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# **Rebuilding the Barrier: How GLP-1-Engineered Probiotics Transform the Management of Fibre-Deficient Colitis**

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The global burden of chronic colitis, particularly ulcerative colitis, highlights a pressing need for deeper mechanistic insights and innovative therapies. Recent research has revealed how dietary components, especially fiber intake, dramatically influence the gut ecosystem and immune responses. Understanding the complex interaction between dietary fiber, gut microbiota, and mucosal immunity is essential for developing novel strategies to manage colitis effectively. This chapter delves into these interactions, focusing on the fiber deficiency–driven dysbiosis, the implications for gut barrier integrity, and the promising therapeutic potential of engineered probiotics.

## **The Role of Dietary Fiber in Gut Health**

Dietary fiber is a fundamental element in maintaining gut homeostasis, primarily through its role as a substrate for fermentation by the gut microbiota. When fermentable fibers are consumed, they promote the growth of beneficial bacteria that produce short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. These SCFAs provide vital energy to colonic epithelial cells and function as signaling molecules to suppress inflammation and reinforce barrier functions. However, diets low in fiber induce profound changes in the microbial landscape, reducing SCFA-generating bacteria and allowing pathogenic or mucus-degrading species to proliferate. This shift occurs rapidly, sometimes within days, and results in the thinning of the colonic mucus layer. The diminished mucus layer exposes epithelial cells to luminal antigens and pathogens, triggering immune activation. Consequently, this collagenous defense erosion destabilizes the gut environment and increases the risk of inflammation, setting the stage for colitis development.

## **Pathogenesis: The Fiber Deficiency—Microbiota—Colitis Axis**

Fiber deficiency fuels a cascade of detrimental effects on gut microbiome composition and immune regulation. The loss of SCFA production disrupts epithelial repair mechanisms and weakens anti-inflammatory signaling pathways in the colon. In parallel, epithelial barrier breach due to mucus layer erosion facilitates immune cell infiltration and the release of chemokines such as CXCL2. These chemokines recruit neutrophils, amplifying mucosal inflammation through a feed-forward loop. Animal models have demonstrated that fiber-

depleted states not only induce microbial dysbiosis but also prime the host's immune system for heightened inflammatory responses. When combined with environmental or chemical triggers—such as dextran sulfate sodium (DSS)—this priming results in more severe colitis phenotypes than diets rich in fiber. These findings align closely with clinical observations where low fiber intake correlates with increased disease severity and relapse risk, emphasizing dietary fiber's protective role.

## **GLP-1 Signaling Beyond Glucose Homeostasis**

Glucagon-like peptide-1 (GLP-1) is traditionally recognized for its pivotal role in regulating glucose metabolism through insulin secretion. However, increasing evidence indicates that GLP-1 exerts significant anti-inflammatory functions within the gut. Secreted by intestinal L-cells in response to nutrients and SCFAs, GLP-1 enhances gut barrier integrity by stimulating tight junction proteins like ZO-1 and occludin, which effectively seal the epithelial barrier. Additionally, GLP-1 inhibits the production of proinflammatory cytokines (e.g., TNF- $\alpha$ , IL-1 $\beta$ , IL-6) and reduces the recruitment of neutrophils to the mucosa. Mechanistically, GLP-1 suppresses the activation of key inflammatory signaling pathways, including the nuclear factor-kappa B (NF- $\kappa$ B) and mitogen-activated protein kinase (MAPK) cascades. By engaging the GPR43 receptor on L-cells, SCFAs stimulate GLP-1 secretion, thus linking dietary fiber to immune regulation and mucosal healing. Chronic deficiency in dietary fiber impairs this SCFA-GPR43-GLP-1 axis, removing a crucial anti-inflammatory pathway and increasing vulnerability to colitis. Therapeutic strategies aimed at restoring or mimicking GLP-1 activity are therefore of great scientific and clinical interest.

## **Synthetic Biology Approaches: Engineered Probiotics**

Advancements in synthetic biology have paved the way for the development of engineered probiotics capable of directly synthesizing and releasing GLP-1 or other bioactive immunomodulatory peptides within the gut. These living biotherapeutics—typically utilizing well-characterized, non-pathogenic bacterial chassis such as *Lactobacillus* or *E. coli* Nissle 1917—are designed to survive gastrointestinal transit, colonize the colon, and provide sustained local delivery of therapeutic molecules independent of dietary fiber intake. This localized delivery minimizes systemic exposure and adverse effects. Engineered probiotics not only restore GLP-1 signaling but also modulate the local microbiota by fostering the growth of anti-inflammatory bacterial taxa, collectively contributing to barrier restoration and immune rebalance. The potential for multiplexed strains that deliver combinatorial bioactive factors, such as IL-10 and antioxidant peptides, offers a versatile platform for target-specific, precision microbiome therapies.

## **Preclinical Evidence and the Mechanisms of Action**

Preclinical studies in animal models of colitis provide compelling evidence for the efficacy of engineered probiotics. A single strain engineered to release GLP-1 in situ has been shown to restore normal colon length, improve crypt architecture, and decrease neutrophil infiltration and myeloperoxidase activity, all hallmarks of mucosal healing. In addition, these probiotics replenish beneficial bacterial genera depleted by chronic fiber deficiency and suppress

clinical manifestations such as weight loss, stool irregularity, and bleeding. Mechanistic studies reveal that GLP-1 production by engineered strains inhibits pivotal inflammatory pathways, including AKT/NF- $\kappa$ B and MAPK signaling, thereby reducing the expression of proinflammatory mediators. Similar efficacy has been noted with engineered strains delivering anti-inflammatory cytokines like IL-10, highlighting the therapeutic versatility of this platform. The targeted restoration of local immune homeostasis with minimized systemic side effects distinguishes engineered probiotics from traditional systemic therapies.

## **Expanding Therapeutic Horizons**

Research is rapidly expanding beyond GLP-1-based approaches to develop multiplexed probiotics capable of releasing several bioactive agents simultaneously. These include trefoil factors that promote epithelial wound healing, anti-inflammatory interleukins (IL-10, IL-35), and antioxidant peptides aimed at mitigating oxidative stress in inflamed gut regions. Such multiplexed platforms enable a synergistic therapeutic effect that addresses multiple pathophysiological processes concurrently, providing a tailored approach to managing colitis's complex immunological landscape.

## **Translating Bench Science to Clinical Practice**

Translating engineered probiotics from experimental models to clinical use involves a multifaceted process. Strains must undergo rigorous safety evaluations to ensure non-toxicity, lack antibiotic resistance traits, and possess genetically stable inserts to prevent horizontal gene transfer. Production must adhere to Good Manufacturing Practice (GMP) standards to ensure product consistency and safety. Early regulatory approval focuses on safety and immunogenicity in phase 1 trials, followed by phase 2/3 trials assessing efficacy against standards of care such as 5-aminosalicylic acid, steroids, and biologics. Regulatory frameworks for live biotherapeutic products continue to evolve, adapting to the unique challenges posed by genetically engineered organisms.

## **Patient Selection, Monitoring, and Adjunctive Therapy**

Patients with relapsing or refractory colitis, especially those with persistent dietary fiber insufficiency, represent the initial target population for engineered probiotic therapy. Integration with existing therapeutic regimens—dietary modification, pharmacological anti-inflammatories, and immunosuppressants—is essential during early adoption phases. Clinical monitoring should incorporate biomarkers such as C-reactive protein and fecal calprotectin, alongside periodic endoscopic assessments and microbiome profiling to evaluate therapeutic efficacy and safety.

## **Long-Term Integration and Ethical Considerations**

Long-term success depends on establishing robust clinical registries and biobank infrastructures to monitor safety, genetic stability, and functional durability of engineered strains. Patient and physician education is pivotal to foster understanding and acceptance, addressing concerns around the use of genetically modified organisms. Comprehensive

informed consent processes and transparent communication about potential risks and benefits are fundamental ethical imperatives.

## **Future Directions in Microbiota-Based Therapies**

The field is advancing toward personalized microbiome therapies optimized for individual gut microbial compositions. Innovations include the development of “sense-and-respond” engineered strains equipped with biosensors that release therapeutics only during active inflammation, enhancing safety and efficacy. Preventive deployment in at-risk populations, such as individuals with early signs of dysbiosis or genetic predisposition, offers opportunities for disease interception and improved population health outcomes.

## **Collaborative Innovation and Implementation**

The successful integration of engineered probiotics into clinical practice requires concerted efforts from professional societies, academic institutions, and biotechnology companies. These collaborations facilitate the translation of laboratory discoveries into scalable, patient-centered therapies, supported by regulatory guidance and clinical best practices.

## **Conclusion**

The conclusion of this comprehensive examination of engineered probiotics restoring GLP-1 signaling in colitis therapy can be expanded to underscore the scientific foundations, therapeutic promise, and future directions, as follows:

Engineered probiotics that restore GLP-1 signaling represent a transformative advancement in the management of colitis, particularly forms exacerbated by dietary fiber deficiency. This approach uniquely integrates multiple domains of contemporary biomedical science—dietary factors, gut microbial ecology, and host immune regulation—to orchestrate mucosal healing and maintain gut homeostasis. Importantly, the therapeutic strategy moves beyond traditional pharmacologic interventions by leveraging synthetic biology to introduce living therapeutics capable of local, sustained delivery of bioactive peptides. This precision delivery not only enhances efficacy but minimizes systemic side effects, which is especially crucial in chronic inflammatory diseases such as IBD.

The scientific rationale is firmly rooted in an expanding body of preclinical and emerging clinical evidence demonstrating that GLP-1 plays multifaceted roles beyond its classic incretin function, including potent anti-inflammatory actions and epithelial barrier enhancement. Engineered probiotics delivering GLP-1 locally can reestablish these critical signaling pathways disrupted by fiber deficiency-induced dysbiosis, effectively modulating the inflammatory milieu. Furthermore, the ability to multiplex these engineered strains to release other anti-inflammatory cytokines, wound-healing peptides, and antioxidant molecules broadens their therapeutic horizon, allowing a tailored, multi-pronged approach for complex and heterogeneous disease phenotypes.

From a clinical translational perspective, this paradigm marks a shift towards personalized, microbiome-centered interventions that hold potential not only for disease remission

induction but also for long-term maintenance and prevention strategies. Key challenges remain, including optimizing strain safety, stable colonization, regulatory approval pathways, and patient acceptance of genetically modified live therapies. Yet, ongoing advances in synthetic biology, microbiome science, and clinical trial design continue to address these obstacles.

Looking forward, engineered probiotics stand poised to become integral components within a broader ecosystem of precision medicine tools, potentially coupled with microbial biosensors capable of sensing inflammatory states and releasing therapeutics on demand. Such systems promise unprecedented control over disease course modulation, minimizing flares and enhancing quality of life for millions affected by chronic colitis.

In summary, engineered probiotics restoring GLP-1 signaling exemplify a scientifically robust and biologically rational therapeutic frontier. By harmonizing dietary, microbial, and immune components, they offer a novel, promising avenue to meet the unmet needs in inflammatory bowel disease care. Their continued development and integration into clinical practice could signify a profound paradigm shift, heralding an era of personalized, microbiome-centric therapies that transform outcomes for patients worldwide.

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# Heart Failure Mortality in High-Income Nations: Diabetes, Disparities, and Unmet Challenges in the Modern Era

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Heart failure (HF) has grown into a major public health challenge, defying many of the improvements seen in other cardiovascular diseases, particularly in high-income countries. Over the past twenty years, there has been a dramatic shift in mortality patterns: while deaths from coronary heart disease (CHD) and stroke have steadily declined due to advances in acute care, public health interventions, and aggressive risk factor management, heart failure deaths have stagnated or even increased in many developed regions. This “HF mortality plateau” indicates not only clinical complexity and limitations in existing therapies, but also exposes persistent health system vulnerabilities and rising comorbidity burdens, particularly driven by diabetes, obesity, and aging populations.

The growing prevalence and severity of HF are compounded by demographic transitions. The world's population is aging, and metabolic diseases like obesity and diabetes continue to accelerate globally. In high-income countries, where the expectation is for the greatest clinical resources and preventive capabilities, HF now accounts for an outsized share of cardiovascular mortality. Between 2025 and 2050, for instance, crude cardiovascular mortality is projected to rise sharply, and though age-standardized rates may show minor declines, the absolute number of deaths from HF will likely remain unchanged or increase due to the expanding base of at-risk elderly and chronically ill patients.

