LDL-C and related cardiometabolic factors coexist against a background of rapid urbanisation, dietary transformation, population ageing and unequal access to preventive services [2,31,36]. An important clinical and public-health distinction is the difference between cardiovascular risk factors and cardiovascular symptoms. High LDL-C generally produces no specific symptoms, and uncomplicated hypertension is also frequently clinically silent, headache, dizziness, fatigue, dyspnoea, chest discomfort and numbness are therefore not reliable diagnostic indicators of either condition. Acute or severe symptoms may signal established cardiovascular disease or another urgent disorder and warrant appropriate clinical assessment, but prevention depends primarily on objective measurement rather

than waiting for symptoms to appear. Contemporary hypertension guidance consequently emphasises standardised blood-pressure measurement, repeated assessment and appropriate use of home or ambulatory monitoring [30,34,47].

Another major shift in cardiovascular prevention is the movement from snapshot measurements toward the concept of cumulative exposure. The biological impact of LDL-C is related to both its concentration and the duration over which the arterial wall is exposed to atherogenic particles. *Ference, Braunwald and Catapano (2024)* describe this as the LDL cumulative exposure hypothesis: prolonged exposure increases the number of atherogenic particles retained in the arterial wall, increasing accumulated plaque burden and eventually the probability of an acute clinical event. A parallel concept is increasingly relevant to blood pressure because prolonged haemodynamic load contributes to vascular, cardiac, cerebral and renal organ damage over time. These observations suggest that a person experiencing moderately elevated LDL-C and systolic blood pressure for three decades may have a very different lifetime cardiovascular burden from another person with identical measurements that arose only recently [1,15].

This life-course interpretation has important preventive implications. A strategy that waits until short-term cardiovascular risk becomes high may miss years of preventable arterial injury. Conversely, aggressive treatment based solely on one measurement without considering age, baseline cardiovascular risk, comorbidity, adverse effects and patient preferences may lead to inappropriate care. The contemporary challenge is therefore to combine early identification with individualized risk estimation and proportional intervention. SCORE2, SCORE2-OP and other multivariable tools illustrate this approach by integrating systolic blood pressure and cholesterol parameters with age, smoking and other variables, although models developed in one population should not automatically be assumed to perform equally well in another [44,45]. The issue has particular relevance in Asia. The continent carries a large share of global cardiovascular deaths and exhibits considerable heterogeneity in risk-factor patterns, healthcare financing, treatment access and prevention infrastructure [24].

Hypertension is especially relevant to stroke, while dyslipidaemia increasingly accompanies metabolic disease and urban lifestyles. Asian-focused publications have therefore emphasized local risk assessment, home blood-pressure monitoring, primary-care strengthening and contextualized prevention rather than simple transplantation of Western models [10,11,27,28,58]. Accordingly, this qualitative literature review asks how hypertension and atherogenic cholesterol independently and jointly contribute to cardiovascular disease, through which biological pathways their effects converge, how exposure intensity and duration influence lifetime risk, which lifestyle and pharmacological interventions can address both risks, and what implementation challenges must be overcome in Indonesia and comparable low- and middle-income settings. The central argument developed in this review

is that hypertension and atherogenic lipid exposure should be conceptualized as interacting, cumulative vascular insults, and that cardiovascular prevention should therefore progress from fragmented disease management to integrated, life-course risk reduction.

Literature Review

Hypertension as a Chronic Haemodynamic Exposure

Blood pressure is a continuous biological variable, and cardiovascular risk generally rises progressively as pressure increases. Diagnostic categories remain useful for clinical decision-making, but threshold definitions differ somewhat among professional societies because they balance epidemiological risk, measurement strategy, expected treatment benefit and the possibility of adverse effects differently. Recent European and American guidelines nevertheless converge on several principles: blood pressure should be measured accurately, diagnosis should not rely on an isolated poorly standardised reading, cardiovascular risk matters when treatment intensity is considered, and out-of-office measurement can materially improve diagnosis and follow-up [26,34]. Home and ambulatory blood-pressure monitoring are particularly important because office measurements can misclassify patients. White-coat hypertension occurs when office readings are elevated but out-of-office measurements are not, whereas masked hypertension represents the opposite pattern, both phenotypes have implications for cardiovascular risk assessment and management. Home blood-pressure monitoring can also support longitudinal follow-up and patient engagement, while ambulatory monitoring provides information on nocturnal pressure, morning surges and 24-hour variability that cannot be captured by routine office measurement. Accurate implementation requires validated devices, appropriate cuff size, patient education and standardised measurement protocols [30,47,54].

The biological consequences of sustained hypertension extend beyond large-vessel atherosclerosis. Chronic pressure load contributes to left ventricular hypertrophy, atrial remodelling, heart failure, chronic kidney disease, retinal injury, cerebral small-vessel disease and stroke. Hypertension-mediated organ damage is clinically important because it is evidence that elevated pressure has already produced structural or functional consequences and therefore adds prognostic information beyond a single blood-pressure reading [34]. Randomised trials and individual-participant meta-analyses reinforce the modifiability of this risk. The Blood Pressure Lowering Treatment Trialists' Collaboration reported reductions in major cardiovascular events with pharmacological blood-pressure lowering across broad groups, while age-stratified analyses suggest that benefits extend into older age when therapy is appropriately individualized [5,6]. The final SPRINT report and the STEP trial further support the principle that more intensive systolic-pressure lowering can reduce cardiovascular events in selected higher-risk or older populations, although treatment

intensity must be balanced against adverse events, tolerability, frailty and clinical context [48,57].

Atherogenic Lipoproteins as Cumulative Arterial Exposure

The biology of atherosclerosis is inseparable from exposure to apoB-containing lipoproteins. LDL-C is the most widely used clinical lipid measure and remains a central treatment target, but it represents the cholesterol mass contained within LDL particles rather than the number of atherogenic particles themselves. ApoB is present as one molecule on each major atherogenic particle, including LDL and several remnant particles, and can therefore provide complementary information when cholesterol content and particle number are discordant [20]. The 2025 ESC/EAS focused update reinforces the role of LDL-C and other apoB-containing lipoproteins in atherogenesis and incorporates newer evidence concerning risk estimation and additional lipid-lowering therapies. The contemporary approach is increasingly characterised by earlier identification of high-risk individuals, intensification according to absolute cardiovascular risk, and addition of non-statin treatment were indicated rather than reliance on statin monotherapy regardless of achieved LDL-C [32,33].