Diabetes, in particular, has emerged as a critical amplifier of heart failure risk and mortality. Epidemiological studies show that individuals living with diabetes have up to double the risk of HF death compared to the general population, and this excess has not improved over recent decades, despite declines in other cardiovascular risks. This stagnation is not due to lack of medical innovation; rather, it reflects complex interactions between chronic metabolic damage, healthcare inequities, socioeconomic gradients, and underutilization or inaccessibility of lifesaving therapies.

Moreover, changing epidemiological contexts—such as the transition from HF<sub>rEF</sub> to the more refractory HF<sub>pEF</sub> phenotype, and the additional complexity brought on by COVID-19 disruptions—underscore the urgency for renewed analysis and multifactorial strategies. The imperative is clear: contemporary heart failure must be recognized as both a consequence and a barometer of changing population health, clinical practice, and health system adaptability. This chapter aims to dissect the epidemiology, drivers, disparities, and

mechanisms behind the HF mortality plateau and to present actionable recommendations on clinical, research, and public health fronts, with special attention to diabetic populations who remain at greatest risk.

## **Epidemiological Overview**

### **Global and Regional Mortality Trends**

Recent analyses of cardiovascular mortality covering nearly three million deaths across multiple Western nations illuminate striking patterns. Standardized five-year intervals from 2000 forward show CHD and overall cardiovascular (CV) mortality fell by 11–32%, and stroke death rates also decreased, albeit with international variation. In contrast, HF mortality either plateaued or increased, with pronounced rises in regions such as Ontario, Canada, and only marginal improvements elsewhere. In the U.S., HF was a contributing cause in 425,147 deaths, accounting for roughly 45% of CV deaths as of 2022. Data from the past decade indicate not only that HF mortality is stable or rising, but that this trend is especially intractable among diabetic populations.

### **Disparities by Diabetes Status**

Diabetes substantially magnifies the risk of HF death. Epidemiological studies consistently demonstrate that DM is associated with a twofold or greater incidence of HF, with an even higher risk for cardiovascular-related death among those suffering both conditions. For example, the Framingham study found that people with DM are 2.4–5 times more likely to develop HF. More than one-quarter of HF patients exhibit concurrent DM, with registries showing rates up to 40%, depending upon population demographics. Mortality rate ratios remain stubbornly elevated for diabetics—with crude rates for HF as a contributing cause at 61.2 per million in recent U.S. data. Notably, while death rates from stroke and heart attack in diabetics have improved, those for HF have not.

### **Demographic and Geographic Gaps**

Disparities in HF mortality extend by gender (higher rates in females), race (highest in White individuals; fastest recent rises in Asian and Pacific Islander groups), urban-rural status, and socioeconomic gradients. Mortality post-2010 increased most rapidly among males and some minority groups, reflecting changing patterns of healthcare access and disease management.

## **Drivers of Persistent Heart Failure Mortality**

### **Epidemiological Shifts and the Survival Paradox**

With advances in acute cardiovascular interventions—such as stenting, thrombolysis, and modern antihypertensives—more people are surviving heart attacks and strokes. However, this often leaves a large cohort of people living longer with residual cardiac damage, prone

to chronic HF. Instead of dying acutely, individuals enter protracted courses of heart failure, shifting the makeup of cardiovascular mortality toward this end-stage diagnosis.

### **Diabetes, Obesity, and the "Comorbidities Tsunami"**

Global diabetes prevalence has doubled in the past 15 years, reaching 463 million cases by 2019 and projected to balloon further. This, alongside parallel rises in obesity and hypertension, produces a comorbid burden uniquely hazardous for HF outcomes. DM contributes to HF by promoting myocardial fibrosis, microvascular dysfunction, glycotoxic damage, and renal impairment. Hospitalizations, arrhythmias, and pump failures are more frequent in diabetic patients. Moreover, the aging, obese population increasingly develops HFpEF (heart failure with preserved ejection fraction), a phenotype resistant to many traditional interventions.

### **Mixed Progress in Heart Failure Therapy**

Modern drugs—ACE inhibitors, beta-blockers, ARNIs, MRAs, and SGLT2 inhibitors—have slashed mortality for HFrEF (reduced ejection fraction) but not HFpEF (preserved ejection fraction), which accounts for more than 50% of contemporary HF cases and especially affects older, diabetic, hypertensive women. HFpEF lacks proven mortality-reducing therapies. Moreover, high costs, insurance gaps, and prescriber inertia mean that even the best medicines are underutilized.

### **Health System and Socioeconomic Barriers**

Systemic disadvantage persists for lower-income, racial minority, and rural patients: later diagnoses, poorer care continuity, and limited access to guideline-based therapies mean higher rates of avoidable death. Hospital-based, episodic models dominate over community-based, chronic management, with insufficient transition-of-care and follow-up programs.

### **COVID-19 Effects**

The pandemic further aggravated HF risks, delaying routine care, exacerbating viral-related cardiac injury, and straining health resources worldwide.

### **Underutilization of Novel Therapies**

Even where innovation is available, proven agents (SGLT2i, ARNI, MRAs, device therapy) are given to only a minority of eligible patients, hindered by cost, prescription inertia, insurance policies, and disparities in health system infrastructure.

## **Mechanistic Considerations**

### **Pathophysiology: Why Diabetes Amplifies HF Mortality**

The interplay between DM and HF is complex, synergistic, and bidirectional. Chronic hyperglycemia induces myocardial fibrosis, impairs microvasculature, and causes autonomic imbalance, contributing to diastolic dysfunction, arrhythmias, and increased pump failure. In addition, insulin resistance and elevated insulin levels constrict compensatory cardiac

mechanisms, triggering inflammatory cascades and worsening renal-cardiac interactions ("cardiorenal syndrome"). Patients with DM and HF show rapid disease progression and diminished response to standard HF therapies.

### **HF Phenotypes: HFrEF vs. HFpEF**

While HFrEF (systolic dysfunction) benefits from multiple pharmacologic and device-based interventions, HFpEF (diastolic dysfunction) is growing fastest, particularly in high-risk groups—older women, diabetics, hypertensives, and obese individuals. The absence of proven life-prolonging therapies for HFpEF is now a major contributor to the persistence of HF mortality.

## **Multinational Data and Trend Analysis**

### **CHD and Stroke: Areas of Success**

Public health investments, statin use, expanded antihypertensives, and acute reperfusion therapies have driven steady improvements in MI and stroke mortality for two decades. This success proves that coordinated, systems-level approaches can produce transformative population-wide change.

### **Heart Failure: Mortality Plateau and Data Challenges**

In contrast, both prevalence and deaths from HF continue to climb, especially as populations age and the pool of survivors from acute cardiac events enters chronic failure. Death certificate data may understate the HF burden, yet hospitalization-based metrics confirm continued high rates of admissions and deaths—especially among diabetics.

### **Diabetes—The Unchanging Multiplier**

Despite better glycemic management, diabetics continue to face a doubled risk of HF and HF mortality, with little improvement over the past decade. This lack of progress versus CHD marks a major therapeutic and research gap.

## **Clinical Practice and Research Gaps**

### **Prevention**

Early, intensive management of risk factors—glycemia, blood pressure, obesity, and lifestyle—is fundamental. Community-based and multidisciplinary models outperform episodic hospital-based care, and need expansion globally.

### **HFpEF: New Frontiers**

Significant research investment must address HFpEF, now the dominant heart failure phenotype. SGLT2 inhibitors show promise, but other strategies—precision medicine, anti-fibrotic agents, and biomarkers—are urgently needed.

## **Chronic Disease Management and Equity**

Integrated, multidisciplinary heart failure clinics optimizing transition-of-care, remote monitoring, and social support show improved outcomes but require resource investment. Digital health and self-management can extend reach, but disparities in access must be addressed.

## **Treatment Access and Affordability**

Universal, affordable access to all proven HF therapies and devices is imperative. This will require government procurement, insurance reform, and training programs for providers.

## **Research Recommendations**

Stress must be placed on large-scale, phenotype-stratified studies, robust registry development, data harmonization, and translational insight sharing.

# **Socioeconomic and Public Health Perspectives**

## **Social Determinants**

Social determinants—income, race, education, geography—powerfully shape HF risk, management, and survival. Addressing these factors through tailored interventions and community-based support reduces HF disparities and overall cardiovascular burdens.

## **System Reform and Education**

Patient empowerment, workforce training, and re-engineered care pathways underpin all sustainable improvements. Telehealth, remote monitoring, expanded medication access, and resilient networks are necessary for both current care and future contingencies, as highlighted during the COVID-19 pandemic.

## **Conclusion**

The enduring challenge of heart failure mortality—especially within the context of diabetes, obesity, and aging—demands a paradigm shift in both medical and public health approaches. Contemporary data show that high-income countries, despite sophisticated health infrastructures, are struggling to make substantive progress against HF death rates. Improvements in acute coronary syndrome and stroke mortality have not extended to HF, which now claims the lives of ever-more patients with complex chronic profiles and substantial comorbidity burdens.

Key mechanisms underlie this persistent threat. The increasing prevalence of diabetes and obesity synergistically accelerates both the onset and progression of HF, contributing to myocardial fibrosis, inflammatory cascades, and cardiac-renal dysfunction. Meanwhile, population aging ensures a growing pool of vulnerable individuals who, after surviving initial cardiovascular insults, face long-term declines in cardiac reserve. Healthcare systems face challenges of continuity: hospital-based, episodic care models are poorly suited for the

chronic nature of heart failure, resulting in frequent readmissions, suboptimal long-term management, and unequal access to advanced therapies.

Systemic disparities—whether by income, geography, gender, race, or education—further magnify the burden, particularly among diabetic patients. Despite the availability of life-extending therapeutics, their underutilization—due to cost, complexity, physician familiarity, and insurance gaps—constitutes a major lost opportunity. The COVID-19 pandemic has exacerbated these weaknesses, emphasizing the importance of resilient care pathways, digital health solutions, and universal access to essential medicines and devices.

Moving forward, resolving the HF mortality plateau calls for multi-level action. Prevention must be prioritized by enhancing early risk factor control, integrating community-based chronic disease management, and erasing gaps in care that disproportionately affect the marginalized. For HFpEF and diabetic HF—now the dominant forms—intensive research, precision medicine, and innovative drug/device development are essential. In practice, broadening the reach of proven therapies and optimizing health system design for chronic care, transitions, and self-management will be pivotal.

Ultimately, heart failure serves as both a sentinel and a challenge in modern cardiovascular and metabolic health. Its resistance to declining mortality spotlights wider issues of equity, healthcare delivery, and the limits of current knowledge. Nevertheless, with collective commitment from societies, clinicians, researchers, and policymakers, the next decade offers the potential not only for turning the tide against HF mortality but also for setting new standards in chronic disease management. This shift will require sustained investment, intelligent policy reform, and relentless innovation—ensuring that the benefits of modern medicine extend to every patient, particularly those with diabetes who remain most vulnerable to the consequences of heart failure.

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# **Hypertriglyceridemia: From Biochemical Aberration to Cardiometabolic Syndrome - Emerging Pathophysiology, Clinical Challenges, and Novel Therapeutics**

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For decades, elevated triglycerides (TGs) were mostly considered a minor lipid aberration compared to LDL cholesterol, often overlooked as a tangential risk factor in cardiovascular disease. However, evolving evidence has dramatically altered this perspective. Low to moderate hypertriglyceridemia confers a persistent, independent risk for atherosclerotic cardiovascular disease (ASCVD), especially among patients with diabetes, metabolic syndrome, and obesity. Elevated triglycerides correlate strongly with insulin resistance and atherogenic dyslipidemia, a triad recognized as a major driver of premature atherosclerosis. More severe hypertriglyceridemia, defined by fasting TG concentrations above 500 mg/dL, not only magnifies cardiovascular risk but inherently predisposes to acute, potentially fatal pancreatitis. The range of TG elevations thus spans a clinical spectrum—from silent metabolic risk to emergent organ injury. Clinicians face the complex task of stratifying this heterogeneous syndrome, discerning primary genetic forms from secondary causes, and leveraging expanding therapeutic options that now include promising molecular agents like DR10624.

The surge in obesity and type 2 diabetes globally alongside dietary transitions has propelled the prevalence of hypertriglyceridemia to unprecedented levels. Significantly, South Asian populations including those in India demonstrate a particularly high burden due to genetic predisposition interacting with rapid lifestyle changes. This hypertriglyceridemic dyslipidemia manifests with low HDL cholesterol and small dense LDL particles, conferring heightened atherosclerotic risk that traditional LDL-centric treatments inadequately address. Meanwhile, acute complications such as pancreatitis challenge emergency and critical care management, necessitating rapid TG lowering to avert multisystem failure. The clinical paradigm is thus shifting from reactive treatment to anticipatory management, integrating molecular diagnostics, personalized medicine, and genotype-guided therapies.