Familial hypercholesterolaemia provides a particularly clear illustration of cumulative exposure. Individuals with genetically determined high LDL-C are exposed from birth and can therefore reach a high lifetime arterial cholesterol burden much earlier than people who develop comparable LDL-C levels later through ageing or lifestyle-related metabolic disease. *Beheshti, et al.*, (2020) [4] in a meta-analysis involving more than 11 million individuals, estimated heterozygous familial hypercholesterolaemia at approximately 1 in 313 in the general population, with substantially higher prevalence among people with premature ischaemic heart disease or severe hypercholesterolaemia. *Ference, et al.*, (2024) [15] extend this reasoning into a general cumulative-exposure framework. From this perspective, the relevant biological exposure is not merely today's LDL-C but the integral of atherogenic exposure across time. Earlier lowering can therefore theoretically produce larger lifetime benefit because fewer particles are retained in the arterial wall before mature plaque accumulates. The concept does not eliminate the need for absolute-risk assessment, rather, it adds a temporal dimension to interpretation of current measurements.

Why Hypertension and Atherogenic Lipids Converge

Hypertension and high LDL-C damage the vasculature through distinguishable but mutually reinforcing mechanisms. Elevated pressure increases circumferential wall stress and can worsen endothelial dysfunction, while disturbed blood flow at arterial branch points induces endothelial phenotypes that favour inflammation, permeability and atherogenesis. *Tamargo, et al.*, (2023) [49] describe flow-induced reprogramming of endothelial cells as an important feature of plaque-prone arterial

regions. LDL and remnant particles entering these susceptible areas can become retained within the extracellular matrix, where they trigger inflammatory and immune responses that promote lesion development. Endothelial senescence provides another link between haemodynamic and metabolic injury. Senescent endothelial cells display altered nitric-oxide signalling and pro-inflammatory secretory phenotypes and are increasingly regarded as active participants in vascular ageing and cardiometabolic disease rather than passive markers of chronological age [7]. Broader cardiovascular ageing incorporates mitochondrial dysfunction, altered proteostasis, genomic instability, neurohormonal changes and chronic inflammation, all of which can interact with hypertension and atherosclerosis [1].

A further interaction arises from arterial stiffness. Structural vascular ageing and atherosclerotic change reduce arterial compliance, increasing systolic blood pressure and pulse pressure, while sustained hypertension can accelerate remodelling and stiffening of the arterial wall. This reciprocal process helps explain why the clinical separation of 'blood-pressure disease' and 'cholesterol disease' becomes increasingly artificial as vascular pathology accumulates across the life course [1,49]. Psychosocial and metabolic exposures also intersect. Chronic stress can alter autonomic activity, inflammation, haemodynamics and metabolic regulation, obesity promotes hypertension, insulin resistance, dyslipidaemia and sleep disorders, and inadequate sleep can contribute to sympathetic activation and abnormal blood-pressure regulation [8,35,42,53].

From Single Risk Factors to Total Cardiovascular Risk

An isolated LDL-C or systolic blood-pressure value cannot fully determine an individual's absolute probability of cardiovascular events. Age, smoking, diabetes, kidney disease, sex, family history, established vascular disease and other modifiers influence baseline risk and the absolute benefit expected from intervention. Contemporary prevention frameworks therefore integrate multiple risk domains rather than interpreting a single biomarker in isolation, while still recognising that cumulative exposure over time adds information that cross-sectional risk estimates may not fully capture [13,34,51]. SCORE2 was derived from hundreds of thousands of participants and estimates 10-year fatal and non-fatal cardiovascular risk using age, smoking, systolic blood pressure, total cholesterol and HDL-C, with recalibration to geographical risk regions. SCORE2-OP extends the concept to older adults while accounting for competing non-cardiovascular mortality [45]. These models demonstrate conceptually why pressure and lipids should be interpreted jointly, although the models were developed for European populations and therefore should not be transferred uncritically to Indonesia. Risk prediction is particularly challenging in Asia because of pronounced heterogeneity in ethnicity, diet, stroke-to-coronary disease ratios, health systems, environmental exposures and cardiometabolic phenotypes. Asia-focused reviews published in 2025 consequently emphasize the need for calibrated local or regional risk tools, accessible screening and stronger primary-care prevention architecture [10,11].

Method

Review Design

This study used a Qualitative Literature Review (QLR) design. It was intentionally not structured as a systematic literature review, meta-analysis or PRISMA-based evidence synthesis. The objective was interpretative rather than exhaustive: to integrate contemporary epidemiological, mechanistic, clinical, behavioural and health-system evidence concerning the coexistence and interaction of hypertension and atherogenic cholesterol. A qualitative approach was selected because the research questions span multiple forms of evidence that cannot meaningfully be reduced to a single quantitative endpoint. Randomised clinical trials inform treatment efficacy, prospective cohorts clarify longitudinal risk, mechanistic literature explains vascular pathways, guidelines synthesize clinical implementation, and population-health studies reveal treatment gaps and health-system constraints. The methodological purpose was therefore to build an integrated explanatory narrative.

Literature Identification

Literature published from January 2020 through September 2026 was considered, with emphasis on peer-reviewed studies and guidance relevant to hypertension, atherogenic lipoproteins, atherosclerosis and integrated cardiovascular prevention. Sources were identified through PubMed/MEDLINE-oriented searches, major journal and publisher databases, Scopus- and Web of Science-indexed source tracking where available, and backward and forward citation chaining from highly relevant recent publications. Search concepts included hypertension, high blood pressure, LDL cholesterol, apoB, dyslipidaemia, hypercholesterolaemia, atherosclerosis, endothelial dysfunction, arterial stiffness, cardiovascular risk, cumulative exposure, lifetime risk, integrated prevention, polypill, primary care, Asia and Indonesia. The review preferentially incorporated peer-reviewed randomised trials, large prospective observational studies, individual-participant meta-analyses, high-quality systematic reviews used as background evidence, mechanistic state-of-the-art reviews, and major professional-society recommendations published in established journals. Although systematic reviews were eligible as evidence sources, the present article itself remained a qualitative review.

Thematic Analysis

Evidence was organized iteratively into six principal domains: epidemiological coexistence, haemodynamic and lipid-mediated vascular mechanisms, cumulative exposure and vascular ageing, shared lifestyle determinants, integrated pharmacological prevention, and implementation gaps. A seventh cross-cutting domain concerned Asian and Indonesian applicability. Rather than counting how many publications supported each proposition, the synthesis assessed convergence and complementarity among evidence types. Contradictory findings were interpreted in relation to differences in study population, intervention, follow-up, baseline risk and outcome definitions. Causal language was reserved for relationships supported by strong mechanistic and intervention

evidence; observational associations were described accordingly.

Scope and Limitations of the Method

Because the review was qualitative and purposive, it does not claim exhaustive retrieval of all studies published from 2020 to 2026 and no PRISMA flow diagram or pooled effect estimate is presented. This is a methodological choice rather than an omission. The strength of the approach lies in connecting biological, epidemiological and implementation evidence, its principal limitation is that study selection depends partly on relevance-based judgment and therefore does not provide the reproducibility of a formal systematic review.

Results: Thematic Findings

Theme 1: Hypertension and Dyslipidaemia Commonly Cluster

The contemporary literature consistently portrays cardiovascular risk factors as clusters rather than isolated abnormalities. Obesity, diabetes, hypertension and dyslipidaemia frequently coexist because they share behavioural, metabolic and socioeconomic determinants. *Powell-Wiley, et al., (2021) [42]* emphasized that obesity contributes directly to incident hypertension, dyslipidaemia, type 2 diabetes and sleep-related abnormalities. *He, et al., (2021) [23]* also reported associations between lipid patterns and subsequent new-onset hypertension in a community-based Chinese cohort, illustrating that lipid and blood-pressure abnormalities may develop within a common metabolic trajectory rather than independently [42,23].

The importance of clustering is demonstrated by *Wang, et al., (2022) [52]*. In more than 133,000 middle-aged and older Chinese adults, cardiometabolic morbidities were associated with progressively greater cardiovascular risk when present together. Participants with hypertension plus dyslipidaemia had higher event risk than individuals without the major cardiometabolic conditions, and those with hypertension, diabetes and dyslipidaemia together had the greatest risk among the combinations studied. Although observational designs cannot prove that every component interacts multiplicatively, the results support comprehensive cardiometabolic management rather than focusing on one abnormal biomarker at a time.

This pattern is highly relevant to Southeast Asia. *Mohammed Nawi, et al., (2021) [36]* estimated a pooled hypertension prevalence of approximately one-third in urban Southeast Asian populations and identified obesity, smoking, dyslipidaemia and socioeconomic factors among commonly reported correlates. *Lee, et al., (2021) [31]* found a substantial burden of plasma lipid abnormalities across selected Asia-Pacific countries, their synthesis reported high LDL-C in a large proportion of Indonesian participants in national survey data, while also highlighting treatment-cost and geographic barriers.

Theme 2: Pressure Injury and Lipid Retention Converge in the Arterial Wall

The second major theme concerns biological convergence. Hypertension creates repetitive mechanical stress, particularly in vascular regions experiencing disturbed flow, while apoB-containing particles provide the substrate for atherosclerotic lipid accumulation. This combination is biologically important because endothelial injury and dysfunction can increase vascular permeability and inflammatory signalling, whereas lipid retention perpetuates immune-cell recruitment and plaque development. *Tamargo, et al., (2023) [49]* describe atherosclerosis-prone regions as areas in which disturbed flow induces pro-atherogenic endothelial reprogramming. *Bloom, et al., (2023) [7]* similarly emphasize that endothelial cells exposed to damaging haemodynamic and circulating factors can enter senescent states characterised by inflammatory signalling and impaired vascular function. *Glavinovic, et al., (2022) [20]* explain why the number of apoB-containing particles can be important: each particle represents an opportunity for an atherogenic particle to enter and become retained in the arterial wall. The interaction between blood pressure and atherogenic lipoproteins is summarized in Figure 1. The figure conceptualizes two initial pathways—haemodynamic stress and atherogenic particle exposure—that converge on endothelial dysfunction, inflammation and arterial remodelling before producing subclinical and ultimately clinical cardiovascular disease.

Figure 1 illustrates that the two risk factors should not be interpreted as producing identical lesions. Blood pressure has substantial effects on small and large vessels and on cardiac and renal loading, whereas LDL/apoB exposure is directly related to atherogenesis. Nevertheless, the pathways converge at the level of endothelial injury, inflammatory activation, arterial remodelling and vascular ageing. Consequently, lowering only one exposure may leave substantial preventable residual risk from the other. This provides a mechanistic foundation for integrated cardiovascular [7,15,49].

Theme 3: Duration of Exposure Is a Critical Dimension of Risk

One of the strongest conceptual developments in recent literature is the recognition that cardiovascular risk depends on cumulative exposure. *Ference, et al., (2024) [15]* articulate this particularly clearly for LDL-C: atherosclerosis progresses as apoB-containing particles are retained over time, meaning the biological consequences of LDL depend on both concentration and duration. Thus, maintaining lower LDL-C throughout adulthood has potentially much greater lifetime effects than achieving the same LDL-C reduction only after decades of plaque accumulation. The same temporal principle is relevant to blood pressure, although 'BP-years' is not yet used clinically in the same standardised manner as cumulative lipid-exposure concepts. Longitudinal cohort evidence indicates that cardiovascular risk is influenced by both the severity and duration of blood-pressure exposure, and cumulative measures can capture information that is missed by a single clinic reading. In CARDIA, cumulative exposure to blood-pressure and lipid variables from young adulthood was independently associated

with incident cardiovascular disease, while a 2024 Kailuan cohort analysis similarly linked higher 10-year cumulative blood-pressure exposure with subsequent ASCVD risk [13,21]. Trial evidence further shows that sustained blood-pressure lowering reduces

cardiovascular events across broad baseline categories, with more intensive treatment benefiting appropriately selected populations [5,6,48,57].

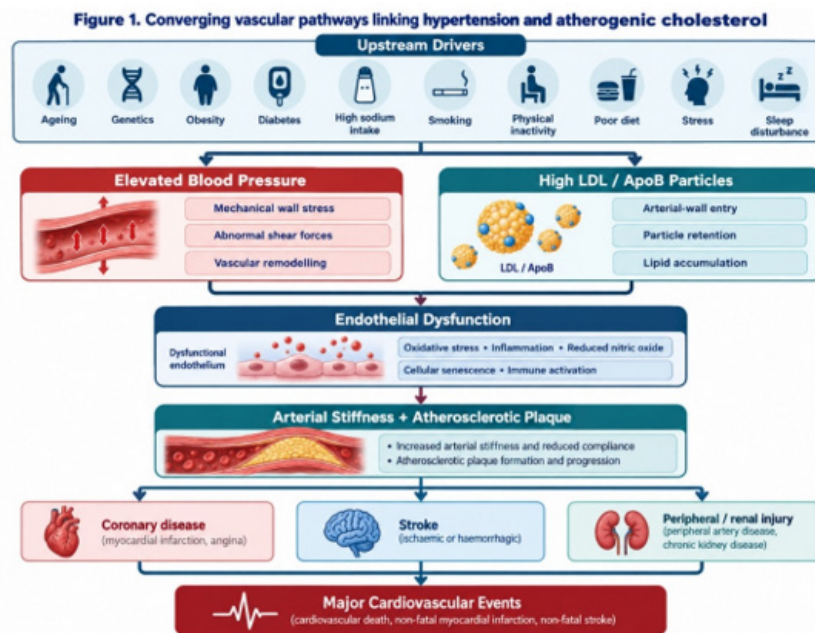


Figure 1: Converging vascular pathways linking hypertension and atherogenic cholesterol.