This comprehensive, 4500-word narrative aims to provide an advanced, holistic review tailored for clinicians and scholars. Each section unpacks the mechanisms influencing plasma

triglycerides, genetic drivers, epidemiological trends, clinical implications, and treatment strategies—from lifestyle to cutting-edge therapeutics including apoC-III inhibitors and novel triple agonists. Through case insights and critical reflection on evolving management frameworks, this review empowers practitioners to navigate this dynamic landscape and optimize patient outcomes.

## Historical Perspective

The recognition of triglycerides as pivotal in human disease is relatively recent. Early lipidology focused heavily on cholesterol fractions as central drivers of atherosclerosis. However, familial syndromes of massive triglyceride elevation and recurrent pancreatitis were documented in the late 20th century, sparking interest in triglyceride-rich lipoprotein metabolism disorders. Foundational studies involving lipid electrophoresis and enzyme assays helped identify lipoprotein lipase (LPL) deficiency syndromes, revealing their severe clinical phenotypes marked by eruptive xanthomas, hepatosplenomegaly, and catastrophic pancreatitis. Yet, it took the advent of genetic sequencing and proteomics in the 21st century to unravel the complex molecular pathways regulating triglyceride homeostasis and catabolism.

The epidemiological transition with increasing obesity, type 2 diabetes, and westernized diets paralleled a surge in hypertriglyceridemia prevalence worldwide. Public health and clinical trials initially adopted LDL cholesterol as the primary target, theorizing that lowering LDL would sufficiently mitigate cardiovascular risk. However, clinical observations and randomized controlled trials increasingly revealed residual risk linked to triglyceride elevations, especially post-statin therapy. This gap spurred clinical innovation and drug development targeting triglyceride metabolism modifiers such as PPAR agonists, omega-3 fatty acids, and antisense nucleotides targeting apolipoproteins.

In parallel, advanced imaging and biomarkers have confirmed the atherogenic role of triglyceride-rich remnants, solidifying triglycerides' place as a key causal factor in cardiovascular disease and pancreatitis risk. From purely biochemical curiosity to critical clinical phenotype, hypertriglyceridemia is now rightly considered a significant syndrome requiring comprehensive care.

## Classification and Diagnostic Framework

Hypertriglyceridemia is clinically classified according to fasting plasma triglyceride concentrations, which dictate risk profiles and therapeutic urgency:

- Mild: 150–199 mg/dL
- Moderate: 200–499 mg/dL
- Severe: 500–1,000 mg/dL
- Very severe: >1,000 mg/dL

These thresholds are critical to clinical decision-making. Even mild elevations confer increased atherosclerotic risk, especially when coupled with other metabolic abnormalities such as low HDL and small dense LDL particles. When TGs rise above 500 mg/dL, the risk of acute pancreatitis rises steeply, prompting urgent intervention. Extremely elevated levels (>1,000 mg/dL) warrant immediate attention to prevent multisystem organ failure.

Hypertriglyceridemia encompasses both primary (genetic) and secondary forms. Primary forms are rare but often severe, resulting from mutations affecting lipoprotein lipase, apolipoproteins C-II and A-V, or regulatory enzymes such as GPIHBP1. These genetic syndromes frequently manifest in childhood or adolescence and present with recurrent pancreatitis and cutaneous xanthomas. Secondary hypertriglyceridemia is by far more prevalent and results from acquired conditions such as poorly controlled diabetes, metabolic syndrome, obesity, hypothyroidism, nephrotic syndrome, excessive alcohol intake, and medications like corticosteroids or antipsychotics.

A thorough laboratory evaluation begins with fasting lipid profiles, complemented by glucose, thyroid function, renal screening, and targeted genetic testing in severe or refractory cases. Physical examination for characteristic xanthomas, lipemia retinalis, and hepatomegaly provides important diagnostic clues. Longitudinal monitoring accounts for fluctuations driven by dietary intake, metabolic status, and therapy adherence.

## **Epidemiology: Hidden Epidemic**

Hypertriglyceridemia is widely prevalent yet underdiagnosed until complications arise. In the U.S., approximately 30% of adults have triglyceride levels exceeding 150 mg/dL, with 1–2% exceeding the critical 500 mg/dL threshold. Globally, prevalence is rising, mirroring trends in obesity, diabetes, and sedentary lifestyles. South Asia, notably India, reports some of the highest hypertriglyceridemia rates worldwide, reflecting interactions between genetic predisposition and rapid urbanization.

The coexistence of atherogenic dyslipidemia—high TGs, low HDL cholesterol, and small dense LDL particles—forms a metabolic triad strongly linked to insulin resistance, endothelial dysfunction, and accelerated atherosclerosis. This phenotype drives premature cardiovascular morbidity and challenges conventional risk-reduction strategies focused solely on LDL cholesterol. Consequently, hypertriglyceridemia increasingly commands clinical attention as a modifiable risk factor for global cardiometabolic disease burdens.

## **Molecular Pathophysiology: What Drives Triglycerides Up?**

Fundamentally, elevated plasma triglycerides result from an imbalance among production, clearance, and hydrolysis of triglyceride-rich lipoproteins (TRLs), mainly chylomicrons and very-low-density lipoproteins (VLDL). Increased hepatic VLDL production is a hallmark of insulin resistance states and excessive caloric intake, often exacerbated by the dysregulated adipose tissue lipolysis releasing free fatty acids.

Concurrently, impaired catabolism of TRLs happens predominantly through deficiency or dysfunction of lipoprotein lipase (LPL), the essential enzyme anchoring triglyceride hydrolysis at the endothelial surface of capillaries. Genetic mutations or acquired inhibitors such as apoC-III and angiopoietin-like proteins negatively regulate LPL activity, delaying TRL clearance and promoting remnant accumulation.

Hormonal regulation is pivotal: insulin suppresses hepatic VLDL production and stimulates LPL activity; insulin resistance hampers these controls, causing further TG elevation. Moreover, inflammatory cytokines and medical therapies disrupt apolipoprotein expression and lipoprotein receptor function, further tipping balance toward hypertriglyceridemia.

## **Clinical Consequences: More Than a Number**

### Cardiovascular Disease

TGs and remnant lipoproteins directly contribute to atherosclerosis via endothelial dysfunction, inflammatory activation, and foam cell formation. Despite statin therapy reducing LDL cholesterol, a significant residual cardiovascular risk remains attributable to elevated triglycerides, especially in populations with metabolic syndrome or diabetes. Reducing this "residual risk" is a contemporary therapeutic priority, underscored by clinical trial data demonstrating benefit from TG-lowering agents in selected patients.

### Acute Pancreatitis

Severe hypertriglyceridemia (>1,000 mg/dL) triggers acute pancreatitis by lipoprotein lipase-mediated release of free fatty acids within pancreatic capillaries. These fatty acids induce local cytotoxicity, microvascular thrombosis, ischemia, and amplified inflammation. Pancreatitis severity correlates with TG concentration and other factors like alcohol. Prompt reduction of TG levels is lifesaving, requiring aggressive medical and sometimes plasmapheresis interventions.

## **Conclusion**

The contemporary view of hypertriglyceridemia has transformed from a neglected lipid metric to a pivotal clinical syndrome encompassing cardiometabolic risk and acute organ injury. The evidence is compelling that triglycerides—and their remnant particles—play a causal role in atherosclerosis and cardiovascular events, independent of LDL cholesterol. This knowledge has redefined treatment goals, emphasizing not only LDL lowering but also aggressive management of elevated triglycerides to reduce residual cardiovascular risk, particularly in patients with diabetes and metabolic syndrome.

Simultaneously, clinicians must remain vigilant about the extreme consequences of very high triglyceride levels, notably the danger of acute pancreatitis. Advances in the understanding of pathophysiology, including the interplay of free fatty acids, inflammation, and endothelial injury, have improved acute management strategies and outcomes.

The management landscape is rapidly evolving with the arrival of targeted therapeutics that modulate triglyceride metabolism at the molecular level. ApoC-III inhibitors, ANGPTL3 antagonists, and especially novel triple agonists like DR10624 hold promise for unprecedented triglyceride reduction and multi-domain metabolic benefits—including glucose control, weight reduction, and improved hepatic steatosis. The clinical trials demonstrating dramatic triglyceride lowering and improved biomarkers herald a new era in the personalized treatment of HTG.

However, challenges remain in translating these advances into widespread impact. The diagnostic complexity of distinguishing primary from secondary forms, the importance of holistic lifestyle interventions, management of comorbidities, and accessibility of expensive novel drugs require coordinated multidisciplinary approaches. Furthermore, patient education, close monitoring, and addressing social determinants are crucial to optimize adherence and clinical outcomes.

Looking forward, genetic insights and precision medicine promise to further tailor therapies and refine risk stratification. Combined with continuing advances in drug development and meaningful public health initiatives, these innovations offer hope to reduce the burden of hypertriglyceridemia and its devastating cardiovascular and pancreatic complications.

In essence, hypertriglyceridemia now stands as a clinical syndrome of great significance—one that demands nuanced understanding, integrative care, and incorporation of cutting-edge therapies. As research translates into practice, patients and clinicians alike can anticipate strides toward mitigating atherogenic risk and preventing catastrophic acute events, ultimately improving long-term cardiometabolic health.

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# **Battle of the Incretins: Do Tirzepatide and Semaglutide Change the Cardiovascular Game in Diabetes and Obesity?**

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## **A Paradigm Shift in Diabetes and Obesity Management**

The treatment landscape for type 2 diabetes and obesity has undergone a remarkable transformation over the past decade, driven largely by advances in incretin-based therapeutics. Among these, GLP-1 receptor agonists such as semaglutide and the novel dual GIP/GLP-1 receptor agonist tirzepatide have emerged as potent agents not only for glucose lowering but also for weight reduction and cardiovascular risk mitigation. These pharmacologic advances represent a paradigm shift from traditional glucose-centric management toward multifaceted cardiometabolic care.

Cardiovascular disease (CVD) is the leading cause of mortality in individuals with diabetes and obesity. In response, regulatory agencies have mandated cardiovascular outcome trials (CVOTs) as a requirement for approval of new glucose-lowering drugs. Semaglutide and tirzepatide have both demonstrated favorable outcomes in reducing major adverse cardiovascular events (MACE) in high-risk populations. However, direct comparative data on their cardiovascular benefit have been lacking, leaving practicing clinicians to rely on indirect and sometimes conflicting evidence to guide treatment choices.

Recent real-world data and sophisticated trial emulation studies have begun filling this critical gap by simulating head-to-head comparisons in broad patient populations approaching everyday clinical practice. This review distills this emerging evidence base, clarifies the comparative cardiovascular effects of tirzepatide and semaglutide, and synthesizes mechanistic insights that help explain their clinical profiles. By focusing on cardiovascular risk reduction, weight management, safety, and practical treatment implications, this evaluation aims to inform personalized therapy decisions and optimize outcomes for patients facing the dual burdens of diabetes and obesity.

## **Why Cardiovascular Benefit Matters: Beyond Glycemic Control**

Cardiovascular complications remain the primary cause of death and disability in patients with type 2 diabetes and obesity. Traditionally, glycemic control was regarded as paramount.

However, epidemiological and clinical research has steadily demonstrated that glucose lowering alone does not fully address the heightened cardiovascular risk inherent in these populations. Consequently, cardiovascular risk reduction has become an explicit therapeutic goal in diabetes management guidelines worldwide.

GLP-1 receptor agonists initially gained prominence for their powerful glucose-lowering effects, but their cardioprotective properties have elevated their status to that of essential cardiovascular medicines. Semaglutide was among the first therapies to demonstrate significant reductions in MACE, including myocardial infarction, stroke, and cardiovascular death, in dedicated outcome trials such as the SUSTAIN-6. Tirzepatide, a newer agent acting on both GIP and GLP-1 receptors, has not only surpassed expectations in glycemic efficacy and weight loss but has also shown promising cardiovascular benefit in the SURPASS-CVOT trial when compared with dulaglutide, another GLP-1 agonist.

The dual focus on cardiovascular outcomes and metabolic control addresses the complex pathophysiology of diabetes and obesity-related cardiovascular disease. Weight loss, improvement in insulin sensitivity, lipid profile optimization, and anti-inflammatory effects all contribute to the cardiovascular protection offered by these agents. Understanding and quantifying the comparative cardiovascular benefits of these drugs is vital for clinicians aiming to individualize treatment—minimizing cardiovascular risk while enhancing quality of life and long-term metabolic health.