Figure 2 translates this literature into the proposed concept of dual cumulative vascular exposure. The model does not imply a validated mathematical multiplication of LDL-years by BP-years,

rather, it illustrates that simultaneous exposure to both risk factors can accelerate movement toward an individual's threshold for clinically manifest vascular disease.

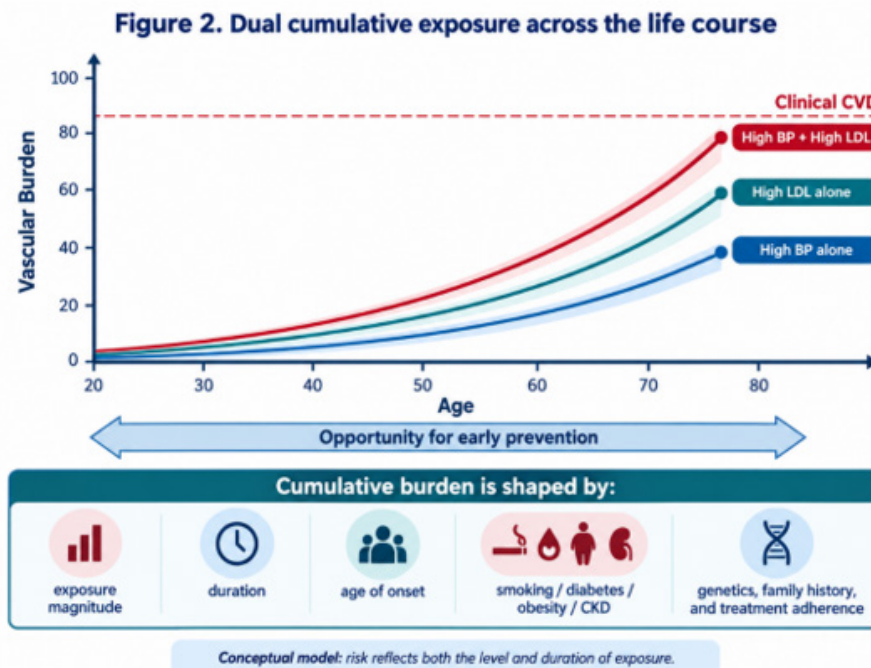


Figure 2: Dual cumulative exposure across the life course.

Figure 2 illustrates that the key implication is temporal: cardiovascular burden reflects not only the level of a risk factor but also how long the vasculature is exposed to it. A modest reduction sustained over decades may prevent more cumulative vascular injury than the same change achieved only after substantial plaque or target-organ damage has developed, which supports earlier detection and durable adherence. The figure is conceptual rather than a validated quantitative risk equation, treatment decisions must still incorporate absolute risk, safety, patient preferences and uncertainty about very-long-term pharmacotherapy in otherwise low-risk young adults [13,15,21,51].

Theme 4: Shared Lifestyle Drivers Provide Opportunities for Joint Intervention

Diet is an important area in which interventions can affect multiple cardiovascular pathways simultaneously. The DASH dietary pattern has strong evidence for lowering blood pressure. A meta-analysis of 30 randomised trials involving more than 5,000 participants found significant reductions in blood pressure, and subsequent analyses of modified DASH approaches and chronic-disease populations found favourable changes not only in pressure but in selected anthropometric and metabolic outcomes [17,22,29]. Mediterranean-style dietary patterns represent another evidence-supported strategy. Randomised-trial and observational syntheses have associated greater adherence with modest blood-pressure improvements and broader cardiovascular benefits, although the precise dietary composition, comparator and population vary considerably between studies [3,16]. The practical significance is less that one branded dietary pattern should replace all others than those diets emphasizing vegetables, fruits, legumes, minimally processed grains, nuts and healthier unsaturated fats while limiting excess sodium, processed foods and excessive saturated-fat exposure can simultaneously address several cardiometabolic mechanisms. Sodium reduction is particularly relevant in hypertension prevention, including in many Asian dietary environments. The Salt Substitute and Stroke Study randomised more than 20,000 high-risk participants in rural China and found lower rates of stroke, major cardiovascular events and death with a potassium-enriched salt substitute compared with regular salt [38]. Such strategies require safety considerations in people at risk of hyperkalaemia, particularly those with advanced renal impairment or medications affecting potassium handling, but the trial illustrates how a relatively simple food-environment intervention can influence hard cardiovascular outcomes.

Physical activity also lowers blood pressure and improves cardiometabolic health. A large network meta-analysis by *Edwards, et al.*, (2023) [14], incorporating 270 randomised trials, found significant resting blood-pressure reductions across aerobic, resistance, combined, high-intensity interval and isometric exercise modalities. Exercise can additionally assist weight management, glycaemic control and lipid metabolism, making it especially relevant to patients with clustered risk factors. Smoking cessation is another high-priority intervention because continued smoking

magnifies cardiovascular risk independently of blood pressure and cholesterol. *Jeong, et al.*, (2021) [25], analysing a large Korean cohort, found lower risks of stroke and myocardial infarction among sustained quitters, while reducing cigarette consumption without quitting did not confer the same benefit. Alcohol consumption is also relevant: a 2023 dose-response meta-analysis of longitudinal studies found progressively higher blood pressure with increasing alcohol exposure, reinforcing moderation or avoidance as part of blood-pressure management rather than viewing small amounts of alcohol as a hypertension intervention [12,25]. Sleep and psychosocial conditions add further dimensions. Short or disrupted sleep can influence sympathetic activity, metabolic regulation, inflammation and blood-pressure control, while chronic stress may alter haemodynamics, inflammatory signalling and behavioural risk patterns. These relationships are complex and can involve bidirectional causation, but they reinforce the broader principle that cardiovascular prevention is not reducible to medication alone [8,35,53].