## **The Anatomy of Real-World Comparison: Filling the Evidence Gap**

While randomized controlled trials (RCTs) remain the gold standard for evaluating drug efficacy, direct head-to-head trials between tirzepatide and semaglutide for cardiovascular outcomes are still pending. This leaves an evidence gap importantly filled in part by real-world evidence (RWE) studies and trial emulation methodologies.

Real-world data leverage large administrative databases, insurance claims, and electronic health records reflecting the heterogeneous populations encountered in clinical practice—including patients often excluded from classical RCTs due to age, comorbidities, or polypharmacy. Advanced statistical techniques such as propensity score matching and instrumental variable analysis further enhance the credibility of these analyses by simulating randomized conditions.

Emulation of landmark trials such as SUSTAIN-6 and SURPASS-CVOT within RWE platforms involves replicating trial inclusion criteria, endpoints, and follow-up times to assess how these therapies perform in routine care. Such studies enable practical comparisons—evaluating major adverse cardiovascular events, mortality, and hospitalization outcomes in real populations.

Recent analyses have found semaglutide to reduce the risk of myocardial infarction and stroke by approximately 18% compared to sitagliptin. Tirzepatide showed a trend toward similar risk reduction versus dulaglutide, with hazard ratios approximating parity when directly compared in RWE settings. These findings dovetail with trial data while expanding

generalizability. However, limitations including residual confounding and incomplete clinical detail in claims data necessitate cautious interpretation, underscoring the need for ongoing direct RCT comparisons.

## **Reviewing Landmark Trials: SUSTAIN-6 and SURPASS-CVOT in Context**

The SUSTAIN-6 trial was a pivotal cardiovascular outcome trial evaluating subcutaneous semaglutide versus placebo in patients with type 2 diabetes and established cardiovascular disease or high cardiovascular risk. The trial showed that semaglutide significantly reduced the composite primary endpoint of major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) with a hazard ratio of approximately 0.74, confirming GLP-1 receptor agonists' cardiovascular benefit.

SURPASS-CVOT evaluated tirzepatide compared to dulaglutide (a GLP-1 receptor agonist) focusing on MACE in patients with type 2 diabetes and high cardiovascular risk. Although the SURPASS trial was primarily powered for glycemic and weight outcomes, the cardiovascular analyses suggested non-inferiority but did not conclusively demonstrate superiority, with hazard ratios close to 1 for MACE outcomes.

These trials established the cardiometabolic efficacy of both drugs in their respective populations. However, variations in comparator arms, patient characteristics, and endpoint definitions complicate direct comparisons. Real-world emulation studies applying consistent criteria to broader populations now offer complementary insights and allow evaluation of drug performance in real practice outside the clinical trial environment.

## **Summary of Recent Evidence: Real-World Impact of Tirzepatide and Semaglutide**

New real-world studies analyzing US insurance claims data from 2018–2025 strategically compared semaglutide to sitagliptin and tirzepatide to dulaglutide using propensity score matching and rigorous controls. Cardiovascular endpoints included hospitalization for myocardial infarction, stroke, and all-cause mortality.

Key findings demonstrated:

- Semaglutide reduced combined MI and stroke risk by 18% compared to sitagliptin (hazard ratio [HR], 0.82).
- Tirzepatide showed a trend toward reduced all-cause mortality or major cardiovascular events versus dulaglutide (HR 0.87), though without statistical significance in some analyses.
- Direct comparison between tirzepatide and semaglutide revealed no significant difference in cardiovascular outcomes (HR 1.06).

Subgroup analyses suggested nuanced differences. Populations with established cardiovascular disease and obesity showed potential superiority of semaglutide for MACE reduction, whereas more heterogeneous cohorts sometimes favored tirzepatide in metabolic parameters. Safety profiles were comparable, with gastrointestinal side effects predominant but manageable.

These studies support the inclusion of both agents as integral to cardiovascular risk management in diabetes and obesity, endorsing their use within guideline-based frameworks. They highlight the importance of individualizing therapy based on patient comorbidities, weight loss needs, tolerability, and preferences.

## **Mechanistic Overview: Dual vs. Selective Incretin Agonism**

The distinct pharmacologic mechanisms of tirzepatide and semaglutide underpin their clinical effects. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, amplifies incretin signaling pathways, resulting in enhanced insulin secretion, reduced glucagon release, improved insulin sensitivity, and greater weight loss than GLP-1 agonists alone. Its broader receptor engagement may potentiate lipolysis and energy expenditure.

Semaglutide selectively stimulates GLP-1 receptors, exerting potent glucose-lowering, weight-loss, and cardiovascular effects well characterized in multiple CVOTs. It promotes satiety, delays gastric emptying, and modulates vascular and inflammatory pathways.

Despite tirzepatide's advantages in weight and HbA1c reduction, these have yet to translate unequivocally into superior cardiovascular outcomes, possibly because both drugs already achieve maximal GLP-1 mediated vascular benefit or due to differing trial designs and populations. Future head-to-head cardiovascular outcomes trials will clarify these mechanistic and clinical nuances.

## **Implications for Practice: Tailored Agent Selection**

Clinical decision-making should leverage the robust cardiovascular protection offered by both agents while considering individual patient factors.

- For patients with high cardiovascular risk or established atherosclerotic disease, semaglutide—with its longer safety track record and consistent CV benefit—may be preferred.
- Tirzepatide may be favored when profound weight loss and glycemic lowering are priorities, such as in severe obesity or difficult glycemic control.
- Side effect profiles are similar, with nausea, vomiting, and gastrointestinal discomfort common but generally transient.
- Cost, formulation preference, and patient comorbidities guide shared decision-making.

- Both agents should be integrated within broader multifactorial cardiovascular risk reduction strategies including lipid management, blood pressure control, and lifestyle interventions.

## Conclusion

The advent of incretin-based therapies, particularly semaglutide and tirzepatide, represents a watershed moment in managing type 2 diabetes and obesity, emphasizing cardiovascular protection alongside metabolic control. Both agents have consistently demonstrated significant reductions in major adverse cardiovascular events (MACE) across diverse randomized controlled trials and have extended their impact through real-world data analyses emulating trial populations.

Real-world evidence from large U.S. insurance claims databases reinforces that semaglutide and tirzepatide provide robust cardiovascular benefit consistent with their trial findings. Semaglutide shows hazard ratios (HR) around 0.82 for myocardial infarction and stroke reduction compared to sitagliptin, while tirzepatide exhibits cardiovascular event risk profiles comparable to dulaglutide and numerically similar outcomes to semaglutide when assessed directly in routine clinical practice. These findings substantiate their effectiveness beyond the controlled trial environment, offering reassurance of broad applicability for patients often excluded from trials due to comorbidities or age.

However, nuanced differences emerge in subgroup analyses and specialized cohort studies. For patients with established cardiovascular disease and obesity, some analyses report up to a 57% MACE reduction favoring semaglutide over tirzepatide. Conversely, broader or primary prevention populations sometimes show parity or slight numeric advantages with tirzepatide, particularly attributable to its superior weight loss and glycemic control. These variations highlight the critical importance of individualized therapy selection based on patient phenotype, comorbidities, and treatment goals.

Mechanistically, tirzepatide's dual agonism of GIP and GLP-1 receptors translates into superior metabolic outcomes, including enhanced insulin sensitivity and weight reduction, yet this has yet to conclusively translate into superior cardiovascular outcomes compared to selective GLP-1 receptor activation by semaglutide. Ongoing long-term outcome trials, including the SURMOUNT series, are poised to clarify these effects further.

From a clinical standpoint, the data empower an evidence-based, patient-centered approach. Both agents qualify as effective cardiometabolic therapies in type 2 diabetes with elevated cardiovascular risk. Tirzepatide may be prioritized when significant weight loss is a primary objective, while semaglutide's extensive cardiovascular outcome evidence positions it as a preferred agent for patients with established cardiovascular disease or concerns over tirzepatide-specific tolerability.

In summary, the "battle of the incretins" is less about declaring a definitive winner and more about enhancing the therapeutic arsenal available to clinicians. The emerging landscape supports clinicians confidently incorporating these agents into comprehensive,

individualized care strategies that engage both metabolic and cardiovascular pathways. This dual benefit heralds a new era in diabetes and obesity management—one focused equally on extending longevity and improving quality of life through targeted, mechanism-informed therapies.

As research matures and direct comparative trials become available, finer distinctions will inform guideline updates and optimize patient outcomes further. For now, tirzepatide and semaglutide represent potent and complementary tools in combating the intertwined epidemics of diabetes, obesity, and cardiovascular disease.

This expansion builds on the data from multiple recent high-impact studies (Nature Medicine 2025, academic.oup.com 2025, cardiology-focused reports) and integrates mechanistic and clinical insights to present a nuanced, forward-looking conclusion suitable for professional publication.

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# Comprehensive Review: Oral Antidiabetic Agents and Adjunctive Drugs in Diabetes and Peripheral Artery Disease (PAD)

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Peripheral artery disease (PAD) and diabetes mellitus (DM) frequently coexist, substantially increasing the risk of cardiovascular complications and limb-related adverse outcomes. Epidemiological studies demonstrate that approximately 20–30% of diabetic patients develop PAD, contributing to increased rates of critical limb ischemia, major amputations, and cardiovascular mortality. The complex interplay between hyperglycemia-driven endothelial dysfunction, accelerated atherosclerosis, neuropathy, and microvascular disease exacerbates the progression and severity of PAD in diabetic populations.

Modern management paradigms have evolved to emphasize a comprehensive, multifactorial approach targeting glycemic control, lipid management, hypertension, thrombosis prevention, renal protection, and ischemic tissue salvage. Therapeutic regimens must be tailored to balance efficacy, safety, tolerability, and patient-specific considerations, incorporating multidisciplinary care including endocrinology, cardiology, vascular surgery, and podiatry.

This review systematically explores the mechanisms of action, clinical efficacy, cardiovascular and limb benefits, and safety profiles of oral antidiabetic agents including metformin, sulfonylureas, SGLT2 inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, dual incretin agonists, thiazolidinediones, alpha-glucosidase inhibitors, and insulin secretagogues. Additionally, adjunctive therapies such as statins, PCSK9 inhibitors, antiplatelet/anticoagulants, renoprotective agents, and vascular supportive treatments are examined. The CARABIAZEM framework synthesizes this evidence to guide clinical decision-making in this high-risk population.

## Oral Antidiabetic Agents: Major Classes and Mechanisms

### Metformin

As the cornerstone of type 2 diabetes therapy, metformin primarily reduces hepatic gluconeogenesis and enhances peripheral insulin sensitivity via activation of AMP-activated protein kinase (AMPK). Moreover, it enhances endogenous incretin hormones—glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)—augmenting

insulin secretion and glucose regulation. Metformin further improves endothelial function by promoting nitric oxide (NO) bioavailability, critically relevant in PAD-associated vascular impairment.

Clinically, metformin reduces HbA1c by 1 to 1.5%, contributes to modest weight loss or weight neutrality, and carries cardiovascular protective effects demonstrated in multiple large-scale studies. While clinical trials such as PERMATE did not show walking distance improvements in nondiabetic PAD patients, experimental evidence suggests enhanced endothelial responsiveness and microcirculation that may benefit ischemic tissues.

Gastrointestinal intolerance (nausea, diarrhea) is common but manageable; rare lactic acidosis occurs in advanced renal or hepatic insufficiency. Long-term use requires monitoring for vitamin B12 deficiency.

## **Sulfonylureas**

Sulfonylureas stimulate pancreatic  $\beta$ -cell insulin secretion via closure of ATP-sensitive potassium channels. Their HbA1c reduction efficacy typically ranges from 1 to 1.5%. However, they induce weight gain and bear a significant hypoglycemia risk, limiting their use, especially in elderly or obese patients.

Evidence on cardiovascular safety is mixed, with older agents showing possible harm, while newer sulfonylureas appear safer but without cardiovascular or limb event benefit. They have little direct influence on PAD progression and are primarily reserved for combination therapy in select patients.

## **SGLT2 Inhibitors**

Sodium-glucose cotransporter-2 inhibitors act by inhibiting glucose reabsorption in the proximal renal tubules, promoting glycosuria, and modest diuresis. These agents reduce HbA1c by approximately 0.5 to 1%, induce weight loss, and lower blood pressure.

Cardiovascular outcome trials revealed significant reductions in heart failure hospitalization and cardiovascular death among diabetics. However, canagliflozin was associated with increased lower-limb amputation in the CANVAS study, particularly in patients with pre-existing PAD or neuropathy. Empagliflozin and dapagliflozin have not consistently demonstrated such a risk but clinical caution is advised. Adverse effects include genital fungal infections and rare cases of diabetic ketoacidosis.

## **DPP-4 Inhibitors**

Dipeptidyl peptidase-4 inhibitors prolong the half-life of endogenous incretins, enhancing glucose-dependent insulin secretion and suppressing glucagon release. These agents lower HbA1c by 0.7 to 1% without increasing hypoglycemia or body weight.

Cardiovascular outcome trials consistently show cardiovascular safety but no significant benefit in major cardiovascular or limb outcomes. Their role is primarily as adjunctive therapy to improve glycemia.

## **GLP-1 Receptor Agonists and Dual Incretin Agonists**

GLP-1 receptor agonists, including semaglutide and liraglutide, enhance insulin secretion, inhibit glucagon, delay gastric emptying, and reduce appetite. These effects produce HbA1c reductions of 1.5 to 2%, significant weight loss, and substantial cardiovascular risk reductions, including stroke and limb events in diabetic PAD.

Dual agonists such as tirzepatide target both GIP and GLP-1 receptors, providing superior glycemic and weight loss outcomes. Their cardiovascular safety and efficacy are promising but direct comparative long-term CVOT data pending.

## **Thiazolidinediones**

These PPAR- $\gamma$  agonists improve insulin sensitivity and reduce HbA1c moderately but cause weight gain, fluid retention, risk of heart failure exacerbation, and increase fracture risk, limiting their use in PAD patients.

## **Alpha-Glucosidase Inhibitors**

By inhibiting carbohydrate breakdown in the intestine, alpha-glucosidase inhibitors blunt postprandial glucose rise modestly, limited by gastrointestinal side effects.

## **Meglitinides**

Meglitinides provide short-acting insulin secretagogue effects controlling postprandial hyperglycemia, useful in patients with irregular meals.

## **Adjunctive Pharmacotherapy in PAD and Diabetes**

### **Statins**

Statins effectively lower LDL cholesterol and reduce cardiovascular and limb events in diabetes and PAD, recommended as standard therapy regardless of baseline LDL levels. High-potency agents such as atorvastatin and rosuvastatin have shown the greatest benefit in reducing plaque progression and ischemic events.

### **PCSK9 Inhibitors**

PCSK9 monoclonal antibodies, alirocumab and evolocumab, dramatically decrease LDL cholesterol and lipoprotein(a), variables linked with residual cardiovascular risk. Data from

FOURIER and ODYSSEY OUTCOMES trials confirm reductions in cardiovascular and limb events in PAD populations with excellent tolerability.

## **Antiplatelet Therapy**

Aspirin or clopidogrel as monotherapy are recommended in PAD for secondary prevention. Dual antiplatelet therapy following revascularization improves surgical and endovascular outcomes but increases bleeding risk and should be time-limited.

## **Anticoagulants**

Low-dose rivaroxaban plus aspirin, per the COMPASS study, provides superior protection against MACE and limb events in high-risk PAD with diabetes, balanced against an increased bleeding risk mandating patient selection.

## **Renoprotective Agents**

ACE inhibitors or ARBs improve renal outcomes and reduce cardiovascular risk, recommended for patients with diabetes and PAD with hypertension or albuminuria. Mineralocorticoid receptor antagonists such as finerenone further slow progression of diabetic kidney disease and contribute to cardiovascular protection.

## **Blood Pressure Management**

The therapeutic target for blood pressure is typically less than 130/80 mmHg, individualized by patient factors. Preferred agents include ACE inhibitors, ARBs, calcium channel blockers, and thiazide diuretics.

## **Nitric Oxide Donors and Vascular Support**

Nitric oxide donors improve endothelial function, vasodilation, and angiogenesis. Agents such as L-arginine and newer hybrid molecules have demonstrated improved microcirculation and could aid tissue perfusion in ischemic limbs, including diabetic foot ulcers. Studies remain preliminary but represent promising adjuncts for limb salvage.

## **Comprehensive Management and Guidelines**

Effective PAD and diabetes management requires integration of pharmacological therapy with lifestyle modification and multidisciplinary care. Early initiation of agents with cardiovascular benefit such as GLP-1 receptor agonists and SGLT2 inhibitors is advocated by major societies. Regular podiatric assessment, smoking cessation, glycemic control, and blood pressure optimization are pillars of prevention and care.

## Practical Clinical Pearls

- Individualize therapies considering comorbidities, risk of hypoglycemia, and tolerability.
- Avoid hypoglycemia in elderly and frail patients by tailoring glycemic targets.
- Use antiplatelet and anticoagulant combinations judiciously, balancing ischemic and bleeding risks.
- Combine statin and PCSK9 inhibitors in high-risk PAD with resistant hyperlipidemia.
- Consider vascular supportive agents as adjuncts while pursuing revascularization and meticulous wound care.

## Conclusion

The co-occurrence of diabetes mellitus and peripheral artery disease presents a complex therapeutic challenge, demanding a holistic, multifactorial management approach tailored to reduce cardiovascular and limb complications. Diabetes substantially increases the prevalence, severity, and adverse outcomes of PAD, including critical limb ischemia and major amputations, underscoring the urgency of optimizing pharmacologic and lifestyle interventions.

Oral antidiabetic agents form the backbone of glycemic management but their vascular effects vary widely. Metformin, recognized for its robust safety profile and cardioprotective effects, remains first-line therapy. Sulfonylureas continue to have limited utility due to hypoglycemia and uncertain cardiovascular safety. The emergence of SGLT2 inhibitors and GLP-1 receptor agonists has revolutionized care by incorporating cardiovascular and renal protective benefits, with evidence for limb outcome improvements particularly for GLP-1 receptor agonists like semaglutide.

Adjunctive cardiovascular therapies—high-intensity statins, PCSK9 inhibitors, antiplatelets such as aspirin or clopidogrel, and selective anticoagulation with agents like low-dose rivaroxaban—complement glycemic management by mitigating atherosclerosis and thrombotic risk. Blood pressure control and renoprotective agents (ACE inhibitors, ARBs, mineralocorticoid receptor antagonists) form essential components of comprehensive vascular protection.

Nitric oxide donors and vascular supportive therapies represent promising adjuncts to improve microcirculation and enhance ischemic tissue viability, particularly in diabetic foot management, though further evidence is awaited to clarify clinical roles.

Clinical outcomes hinge on integrated, multidisciplinary strategies emphasizing glycemic optimization, cardiovascular risk reduction, limb surveillance, lifestyle modification, and judicious use of pharmacotherapy. Early initiation of agents with proven cardiovascular benefit, especially in high-risk patients with PAD and diabetes, is imperative. Patient-centered care models incorporating individualized risk assessment, adherence promotion, and health equity considerations are indispensable.

In summary, the management of diabetes complicated by PAD requires a nuanced, evidence-driven approach leveraging advances in oral antidiabetic therapies, lipid-lowering, and antithrombotic agents — embodied in the CARABIAZEM framework. As research continues to elucidate mechanistic insights and novel treatments emerge, the opportunity to improve both limb salvage and cardiovascular mortality in this vulnerable population grows. Clinicians must maintain vigilance, remain up to date with evolving guidelines, and employ comprehensive, multidisciplinary care to effectively combat the intertwined epidemics of diabetes and peripheral artery disease.

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# **Beta-Blockers Across the Cardio-Diabetes-Renal Axis: An Engaging, Comprehensive Guide**

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## **The Evolving Role of Beta-Blockers in Contemporary Cardiorenal and Metabolic Medicine**

Beta-blockers have long been integral to cardiovascular practice, valued for their ability to reduce heart rate, lower blood pressure, and attenuate myocardial oxygen demand. Traditionally viewed as a homogenous drug class primarily acting on cardiac  $\beta_1$ -adrenergic receptors, the narrative surrounding beta-blockers has become substantially more sophisticated. The last two decades have witnessed a nuanced understanding of the diverse mechanisms, molecular variations, and clinical applications of beta-blockers, especially in complex patient populations burdened by diabetes and chronic kidney disease (CKD).

This complexity arises from heterogeneity in receptor selectivity, vasodilatory properties, central nervous system penetration, and effects on metabolic and inflammatory pathways. Beta-blockers vary in whether they target  $\beta_1$ ,  $\beta_2$ , and even  $\alpha_1$  receptors, altering systemic vascular resistance, arterial compliance, and sympathetic tone in ways crucial for organ protection but also impose differing safety and tolerability profiles.

New evidence highlights that beta-blockers influence central aortic blood pressure—the pressure experienced by key organs such as the brain and heart—more meaningfully than peripheral brachial pressures alone, explaining differences in clinical outcomes among agents. Furthermore, in diabetes and CKD—conditions characterized by heightened sympathetic nervous system activity and metabolic disturbances—the choice of beta-blocker demands precision: some agents exacerbate glucose intolerance and lipid abnormalities, while novel vasodilatory beta-blockers improve insulin sensitivity, arterial health, and inflammation.

Moreover, beyond hypertension and post-myocardial infarction care, beta-blockers play increasingly recognized roles in modulating renal outcomes, attenuating proteinuria, and potentially slowing diabetic nephropathy progression. The shift from “one beta-blocker fits all” to individualized selection based on molecular pharmacology, comorbidities, and patient phenotype symbolizes an important advance in cardio-nephro-metabolic therapeutics.

This comprehensive guide explores beta-blocker mechanisms, contemporary clinical evidence, vascular and metabolic effects, and current guideline recommendations. It aims to support clinicians in navigating the art and science of beta-blocker use to optimize outcomes across the interconnected cardio-diabetes-renal patient population.

## **Unpacking Beta-Blocker Mechanisms: Old Drug, Nuanced Effects**

Beta-blockers antagonize adrenergic beta receptors, primarily  $\beta_1$  receptors located in cardiac tissue, responsible for increasing heart rate and myocardial contractility when stimulated by catecholamines like norepinephrine. Blockade of  $\beta_1$  receptors thereby slows the heart rate (negative chronotropy), reduces contractility (negative inotropy), and lowers myocardial oxygen consumption—mechanisms underpinning their effectiveness in ischemic heart disease, heart failure, and arrhythmias.

However, many beta-blockers also variably block  $\beta_2$  receptors found in bronchial smooth muscle, vascular beds, and metabolic tissues, resulting in effects on airway constriction, peripheral vasculature, and glucose metabolism. Beta-blockers range from cardioselective agents (high  $\beta_1$  selectivity) such as bisoprolol and metoprolol to non-selective agents like propranolol and carvedilol that affect  $\beta_2$  and  $\alpha_1$  adrenergic receptors, producing vasodilation.

Beyond receptor selectivity, some beta-blockers invoke vasodilatory actions through the release of nitric oxide (NO), antagonism of  $\alpha_1$  receptors, or antioxidant effects, which improve arterial compliance and reduce afterload, benefiting hypertensive and heart failure patients.

These pharmacodynamic differences profoundly influence not only blood pressure control but also peripheral and central hemodynamics, sympathetic nervous system activity, metabolic consequences—including insulin sensitivity and lipid profiles—and inflammation. For example, nebivolol's NO-mediated vasodilation improves endothelial function and may positively affect metabolic parameters, in contrast to older beta-blockers that impair glucose tolerance.

Given these diverse mechanisms, beta-blocker choice can optimize benefits and minimize adverse effects tailored to patients with diabetes, kidney disease, or complex comorbidities.

## **The Modern Antihypertensive Landscape: Where Beta-Blockers Stand Today**

Blood pressure control is critical to prevent silent vascular injury manifesting as stroke, myocardial infarction, heart failure, and renal decline. Despite their efficacy in lowering brachial blood pressure, older beta-blockers such as atenolol and metoprolol show less effect on central aortic pressure—the pressure load most relevant to myocardial and cerebral perfusion—compared to calcium channel blockers (CCBs), ACE inhibitors, or

angiotensin receptor blockers (ARBs). This differential may partly explain why non-vasodilating, non-selective beta-blockers confer inferior stroke protection and overall mortality benefits.

Conversely, newer vasodilatory beta-blockers like nebivolol, carvedilol, and labetalol reduce central aortic pressure more effectively due to beneficial effects on arterial compliance and wave reflection patterns.

Recognizing these differences, hypertension treatment guidelines increasingly reserve beta-blockers for specific clinical contexts such as post-myocardial infarction, heart failure with reduced ejection fraction, angina, arrhythmias, or patients with elevated sympathetic tone. For general essential hypertension without compelling indications, calcium channel blockers and RAAS blockers remain first-line due to better stroke and mortality prevention and favorable metabolic profiles.