Theme 5: Pharmacological Risk Reduction Is Complementary Rather Than Competitive

The evidence for blood-pressure-lowering therapy is substantial. The Blood Pressure Lowering Treatment Trialists' Collaboration reported that pharmacological blood-pressure reduction lowers the risk of major cardiovascular events and that benefit is not confined to people with extremely high pretreatment readings. Intensive-control trials add evidence that lower systolic targets can improve outcomes in appropriately selected populations, although adverse events, orthostatic symptoms, renal function, comorbidities and frailty must remain part of individual treatment decisions [5,6,48,57]. Lipid lowering has likewise evolved beyond a statin-only framework. Statins remain foundational because of their extensive cardiovascular-outcomes evidence, but ezetimibe, PCSK9 monoclonal antibodies and other agents can provide additional LDL-C reduction when clinically indicated. The 2022 ACC expert pathway described sequencing of non-statin therapies according to clinical setting, achieved LDL-C and residual risk, while the 2025 ESC/EAS focused update incorporated evidence for newer agents and refined the role of combination therapy [32,33].

Bempedoic acid is noteworthy because CLEAR Outcomes provided randomised cardiovascular-outcomes evidence in statin-intolerant patients. *Nissen, et al.*, (2023) [39] reported a significant reduction in the primary composite cardiovascular endpoint, accompanied by expected safety considerations including greater rates of gout and some biochemical abnormalities. Inclisiran, an siRNA therapy that reduces hepatic PCSK9 synthesis, produces substantial LDL-C lowering with infrequent dosing, long-term safety analyses have been encouraging, although its place in cardiovascular outcomes prevention must be distinguished from agents for which definitive event-reduction trials are already available [39,55]. Familial hypercholesterolaemia, established ASCVD, chronic kidney disease, diabetes and very high absolute risk can justify more intensive lipid management than would be

appropriate for a young low-risk person with a modest isolated abnormality. This distinction highlights why integrated prevention does not mean that every patient should receive the same combination of drugs. Instead, both BP-lowering and lipid-lowering intensity should be proportional to clinical risk and expected net benefit [4,28,50].

Theme 6: Simultaneous Treatment Can Simplify Prevention

Clinical evidence also supports the concept that several risk factors can be addressed simultaneously. The long-term follow-up of HOPE-3 showed sustained cardiovascular benefit from cholesterol lowering in an intermediate-risk population, blood-pressure lowering was particularly beneficial in participants with higher baseline systolic pressure, illustrating why baseline risk and pretreatment level matter [27]. TIPS-3 evaluated a polypill containing lipid- and blood-pressure-lowering agents in people without established cardiovascular disease who were at elevated risk. The trial demonstrated that a multidrug prevention strategy could reduce major cardiovascular events, with aspirin-related findings requiring individualised consideration of bleeding risk [56]. SECURE subsequently demonstrated in secondary prevention that a polypill containing aspirin, ramipril and atorvastatin after myocardial infarction reduced major cardiovascular events relative

to usual care and improved medication adherence [9]. A subsequent meta-analysis of randomised trials in secondary prevention found that polypill-based strategies improved adherence and produced modest additional reductions in systolic blood pressure and LDL-C, supporting regimen simplification as an implementation strategy for suitable patients [43].

These studies should not be interpreted as evidence that one fixed formulation is appropriate for everybody. Their broader significance is behavioural and organisational: pill burden, regimen complexity and long-term adherence can materially affect real-world effectiveness. A theoretically optimal prescription that is not taken consistently produces little population benefit, whereas carefully selected fixed-dose combinations can reduce treatment friction and improve persistence. Integrated strategies therefore need to optimise not only pharmacology but also usability, access and follow-up [9,43]. This treatment logic is summarised in Figure 3, which proposes a sequential integrated prevention pathway rather than independent 'hypertension clinics' and 'cholesterol clinics'. The pathway links screening and confirmation to total-risk stratification, lifestyle management, risk-appropriate pharmacotherapy, adherence support and iterative reassessment, thereby showing where coordinated care can replace fragmented risk-factor management.

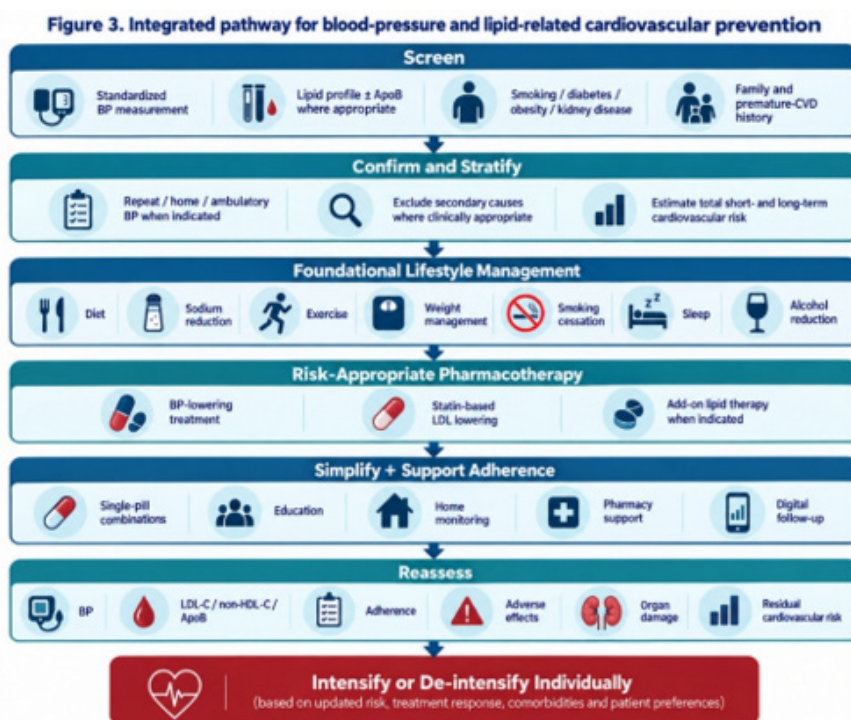


Figure 3: Integrated pathway for blood-pressure and lipid-related cardiovascular prevention.

Figure 3 illustrates that integrated cardiovascular care is cyclical rather than a one-time prescription. Accurate measurement precedes risk estimation, lifestyle modification remains foundational, pharmacological treatment is matched to expected benefit, and follow-up evaluates both biological response and adherence. This framework is consistent with modern hypertension, lipid, and cardiovascular-prevention recommendations and with the real-world need to simplify chronic treatment wherever possible [33,34,55].