Nonetheless, beta-blockers continue to be critical in pregnant patients for hypertension management, where labetalol is commonly used, and in young patients with marked sympathetic activation.

## **The Power of the Sympathetic Nervous System and Beta-Blockade in Renal Disease**

Chronic kidney disease drives heightened sympathetic nervous system activity, mediated by damaged kidneys sending excessive neural signals to the central nervous system. This neurogenic hypertension aggravates left ventricular hypertrophy, accelerates atherosclerosis, promotes arrhythmogenesis, and hastens kidney function decline.

Beta-blockers that are lipophilic, like carvedilol and nebivolol, penetrate the blood-brain barrier, suppressing this pathological sympathetic overdrive effectively. Early and sustained sympathetic blockade in CKD slows glomerulosclerosis and improves cardiovascular outcomes by reducing systemic vasoconstriction, aldosterone release, and cardiac workload.

Clinical trials demonstrate that beta-blockers are indispensable adjuncts in comprehensive antihypertensive regimens for diabetic nephropathy, helping disrupt the vicious cycle linking sympathetic hyperactivity, hypertension, and renal-cardiac injury.

## **Beta-Blockers: Molecular Variations and Clinical Pearls**

Cardioselective beta-blockers such as bisoprolol, metoprolol, atenolol, and nebivolol preferentially target  $\beta_1$  receptors, reducing cardiac risks while minimizing bronchospasm in patients with reactive airway disease. Nebivolol offers the additional benefit of endothelial NO release, improving vascular tone and offering a better metabolic profile.

Non-cardioselective agents like propranolol, nadolol, carvedilol, and labetalol affect multiple adrenergic receptors and are indicated in portal hypertension, migraine prophylaxis,

hypertensive emergencies, and pregnancy. However, their broader receptor blockade increases risks for bronchospasm and worsened metabolic parameters.

Vasodilatory agents like carvedilol combine  $\beta$ -blockade with  $\alpha_1$  antagonism, improving insulin sensitivity and lipid metabolism, while labetalol is highly useful in hypertensive crises and pregnancy.

Selecting beta-blockers according to clinical context maximizes benefits, minimizes adverse metabolic effects, and ensures better tolerability.

## **Beta-Blockers and Diabetes: Implications for Metabolic Health**

Older non-selective beta-blockers blunt sympathetic warning symptoms of hypoglycemia and can worsen glycemic control and lipid profiles, making them less ideal in diabetic hypertensives. In contrast, carvedilol and nebivolol show metabolic neutrality or improvement, with better insulin sensitivity, minimal weight gain, and reduced inflammation, favoring their use in diabetes.

## **Proteinuria, Renal Protection, and Inflammation**

While beta-blockers contribute to blood pressure reduction essential for renal preservation, their anti-proteinuric effects are less potent than RAAS inhibitors. However, vasodilatory beta-blockers may provide incremental benefits on albuminuria and reduce microvascular inflammation.

Combination therapy with ACE inhibitors or ARBs remains the mainstay for slowing CKD progression, with beta-blockers augmenting hemodynamic and cardioprotective effects.

## **Combination Therapies: Beta-Blockers with Other Antihypertensives**

Combining beta-blockers with dihydropyridine calcium channel blockers like amlodipine enhances blood pressure control while preserving heart rate and minimizing peripheral edema. Non-dihydropyridine CCBs (verapamil, diltiazem) require careful co-administration due to bradycardia risk.

Combination with RAAS blockers yields synergistic hemodynamic and vascular protection. Diuretics complement especially in resistant hypertension.

Integrating beta-blockers with emerging cardiometabolic therapies such as SGLT2 inhibitors and GLP-1 receptor agonists represents the pinnacle of modern cardiorenal metabolic care.

## **Beta-Blockers in Practice: Guideline Recommendations and Special Considerations**

Guidelines restrict beta-blockers as first-line agents in hypertension to patients with compelling indications including heart failure with reduced ejection fraction, post-myocardial infarction, angina, symptomatic arrhythmias, and pregnancy. They are specially favored in patients with elevated sympathetic tone and younger demographics.

Special populations, such as pregnant patients, benefit from labetalol and metoprolol for safety; cardioselective agents are preferred in patients with pulmonary disease; nebivolol is favorable in those with erectile dysfunction.

## **Beta-Blocker Therapy Post-Myocardial Infarction and in Heart Failure**

Emerging evidence challenges prolonged beta-blocker therapy after MI in patients with preserved ejection fraction, showing no mortality benefit, although those with reduced EF or ongoing ischemia continue to benefit. In heart failure with reduced EF, carvedilol, bisoprolol, and metoprolol succinate remain anchor therapies with proven mortality reduction. Their utility in heart failure with preserved EF remains uncertain and limited to symptomatic rate control.

## **Emerging Research and Future Perspectives**

Vasodilatory beta-blockers show superior central aortic pressure reduction, heralding improved cerebrovascular protection. The role of beta-blockers in modulating sympathetic tone underscores their importance in slowing progression in CKD, especially diabetic nephropathy.

Combination therapies with calcium channel blockers and RAAS inhibitors offer refined control of vascular and cardiac profiles in complex patients.

Personalizing beta-blocker therapy remains a nuanced, evolving domain.

## **Conclusion**

Beta-blockers have evolved from a broad class of heart rate–lowering drugs to a sophisticated pharmacologic toolkit essential to cardio-diabetes-renal health. The wide range of molecular heterogeneity within beta-blockers—covering receptor selectivity, vasodilatory and metabolic effects—and robust evidence from clinical trials and real-world data inform selective use tailored to individual patient need.

While no longer first-line for all hypertensives, beta-blockers remain irreplaceable for reducing mortality and morbidity in heart failure with reduced EF, following myocardial infarction, managing arrhythmias, and mitigating sympathetic overactivity in chronic kidney disease and diabetes. Newer vasodilatory agents carvedilol and nebivolol provide superior central blood pressure control, improved metabolic profiles, and endothelial function, expanding their utility.

Integration of beta-blockers with other antihypertensive and cardiometabolic agents, including RAAS blockers, calcium channel blockers, SGLT2 inhibitors, and GLP-1 receptor agonists, forms the core of contemporary comprehensive care.

Future research on their anti-inflammatory and antioxidant properties may unveil more potent vascular protective mechanisms. Personalized therapy considering patient comorbidities, risk profiles, and tolerability is paramount.

Ultimately, beta-blockers exemplify precision medicine where mechanistic insight meets individualized clinical care to optimize outcomes across the cardio-diabetes-renal interface.

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# **Fighting Against the Odds: Reducing Cardiovascular Mortality in CKD**

A Practical, Modern Guide to Lipids, Drugs, and Disease Modulation

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## **Navigating the Cardiovascular Challenge in Chronic Kidney Disease**

Chronic kidney disease (CKD) presents one of the most formidable challenges bridging nephrology and cardiology. Over 650 million people worldwide live with CKD, and its prevalence is rising rapidly, fueled by demographic changes and the increasing burden of diabetes and hypertension. Unlike many chronic diseases, cardiovascular mortality among CKD patients dramatically eclipses the risk of progressing to kidney failure requiring dialysis. Scientific evidence shows that patients with moderate to advanced CKD face cardiovascular mortality rates two to four times higher than age-matched individuals without kidney impairment.

The reasons behind this heightened risk are complex and multifactorial. Traditional risk factors common in CKD such as hypertension, diabetes, and dyslipidemia are compounded by “kidney-specific” mechanisms including persistent anemia, non-traditional inflammation, oxidative stress, disturbed mineral metabolism, and widespread vascular calcification. These factors contribute to arterial stiffening, left ventricular hypertrophy, and microvascular dysfunction—effectively transforming the vascular system into a “calcified battlefield.” The cardiovascular system, in turn, imposes stress on residual renal function, creating a vicious cycle accelerating both cardiovascular disease and kidney failure.

Yet this bleak outlook is not immutable. Recent advances in understanding CKD’s unique pathophysiology, alongside emerging therapeutic options, offer practical avenues for intervention. Smarter dyslipidemia management, innovative therapies targeting inflammation and sympathetic overdrive, and refined strategies to control blood pressure and proteinuria are reshaping care pathways. The key lies in early, individualized, and evidence-driven interventions that address the full spectrum of risks to blunt cardiovascular mortality.

This comprehensive review synthesizes modern knowledge about lipid targets, novel therapeutics including PCSK9 inhibitors and high-dose fish oils, optimal blood pressure management, sympathetic regulation, and antithrombotic strategies in CKD patients. It

offers clinicians an actionable framework to improve survival outcomes amidst the cardio-kidney convergence.

## **The Cardio-Kidney Crossroads: Why CKD Patients Face Steep Cardiovascular Mortality Odds**

The interplay of kidney dysfunction and cardiovascular risk is unrelenting. Patients with CKD—especially stages 3 through 5—are burdened with an elevated incidence of coronary artery disease, heart failure, arrhythmias, and stroke. Epidemiological data reveal that cardiovascular disease accounts for approximately 40 to 50 percent of deaths in advanced CKD patients, far exceeding mortality risks from progression to dialysis.

Traditional risk factors—hypertension, diabetes—are highly prevalent yet insufficient alone to explain this excess risk. CKD-specific factors such as persistent low-grade inflammation, accumulation of uremic toxins, altered calcium-phosphate metabolism leading to vascular calcification, anemia-induced hypoxia, and increased oxidative stress aggravate endothelial dysfunction and promote atherosclerosis.

Notably, arterial stiffness and microvascular mismatch impair organ perfusion, and left ventricular hypertrophy develops early, predisposing patients to heart failure and sudden cardiac death. CKD also amplifies the risk of arrhythmias through electrolyte imbalance and sympathetic overactivity.

Importantly, these cardiovascular risks manifest early in CKD, occasionally even during mild to moderate kidney insufficiency, and worsen with disease progression. Dialysis patients face unique challenges including fluid shifts and electrolyte changes that precipitate arrhythmic events, making tailored cardiovascular risk mitigation a clinical imperative.

## **Beyond the Basics: Rethinking Lipid Management in CKD**

Lipid abnormalities in CKD differ significantly from the general population. Though LDL cholesterol promotes atherosclerosis across CKD stages, characteristic dyslipidemia in CKD also involves elevated triglycerides, reduced HDL cholesterol, and increased small, dense LDL particles—all highly atherogenic.

Statins continue to form the mainstay for lipid management in early to moderate CKD (stages 1-4), reducing myocardial infarction, stroke, and cardiovascular interventions. High-intensity statins such as atorvastatin or rosuvastatin are preferred except in cases of intolerance. However, clinical trials like SHARP have demonstrated that initiating statins at dialysis onset does not confer significant benefits in primary cardiovascular prevention, although continuing pre-existing statins during dialysis transition may reduce events.

For patients who fail to reach LDL cholesterol targets or cannot tolerate statins, addition of ezetimibe is endorsed. This agent works by inhibiting intestinal cholesterol absorption and synergizes with statins effectively.

A revolutionary development in lipid therapy has been PCSK9 inhibitors, which profoundly reduce LDL cholesterol by up to 60 percent and also reduce lipoprotein(a), a potent residual cardiovascular risk factor frequently elevated in CKD. Meta-analyses affirm their safety and efficacy in both advanced CKD and dialysis patients, though renal dosing and long-term safety require continued monitoring.

## **Omega-3 Polyunsaturated Fatty Acids: The Fish Oil Comeback in CKD**

Unlike previous neutral or disappointing omega-3 studies, emerging evidence with high-purity, high-dose eicosapentaenoic acid (EPA) formulations has demonstrated striking cardiovascular risk reduction in dialysis patients. The PISCES trial reported a substantial decrease in myocardial infarction, cardiac death, and major vascular events with daily 4g fish oil supplementation in hemodialysis patients.

While the mechanistic basis, possibly linked to anti-inflammatory effects, triglyceride lowering, and plaque stabilization, is not fully elucidated, these findings redefine fish oil as a cornerstone adjunctive therapy for cardiovascular protection in hemodialysis, prompting reevaluation of supplementation guidelines for this high-risk group.

## **Blood Pressure Management: Central Aortic Pressure and Sympathetic Overdrive in CKD**

Hypertension in CKD is complicated by arterial stiffness and frequent white coat or masked hypertension. Current evidence points to central aortic pressure as a more relevant measure than traditional brachial readings, as it directly reflects load on the heart and brain.

Vasodilating beta-blockers such as carvedilol and nebivolol favorably reduce central aortic pressure, offering possibly better stroke and cardiovascular event prevention compared to older beta-blockers. Dihydropyridine calcium channel blockers are effective at volume control and blood pressure reduction, especially useful in volume-overloaded hemodialysis patients. ACE inhibitors and ARBs remain fundamental for both blood pressure and proteinuria reduction.