Theme 7: Indonesia Illustrates the Implementation Gap

Indonesia provides an important example of the difference between evidence availability and implementation. Analysis of Riskesdas data has demonstrated substantial geographic variation in hypertension across Indonesian districts. *Oktamianti, et al.*, (2022) [40] found marked differences by region, age, sex and socioeconomic characteristics, illustrating that national averages can conceal subnational heterogeneity relevant to programme design. The challenge extends beyond prevalence to diagnosis. *Oktamianti, et al.*, (2023) [41] reported a substantial burden of undiagnosed hypertension across Indonesian districts, showing that many individuals with elevated measured pressure may remain outside effective treatment pathways. This is especially concerning for an asymptomatic condition because absence of symptoms provides little reassurance about underlying vascular risk. Treatment and adherence constitute additional gaps. In Indonesian primary-care settings studied by *Setiadi, et al.*, (2022) [46], many treated patients remained above blood-pressure targets, and substantial proportions reported suboptimal medication adherence, inadequate physical activity and discretionary salt use. These findings emphasize that prescribing medication is only one component of effective hypertension control.

The global NCD-RisC analysis similarly identified Indonesia among countries where hypertension treatment and control were particularly limited in 2019. A multicountry study involving demographic-surveillance sites in Bangladesh, India, Indonesia, Malaysia and Viet Nam also demonstrated weaknesses in hypertension-care cascades, reinforcing the relevance of health-system design, detection and continuity of care [19,37]. Dyslipidaemia presents comparable challenges. *Lee et al.* (2021) documented substantial lipid abnormalities in Asia-Pacific settings and identified physician, patient, geographic and cost barriers. *Thongtang, et al.*, (2022) [50] emphasized the central role of primary-care practitioners in recognising and treating dyslipidaemia before cardiovascular disease develops. In Indonesia, *Arsyad, et al.*, (2022) [2] further demonstrated substantial burdens of modifiable risk factors among adults both with and without established CVD, indicating missed opportunities for primary and secondary prevention.

Discussion and Analysis

Reframing the Problem: From Two Diagnoses to One Vascular-Risk Architecture

The central synthesis of this review is that hypertension and atherogenic cholesterol should be managed as distinct biological exposures within a shared vascular-risk architecture. They are not interchangeable: elevated blood pressure exerts important effects on the heart, brain, kidneys and small vessels that are not reducible to atherosclerosis, while apoB-containing particles play a direct role in arterial plaque formation. Nevertheless, their cumulative effects operate simultaneously in the same individual, so independent management can underestimate preventable total risk [13,15,34]. This argument is supported by mechanistic, epidemiological and interventional evidence. Mechanistically, haemodynamic forces alter endothelial biology while atherogenic particles exploit susceptible arterial regions. Epidemiologically, hypertension and dyslipidaemia cluster with obesity, diabetes and smoking. Clinically, lowering either blood pressure or LDL-C reduces cardiovascular risk in appropriate populations. Integrated prevention therefore does not require evidence that hypertension “causes cholesterol” or vice versa, it requires recognition that patients experience the combined consequences of all exposures simultaneously. The convergence can be described more formally as simultaneous exposure to haemodynamic load and atherogenic particle burden. Pressure-related mechanical stress alters endothelial and arterial-wall biology, whereas retained apoB-containing particles promote lipid accumulation and inflammatory plaque progression, over time, these processes can converge on arterial stiffness, stenosis, plaque disruption, thrombosis and organ ischaemia. Longitudinal data showing independent associations of cumulative blood-pressure and lipid exposure with incident cardiovascular disease strengthen the rationale for addressing both exposures early and consistently [13,15,49].

The “Silent Risk” Problem

Public-facing cardiovascular messages often emphasise symptoms, yet hypertension and elevated LDL-C are frequently silent until target-organ damage or a clinical event has occurred. Waiting for headache, breathlessness, chest pain or neurological symptoms is therefore not an effective screening strategy, and the absence of symptoms should not be interpreted as evidence of low cardiovascular risk. This distinction is especially important in prevention because objective measurement can identify modifiable exposure years before overt disease becomes clinically apparent [30,34]. This distinction is important for public communication. Messages that imply that headache or tiredness reliably signals hypertension may lead people without such symptoms to conclude that they do not require measurement. Conversely, frequent nonspecific symptoms may cause inappropriate self-diagnosis. The more evidence-based message is that blood pressure must be measured and lipids must be tested. Symptoms consistent with acute cardiovascular disease require medical evaluation, but risk-factor identification depends on objective assessment [34,47].

Why Earlier Prevention Can Be Disproportionately Valuable

The cumulative-exposure concept changes how prevention is

interpreted. If LDL-associated plaque accumulation depends on both concentration and duration, reducing LDL earlier may delay the age at which clinically important plaque burden develops. A parallel principle applies to blood pressure: cumulative exposure from young adulthood is associated with later cardiovascular events and target-organ consequences, indicating that prevention cannot be fully represented by a single late-life measurement [13,15,21]. This does not imply indiscriminate lifelong medication beginning in young adulthood. The evidence base for pharmacological treatment differs across risk groups, and absolute short-term benefit in a healthy low-risk young person may be small. Rather, the cumulative-exposure perspective provides a stronger rationale for primordial and early lifestyle prevention, detection of familial disorders, smoking avoidance, healthy weight maintenance and periodic measurement long before symptoms appear. The evidence also suggests a research direction that combines cumulative blood-pressure and lipid trajectories into clinically useful lifetime-risk measures. Current prediction systems are predominantly based on contemporary risk-factor values, whereas longitudinal electronic health records increasingly make repeated measurements available across years or decades. Models that integrate time-varying exposure may therefore improve individualised prevention, provided they are externally validated, calibrated across diverse populations and shown to add clinically meaningful information beyond established risk tools [13,21].

Lifestyle Modification Should Be Treated as Multidomain Therapy

The evidence synthesized here indicates that lifestyle intervention is not a vague adjunct to pharmacotherapy but a multidomain therapeutic strategy. Dietary improvement can influence blood pressure, body weight, glycaemia and lipid profiles, physical activity can affect blood pressure, insulin sensitivity and fitness, smoking cessation rapidly alters cardiovascular risk, and adequate sleep and alcohol reduction can contribute to blood-pressure control. Dietary strategies are particularly relevant in Indonesia, where prevention must be compatible with local foods, cultural practices and affordability. The evidence for DASH and Mediterranean-style dietary patterns should therefore be translated into principles rather than copied literally. Greater intake of vegetables, fruit, legumes, whole or minimally processed foods and healthier sources of fat, lower sodium exposure, and reduction of highly processed foods can be implemented through local dietary patterns rather than requiring a Western menu. *Filippou, et al.*, (2020, 2021), *Lari, et al.*, (2021) and *Guo, et al.*, (2021) [17,22,29] collectively support the cardiovascular relevance of dietary modification. Population-level food policies may magnify individual counselling. Salt reformulation, clearer food labelling, healthier institutional procurement and reduction of trans fats and excessive saturated-fat exposure can shift risk distributions across entire populations. The salt-substitution evidence from China is especially relevant to Asian public health because it demonstrates

that dietary sodium/potassium modification can influence clinical cardiovascular events rather than only intermediate biomarkers [21].

Pharmacotherapy Should Target Absolute Preventable Risk

Modern cardiovascular prevention increasingly asks not simply whether a measurement exceeds a threshold but how much clinical benefit can be expected from intervention. For hypertension, baseline cardiovascular risk, organ damage, frailty, measurement quality and tolerability all matter. For lipids, established ASCVD, familial hypercholesterolaemia, diabetes, kidney disease and other risk enhancers influence treatment intensity. The 2025 ESC/EAS update is particularly relevant because it integrates newer evidence involving bempedoic acid and evolving combination therapy while maintaining the centrality of total cardiovascular risk [33]. CLEAR Outcomes adds important evidence for individuals unable or unwilling to tolerate conventional statin treatment, but it does not reduce the importance of statins as first-line therapy in patients who can use them [39]. Inclisiran illustrates another dimension: medication delivery architecture. Twice-yearly maintenance dosing has potential adherence advantages, while pooled trial data provide reassuring longer-term safety information. However, LDL reduction, safety and proven cardiovascular-event reduction are distinct evidence domains, therapies should be evaluated on each separately [55].

Adherence Is a Biological Issue Because It Determines Exposure

An important insight from the Indonesian and international evidence is that adherence should not be treated as merely a behavioural afterthought. A drug cannot reduce cumulative exposure when it is not taken. Intermittent antihypertensive use permits repeated periods of high haemodynamic load, intermittent lipid-lowering treatment increases cumulative LDL exposure relative to sustained control. Regimen simplification can therefore contribute directly to vascular prevention. TIPS-3 and SECURE demonstrate the feasibility and potential clinical benefit of fixed-combination approaches in selected populations. The principle extends to single-pill antihypertensive combinations and simplified long-term regimens. Whether a particular polypill is appropriate depends on indication, dose flexibility, contraindications and individual risk, but reducing unnecessary treatment complexity is an evidence-based implementation goal [9,56].

Implications for Indonesia and Comparable LMICs

Indonesia faces a dual challenge: a large population exposed to modifiable cardiovascular risk and substantial heterogeneity across provinces and districts. A predominantly specialist, hospital-centred strategy cannot by itself address risk factors that require detection, treatment and monitoring over decades, particularly when many affected individuals remain asymptomatic.

Primary care, community-based services and reliable referral pathways therefore form the essential infrastructure for sustained prevention [10,11,19,37]. A practical Indonesian pathway could begin with routine opportunistic blood-pressure measurement in adults attending primary-care services, pharmacies or community programmes, using validated automated devices and standardised technique. Abnormal office measurements should be confirmed appropriately rather than automatically labelled after a single reading, with home or ambulatory monitoring used when clinically indicated to identify white-coat, masked, nocturnal or variable hypertension. Lipid screening can then be integrated according to age, risk factors and clinical context, with greater urgency in diabetes, kidney disease, known vascular disease, family history of premature CVD or suspected familial hypercholesterolaemia [30,34,54].

The next step is risk integration. Rather than maintaining separate registers that treat hypertension, diabetes and dyslipidaemia as unrelated programmes, primary care could organize patients by total cardiovascular risk. This would permit more rational prioritization of intensive treatment and follow-up. Indonesian data documenting geographic inequality, undiagnosed hypertension, suboptimal adherence and high modifiable-risk-factor burdens indicate that such integration could address several weaknesses simultaneously [2,40,41,46]. Asian experience supports greater use of out-of-office blood-pressure monitoring where feasible. Home monitoring can improve longitudinal

assessment and reveal masked or white-coat hypertension, whereas ambulatory monitoring is particularly valuable for nocturnal blood pressure, morning surges and 24-hour variability, these features are relevant in Asian populations, where nocturnal hypertension and salt sensitivity may be prominent. Digital transmission of validated home readings could strengthen continuity of care, although technology should complement rather than replace accurate diagnosis, affordable medicines and clinician follow-up [27,30,54].

These implications are consolidated in Figure 4, which presents a multilevel cardiovascular-prevention framework applicable to Indonesia and other resource-variable health systems. The framework makes explicit that sustained reductions in cumulative vascular exposure require aligned action at national policy, health-system, primary-care, community/family and individual levels rather than reliance on patient behaviour alone.

Figure 4 illustrates that cardiovascular prevention cannot depend solely on individual motivation. Food environments, medicine prices, insurance coverage, diagnostic availability, continuity of care and health literacy influence whether biological risk factors are detected and controlled. *Dalakoti, et al., (2025a, 2025b)* [10,11] similarly identify infrastructure, health literacy, financing and context-specific prevention as major issues across Asia. Effective implementation therefore requires alignment between individual behaviour, primary care, community structures and national policy.