CKD also features profound sympathetic nervous system activation, aggravating hypertension and cardiac remodeling. Beta-blockers cross the blood-brain barrier to attenuate sympathetic hyperactivity, reducing morbidity and mortality, particularly in diabetic nephropathy and CKD-associated heart failure.

Combination antihypertensive regimens are typical, with beta-blockers, RAAS inhibitors, and CCBs forming the cornerstone, complemented by diuretics where needed. Careful balance is essential to manage electrolyte disturbances and optimize outcomes.

## **Managing Proteinuria: The Therapeutic Window in CKD**

Proteinuria is both a marker and driver of CKD progression and cardiovascular risk. Even modest reductions in proteinuria correlate with improved outcomes.

ACE inhibitors and ARBs offer the strongest evidence for proteinuria reduction and delay kidney decline. Mineralocorticoid receptor antagonists, such as finerenone, demonstrate additional proteinuria reduction and cardiovascular protection, although hyperkalemia risk warrants caution.

Non-dihydropyridine calcium channel blockers provide adjunctive benefit for proteinuria in select cases. SGLT2 inhibitors have recently emerged as powerful agents in reducing albuminuria and improving kidney outcomes in diabetic CKD.

## **Antiplatelet and Antithrombotic Strategies: Navigating Risk and Benefit**

In CKD, antiplatelet use for secondary prevention of cardiovascular events remains important but must be balanced against increased bleeding risks, particularly in advanced stages and dialysis patients. Aspirin remains first-line unless contraindicated, while P2Y<sub>12</sub> inhibitors like clopidogrel are used after acute coronary syndromes or percutaneous interventions. Newer agents improve outcomes but increase bleeding risk and must be carefully selected. Oral anticoagulation in CKD is nuanced, with warfarin and apixaban preferred options based on kidney function.

## **Revolutionary Agents: SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Emerging Therapies**

SGLT2 inhibitors have transformed CKD and cardiovascular disease outcomes by slowing kidney function decline, reducing heart failure hospitalization, and lowering cardiovascular mortality across diabetic and nondiabetic CKD populations. Trials such as CREDENCE, DAPA-CKD, and EMPA-KIDNEY support their early use.

GLP-1 receptor agonists provide complementary metabolic and vascular benefits, including weight loss and improved albuminuria control, offering additional protection in eligible patients.

## The Unique Landscape of Dialysis Patients: Tailored Cardiovascular Care

In dialysis populations, cardiovascular risk management must consider altered pharmacokinetics and heightened bleeding risks. Statins are rarely initiated at dialysis start but should generally continue if previously established. PCSK9 inhibitors and high-dose EPA fish oil have emerging evidence supporting use and safety in dialysis. Blood pressure control emphasizes volume management, with beta-blockers and calcium channel blockers playing central roles. Antiplatelet and anticoagulant agents require judicious use to balance hemorrhagic complications.

### Conclusion

Cardiovascular mortality drives the grim prognosis of chronic kidney disease, underscoring the need for aggressive and tailored prevention strategies. The complex interplay of traditional risk factors, CKD-specific pathophysiology, and therapeutic challenges demands comprehensive, multidisciplinary management founded on robust evidence.

Advances in lipid management—from statins through PCSK9 inhibitors and high-dose omega-3 fatty acids—offer unprecedented atheroprotection, even in advanced stages of kidney disease. Progressive refinement in blood pressure control, emphasizing central aortic pressure and sympathetic modulation with beta-blockers and other agents, further improve outcomes.

Targeting proteinuria with renin-angiotensin-aldosterone system blockers and SGLT2 inhibitors slows kidney disease progression and cardiovascular complications. Antiplatelet and anticoagulant therapies must be individualized to balance ischemic and bleeding risks, particularly in dialysis patients.

Emerging trial data endorse the early and combined application of these therapies, moving from reactive to proactive cardiovascular risk mitigation in CKD. Personalization based on patient comorbidities, kidney function, and life goals is paramount.

By integrating novel therapeutics and evidence-based clinical strategies, clinicians can defy the odds imposed by CKD, substantially reducing cardiovascular mortality and enhancing patient quality of life. The future holds promise as evolving research broadens the therapeutic toolkit and deepens understanding of cardio-renal interactions.

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# **The Double-Dare of Cholesterol: Why Indian Patients Need Both LDL and ApoB to Outwit Heart & Kidney Risk**

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## **India's Unique Cardiometabolic Challenge and the Lipid Complexity**

In clinics across metropolitan hubs and rural corners of India, cholesterol readings are often the starting point in evaluating cardiovascular risk. However, Indians carry a distinctive lipid fingerprint, vastly different from many global populations, which requires a more precise interpretation. The traditional reliance on LDL cholesterol (LDL-C) as the "bad cholesterol" marker for cardiovascular risk is insufficient for India's diverse and dynamic population. Indians are disproportionately affected by a severe cardiometabolic crisis marked by elevated triglycerides, reduced HDL cholesterol, and notably, elevated apolipoprotein B (ApoB) levels. ApoB reflects the total number of atherogenic lipoprotein particles—including very-low-density lipoproteins (VLDL), intermediate-density lipoprotein (IDL), LDL particles, and lipoprotein(a)—responsible for vascular plaque formation. This lipoprotein count is especially crucial given the predominance of small, dense LDL particles in Indians, which are more atherogenic and frequently not reflected adequately by LDL-C measurements.

This "South Asian dyslipidemia" occurs in the context of an epidemic of insulin resistance, type 2 diabetes, chronic kidney disease, and premature cardiovascular disease (CVD). Recent research shows that up to 50% of Indians, including those with diabetes and CKD, have discordant LDL-C and ApoB levels, meaning that LDL-C targets may appear met, but ApoB—and thus actual atherogenic particle burden—remains dangerously high. This discordance masks true cardiovascular and renal risk.

The epidemiological and genetic factors compounded by rapid lifestyle and dietary shifts present a "perfect storm"—increasing the necessity to measure both LDL-C and ApoB or at least non-HDL cholesterol to fully capture risk. National and international guidelines now acknowledge this paradigm shift, advocating for ApoB assessment particularly in South Asians, diabetic populations, and those with high triglycerides or metabolic syndrome.

Given the insidiousness of this risk profile, failing to incorporate ApoB into routine clinical practice is akin to reading only half the story—a dangerous oversight in a population already grappling with one of the highest cardiovascular death rates globally.

## **The Phenomenon of Lipid Discordance: Understanding Why ApoB Complements LDL-C**

For decades, LDL cholesterol has been the cornerstone lipid marker in assessing atherosclerotic cardiovascular disease (ASCVD) risk. However, LDL-C measures cholesterol mass within LDL particles, which can vary widely in number and size. Each ApoB molecule marks one atherogenic particle, directly counting particles that contribute to plaque formation, regardless of cholesterol content.

Among Indians, this discordance is particularly pronounced due to the predominance of small, dense LDL particles carrying less cholesterol per particle but causing disproportional vascular damage. While LDL-C may appear normal or low, ApoB levels can be elevated, indicating a high number of atherogenic particles “firing” at arterial walls. Conversely, some individuals may have elevated LDL-C but normal ApoB—a scenario often involving larger, less harmful LDL particles.

The clinical importance of this discordance is profound. Numerous studies, including Indian cohorts, demonstrate that ApoB outperforms LDL-C in predicting myocardial infarction, stroke, and CKD progression, especially in patients with diabetes and metabolic syndrome. Approximately half of the adult Indian population exhibits such discordance, reinforcing the need for dual assessment to avoid underestimating risk.

This discordance challenges clinicians familiar with traditional LDL-centric approaches to shift towards integrated lipid evaluation. Recognizing ApoB’s superior predictive value, particularly in South Asians, elevates the opportunity to initiate appropriate preventive strategies earlier, personalized to individual lipid particle burden rather than cholesterol mass alone.

## **Epidemiology and Impact of Dyslipidemia and ApoB-LDL-C Discordance in India**

India faces an unprecedented cardiometabolic crisis with premature cardiovascular mortality at younger ages compared to Western countries. Urban epidemiological studies reveal that nearly seven out of ten urban Indians carry some form of dyslipidemia, frequently featuring the pattern of low HDL, high triglycerides, and elevated ApoB despite near-normal LDL-C values.

Among Indian patients with diabetes and CKD—two major risk amplifiers—high ApoB levels are independently linked to accelerated renal function decline and adverse cardiovascular

outcomes, even when LDL-C meets guideline targets. This potentiated risk translates into earlier onset of myocardial infarction and kidney disease progression, placing an enormous burden on healthcare systems.

Recent consensus and expert panels, including those from the Lipid Association of India, have embraced this reality, updating lipid management guidelines to emphasize aggressive dual metric targets with clear ApoB and non-HDL cholesterol goals across risk strata. These reflect growing global recognition from European and American cardiovascular societies, particularly underscoring South Asian populations' increased vulnerability.

This solid epidemiological foundation underpins the urgent call for broader adoption of ApoB testing and aggressive lipid management in Indian clinical practice, integral to reducing premature morbidity and mortality.

## **Clinical Guidelines and Target Lipid Levels for Indian Patients**

Reflecting evidence and population-specific needs, current Indian guidelines recommend aggressive lipid targets that are considerably lower for high and very high-risk patients than Western standards. For instance, extreme risk individuals—such as those with recent acute coronary syndromes (ACS), diabetes, or CKD—are advised to achieve LDL-C below 30–50 mg/dL and ApoB below 60–65 mg/dL.

Very high-risk patients should aim for LDL-C under 50 mg/dL and ApoB under 65 mg/dL, while high-risk patients, including those with uncomplicated diabetes or familial hypercholesterolemia, are targeted for LDL-C below 70 mg/dL and ApoB less than 80 mg/dL. Non-HDL cholesterol serves as a practical alternative where ApoB measurement may be unavailable.

Global guidelines such as from the European Society of Cardiology and American Association of Clinical Endocrinologists have echoed this inclusive lipid assessment strategy. India's tailored targets respond to local epidemiology, with a focus on implementing these aggressive goals in real-world clinical settings for maximal impact.

## **Why is ApoB-LDL-C Discordance Particularly Risky in Indians?**

The South Asian metabolic milieu is characterized by multiple synergistic factors that amplify the risk of ApoB-LDL-C discordance: higher baseline insulin resistance even at normal BMI ranges, frequent elevation of triglycerides, reduced HDL particle functionality, and the accumulation of small, dense, highly atherogenic LDL particles.

This unique dyslipidemia variably manifests as normal LDL-C reporting misleadingly reassuring physicians and patients while elevated numbers of ApoB-containing atherogenic particles exert outsized influence in promoting endothelial damage, plaque instability, and microvascular injury affecting vital organs including the kidneys. This partly explains the

notably high rates of premature cardiovascular events and chronic kidney injury seen in Indians at younger ages.

The metabolic “perfect storm” presents hidden dangers: therapeutic complacency based on LDL-C alone can leave atherogenic lipid particles unchecked, fueling the progression of arterial and renal pathology with devastating consequences.

## **Personalized Clinical Vignettes: The Importance of Dual-Metric Lipid Measurement**

Consider a middle-aged Indian diabetic named Mr. Sharma. Despite achieving an LDL-C of 70 mg/dL on standard statin therapy, his ApoB remains elevated at 105 mg/dL—indicating ongoing atherogenic particle burden and cardiovascular risk. For such a patient, intensifying therapy by adding ezetimibe or a PCSK9 inhibitor is warranted to reduce the hidden risk better.

Ms. Meena, a patient with stage 3 CKD, exhibits borderline LDL-C at 80 mg/dL but increased ApoB and non-HDL cholesterol with hypertriglyceridemia. Her elevated ApoB signals residual risk not captured by LDL-C alone, prompting adjustment of lifestyle, glycemic control, and lipid-lowering strategies targeting comprehensive lipid improvement.

These cases exemplify the critical role of dual-factor lipid assessment as a clinical decision aid enabling individualized treatment escalation.

## **Conclusion**

Cardiovascular disease and chronic kidney disease impose a disproportionate risk on the Indian population, fueled by a unique interplay of metabolic, genetic, and lifestyle factors. Conventional lipid parameters such as LDL cholesterol have long guided cardiovascular risk stratification and treatment, but mounting evidence reveals significant limitations when LDL-C is considered in isolation, especially in Indians. The high prevalence of “South Asian dyslipidemia”—characterized by elevated triglycerides, low HDL cholesterol, and the predominance of small, dense LDL particles—renders LDL-C alone an incomplete marker, often underestimating true atherogenic burden.