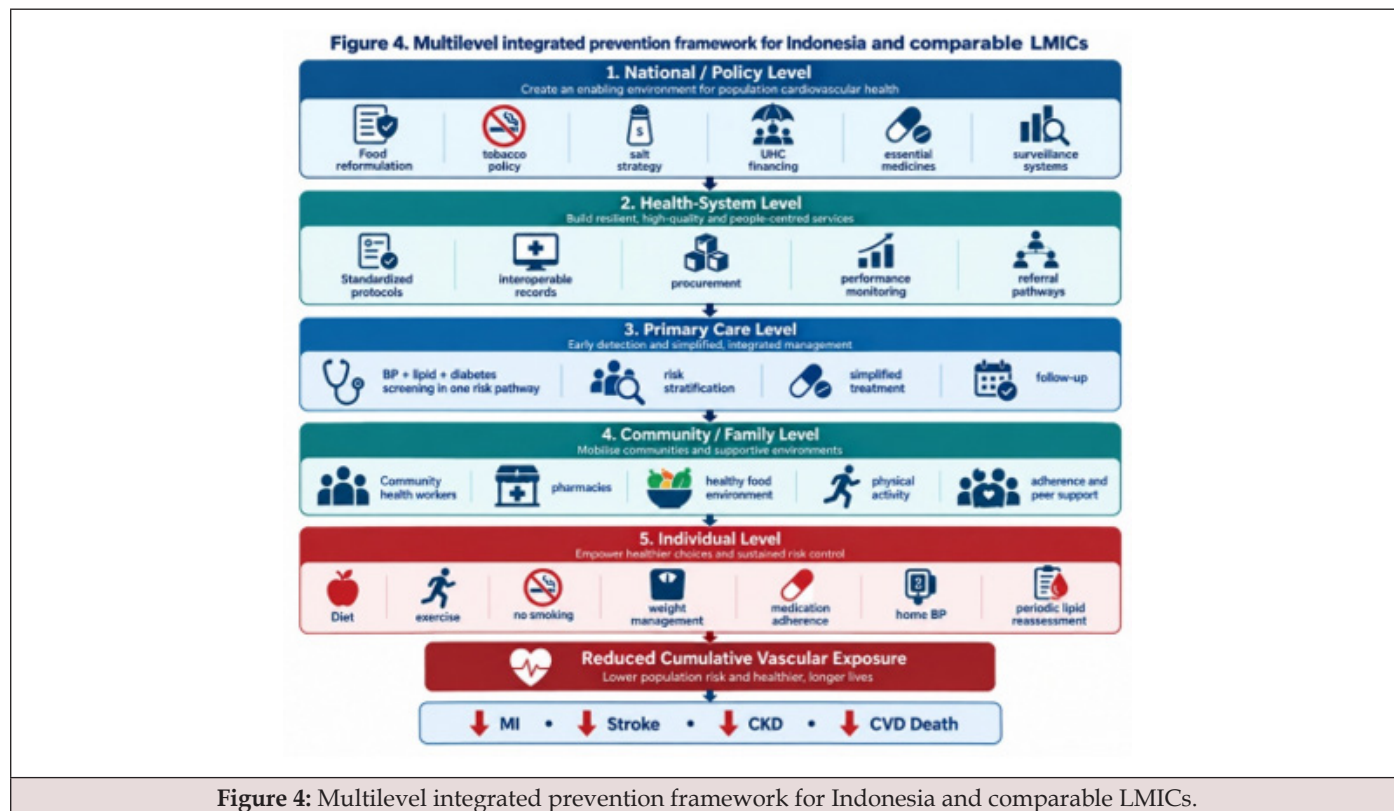


Figure 4: Multilevel integrated prevention framework for Indonesia and comparable LMICs.

Research Gaps

Several gaps remain. First, cumulative LDL exposure is conceptually advanced, but clinically practical lifetime exposure thresholds require further validation across diverse populations. Second, longitudinal blood-pressure burden deserves greater integration into risk models. Third, risk-prediction tools need stronger validation and recalibration in Indonesia and other Southeast Asian populations rather than uncritical use of Western models. Fourth, integrated intervention trials in LMIC primary care should assess whether simultaneous management of blood pressure, lipids, diabetes and smoking produces better adherence and outcomes than disease-specific programmes. Outcomes should include not only biological target attainment but cost-effectiveness, medication persistence, equity and patient experience. Fifth, better evidence is required on implementation strategies using community health workers, pharmacists, digital monitoring and single-pill combinations in geographically dispersed populations. Geldsetzer, *et al.*, (2022), Setiadi, *et al.*, (2022) [19,46] and regional Asian reviews indicate that the problem is not simply absence of effective medicines, it is failure to convert available interventions into sustained population exposure reduction. Finally, prevention research should increasingly examine trajectories rather than isolated cross-sectional measurements. Longitudinal electronic records potentially allow calculation of cumulative LDL, blood-pressure and glycaemic exposure. Integrating these measures with genetics, kidney function, smoking history and subclinical vascular imaging could eventually support more individualized lifetime prevention.

Conclusion

Hypertension and elevated atherogenic cholesterol are two of the most important modifiable contributors to cardiovascular disease. Their coexistence is common, their determinants overlap, and their biological effects converge at several levels of the vascular system. Elevated blood pressure imposes haemodynamic stress and produces cardiovascular and target-organ damage, while LDL and other apoB-containing lipoproteins drive the development and progression of atherosclerotic plaque. Endothelial dysfunction, inflammation, oxidative stress, arterial stiffness, vascular ageing and cardiometabolic comorbidities connect these processes into a broader continuum of vascular injury. A central conclusion of contemporary evidence is that cardiovascular risk reflects exposure over time. A single blood-pressure or LDL-C measurement is important but incomplete. The magnitude, duration and age of onset of these exposures help determine accumulated vascular damage. This insight strengthens the rationale for early screening, primordial prevention and durable risk-factor control rather than waiting until symptoms or cardiovascular events occur. The asymptomatic nature of both conditions also requires careful public-health communication. Headache, dizziness, fatigue or chest symptoms cannot substitute for blood-pressure measurement or lipid testing. Prevention should therefore be organized around

objective detection, confirmation of abnormal measurements, total cardiovascular-risk assessment and longitudinal monitoring.

Lifestyle intervention is foundational because dietary quality, sodium intake, physical inactivity, obesity, smoking, alcohol exposure, inadequate sleep and psychosocial conditions influence several cardiovascular pathways simultaneously. Pharmacological prevention should complement rather than replace these measures. Contemporary evidence supports effective blood-pressure lowering and LDL-C lowering, with combination and non-statin approaches available when clinically justified. Single-pill and polypill strategies may further improve implementation when regimen complexity is an important adherence barrier. For Indonesia, the most important issue may no longer be whether effective interventions exist, but how to deliver them consistently across a large and heterogeneous population. Indonesian evidence demonstrates substantial hypertension prevalence, geographic inequalities, undiagnosed disease, adherence problems and a considerable burden of lipid and other modifiable cardiovascular risk factors. Integration of blood-pressure, lipid, diabetes and smoking management within strengthened primary care offers a logical response. Future cardiovascular prevention should therefore move from fragmented treatment of isolated numerical abnormalities toward a life-course model of cumulative vascular exposure. Earlier detection, simultaneous management of interacting risk factors, simplified medication regimens, adherence support and population-level prevention could collectively reduce the years of arterial exposure that ultimately produce myocardial infarction, stroke, kidney disease and premature cardiovascular death.

Acknowledgement

None.

Conflict of Interest

None.

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