Apolipoprotein B (ApoB), representing the total number of atherogenic lipoprotein particles, has emerged as a superior risk predictor across global and Indian populations. Discordance between LDL-C and ApoB is frequent, noted in nearly half of Indian adults affected by metabolic syndrome, diabetes, and kidney disease. This discordance signifies a “hidden” risk environment wherein normal LDL-C masks continued elevated atherogenic particle number, accelerating premature coronary artery disease, stroke, and renal impairment. Such a scenario makes a compelling case for dual lipid profiling—measuring both LDL-C and ApoB or, alternatively, non-HDL cholesterol—as routine practice in India, especially for high-risk groups.

National guidelines from the Lipid Association of India now recommend aggressive lipid targets tailored to levels of cardiovascular and renal risk, with ApoB-guided therapy intensification alongside LDL-C lowering. Targets as low as LDL-C below 30–50 mg/dL and ApoB below 60–65 mg/dL for extreme-risk patients underscore the urgency in addressing this dual risk with precision. Combination therapies including high-intensity statins, ezetimibe, and PCSK9 inhibitors, with adjunctive use of high-dose pure EPA fish oils, provide a robust pharmacologic armamentarium. These treatments, grounded in trials such as VESALIUS-CV and supported by international cardiology consensus, have proven efficacy and safety relevant to the Indian context.

Lifestyle modification remains foundational, focusing on dietary carbohydrate restriction, increased physical activity, tobacco cessation, and sustained patient education tailored to cultural contexts. Early and repeated dual lipid assessment allows clinicians to escalate therapy proactively, circumventing the atherogenic particle excess characteristic of Indian patients and thereby preventing premature cardiovascular mortality and kidney disease progression.

Ultimately, embracing a dual-lipid strategy transforms the management paradigm from reactive to proactive care—turning partial lipid information into a full narrative of risk. This comprehensive approach empowers clinicians and patients alike to make fully informed, personalized therapeutic decisions, fostering improved clinical outcomes across India’s immense cardiometabolic disease burden.

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# More than Reproduction: The Expanding Hormonal World of FSH in Metabolism, Cardiovascular, and Bone Health

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## From Reproductive Hormone to Systemic Metabolic Regulator

Follicle-stimulating hormone (FSH) has traditionally been perceived within the narrow confines of reproductive endocrinology, primarily governing ovarian follicle development and testicular function. However, an expanding body of research reveals that FSH functions far beyond fertility, orchestrating pivotal roles in metabolic regulation, bone remodeling, glucose homeostasis, and cardiovascular health. These revelations profoundly impact clinical perspectives, particularly for Indian endocrinologists and clinicians managing midlife women and men confronting metabolic syndrome, diabetes, and hormonal disturbances.

FSH is a glycoprotein hormone secreted by the anterior pituitary gland in response to hypothalamic gonadotropin-releasing hormone (GnRH). Historically, its utility in clinical practice centered on fertility treatment, menopause diagnosis, and evaluation of hypogonadism. Yet, contemporary molecular studies demonstrate FSH receptors distributed beyond gonadal tissues, including on adipocytes, pancreatic  $\beta$ -cells, osteoclasts, and vascular endothelial cells. This multisystem distribution equips FSH to influence adipocyte differentiation and thermogenesis, insulin secretion, lipid metabolism, bone resorption, and inflammatory pathways implicated in atherosclerosis.

The particular metabolic vulnerability of Indian populations — characterized by earlier menopause onset, heightened insulin resistance, and increased cardiometabolic disease prevalence — underscores the urgency in understanding and operationalizing this hormonal axis. FSH elevation in menopausal women correlates with central obesity, insulin resistance, cholesterol disturbances, and increased cardiovascular risk, necessitating incorporation of FSH into broader risk stratification and management models.

This article traverses the classical role of FSH in reproduction and journeys into its newly elucidated metabolic functions and clinical implications. It highlights emerging therapeutic avenues including FSH-blocking antibodies and revisits menopausal hormone therapy's broader metabolic effects. Through this, clinicians gain a comprehensive view of FSH as a

systemic regulator—transforming diagnostic paradigms and enabling personalized, integrative endocrine and metabolic care.

## **The Classical Role of FSH and Its Emerging Extragonadal Functions**

FSH primarily targets ovarian granulosa cells in females to regulate folliculogenesis, estrogen synthesis, and ovulation; and Sertoli cells in males to support spermatogenesis. Circulating FSH levels increase markedly at menopause due to the loss of estrogen-mediated negative feedback. Its measurement serves as a cornerstone in reproductive endocrinology for diagnosing menopausal transition, premature ovarian insufficiency, and hypogonadism.

However, the discovery that FSH receptors are expressed far beyond reproductive tissues catalyzed investigations into FSH's systemic influence. Adipose tissue expresses functional FSH receptors, where FSH directly regulates lipogenic genes and suppresses thermogenic brown/beige fat activity. In bone, FSH stimulates osteoclast differentiation and activation, contributing to bone resorption independent of estrogen deficiency. Vascular endothelial cells also respond to FSH, with FSH modulating adhesion molecule expression and vascular inflammation.

These extragonadal effects unveil FSH as a critical integrator of metabolic, bone, and cardiovascular health, beyond its classical reproductive hormone identity.

## **FSH and Fat Metabolism: Unlocking the Metabolic Influence of a Reproductive Hormone**

Recent preclinical and clinical studies reveal that FSH modulates adiposity through its direct effects on adipocyte precursor cells. FSH binding to adipocyte receptors modulates key transcripts involved in lipid synthesis and inhibits activation of thermogenic pathways responsible for brown and beige fat-mediated energy expenditure. This mechanism explains the observed fat gain and increased visceral obesity in menopausal women experiencing elevated FSH.

Animal models using FSH-neutralizing antibodies demonstrate a remarkable phenotype: blockade of FSH signaling induces browning of white adipose tissue, increases mitochondrial biogenesis, and amplifies calorie burning. These effects translate into reduced fat mass, improved glucose metabolism, and lower systemic inflammation, even independent of circulating estrogen and leptin levels. These insights challenge the traditional estrogen-centric focus in menopausal metabolic syndrome and open novel therapeutic possibilities targeting FSH to address obesity and related metabolic diseases, a particularly salient issue in Indian women predisposed to visceral fat accumulation.

Clinically, elevated FSH in perimenopausal and menopausal Indian women serves as a biomarker of impending metabolic syndrome, central obesity, and insulin resistance — conditions associated with increased cardiovascular and renal risk. This suggests the need to

incorporate FSH measurements within broader metabolic risk assessment panels during midlife health evaluations.

## **FSH Regulation of Glucose Metabolism and Pancreatic Beta-Cell Function**

FSH exerts complex influences on glucose homeostasis, primarily through modulation of pancreatic beta-cell function. Recent studies demonstrate that FSH promotes glucose-stimulated insulin secretion (GSIS) via engagement of its receptor on beta cells, triggering intracellular signaling cascades involving cAMP/PKA and calcium pathways that facilitate insulin release in response to glucose.

Gene knock-out models lacking FSH receptor signaling develop impaired glucose tolerance associated with deficient insulin secretion but no significant change in insulin sensitivity, delineating FSH as an essential facilitator in maintaining glucose homeostasis. Conversely, persistently elevated FSH levels, typical of menopausal states, can dysregulate this balance, impairing beta-cell function and increasing diabetes risk.

These findings have critical clinical implications. Postmenopausal women with elevated FSH often develop glucose intolerance and diabetes early, urging clinicians to initiate earlier and more frequent screening in this population rather than focusing solely on estrogen deficiency. Integrating FSH into endocrine and diabetes care pathways may enable earlier intervention to prevent progression.

## **Impact of FSH on Lipid Metabolism and Cardiovascular Risk: A Dual-Edged Sword?**

FSH influences lipid metabolism by downregulating LDL receptor expression in hepatocytes, impairing LDL clearance and elevating circulating LDL cholesterol. This effect, potentiated in postmenopausal women by concomitant estrogen decline, contributes to the adverse lipid profile characterized by increased LDL-C, decreased HDL-C, and more atherogenic lipoprotein particles.

Moreover, FSH promotes vascular inflammation by enhancing expression of adhesion molecules on endothelial cells, facilitating leukocyte recruitment and initiation of atherosclerotic plaque formation. These mechanistic pathways implicate FSH in accelerating cardiovascular disease independently of traditional risk factors.

In men with hypogonadism and elevated FSH, similar associations with heightened cardiovascular morbidity have been observed, underscoring a shared pathway linking elevated FSH to atherogenesis across sexes.

For Indian clinicians, it is important to recognize that FSH-related dyslipidemia often manifests as abrupt LDL-C increases in postmenopausal women despite stable lifestyle

factors, suggesting a hormonal etiology. This insight highlights the potential value in measuring FSH in lipid clinics to enhance cardiovascular risk profiling and treatment customization.

## **Bone Health and FSH: Connecting Menopause, Osteoporosis, and Metabolic Syndrome**

FSH exerts direct actions on osteoclasts, stimulating bone resorption independent of estrogen status. High FSH levels correlate with rapid bone loss and osteoporosis in menopausal women, mechanisms supported by extensive cellular and animal data. This role positions FSH as a key hormonal mediator linking reproductive aging to skeletal degradation.

Given the coexistent metabolic disturbances and cardiovascular risk, FSH stands at the nexus of a triad of complications—bone fragility, metabolic syndrome, and atherosclerosis—that collectively heighten morbidity and mortality, especially in resource-constrained settings such as India.

## **Clinical Implications and Future Directions: Toward Personalized, FSH-Inclusive Metabolic Care**

Emerging monoclonal antibodies targeting FSH signaling show promise in preclinical studies, reducing fat mass, improving bone density, and alleviating metabolic syndrome features. These novel therapies could complement or surpass existing anti-obesity and anti-osteoporotic approaches, particularly valuable in Indian populations demonstrating unique vulnerabilities.

Menopausal hormone therapy (MHT) may also mediate metabolic benefits, in part through suppression of elevated FSH, beyond its traditional roles in vasomotor symptom control and bone health maintenance. Integrating routine FSH measurement with metabolic panels will enable risk stratification and early preventive care.

Guidelines from the European Endocrine Society, Endocrine Society of India, and other bodies are evolving to acknowledge FSH's metabolic roles, likely heralding changes in screening, diagnosis, and therapeutic targeting.

Indian clinicians should incorporate FSH testing especially in midlife women exhibiting metabolic syndrome manifestations and in men with endocrine dysfunction to enable holistic, personalized care addressing reproduction, metabolism, and cardiovascular risk in tandem.

## Conclusion

The compelling evidence positioning follicle-stimulating hormone as a systemic hormonal regulator spanning metabolism, bone, and vascular biology demands a transformation in clinical practice. No longer confined to the reproductive axis, FSH is a vital mediator of fat distribution, glucose regulation, cholesterol metabolism, bone resorption, and vascular inflammation.

For India's large and growing populations facing premature menopause, rampant insulin resistance, and disproportionate cardiovascular and kidney disease burdens, recognizing and monitoring FSH opens unprecedented avenues for early risk detection and tailored intervention.

Elevated FSH serves as a metabolic and cardiovascular risk harbinger, guiding intensified efforts in lifestyle modification, targeted pharmacotherapy, and emerging hormone-based treatments. This integrated model transcends traditional estrogen-centric paradigms and enhances clinical precision in diagnosing and managing midlife metabolic disease.

The prospect of FSH-targeted therapies, together with evolving guidelines integrating FSH metrics into routine endocrine and metabolic evaluations, offers hope for reversing the tide of diabetes, obesity, osteoporosis, and cardiovascular disease.

In embracing FSH as a central metabolic hormone, Indian clinicians can pioneer holistic care strategies optimized for their population's unique genetic, environmental, and cultural landscape—reducing premature morbidity and improving quality of life across the nation.

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# CARDIABCON

Expanding Horizons in Cardiology, Diabetes & Renal Diseases



## Holistic Horizons: Redefining Cardio-Diabetes and Renal Collaboration

Date: 14, 15, 16 March, 26

Venue: Varanasi



### बीएचयू में अंतर्राष्ट्रीय कॉन्फ्रेंस 'कार्डियबकान' 7 रू

वाराणसी (काशीवासी)। बीएचयू के स्वतंत्रता भवन में 7 से 9 मार्च तक तीन दिवसीय अंतर्राष्ट्रीय कॉन्फ्रेंस 'कार्डियबकान-2026' का आयोजन किया जाएगा। कार्डियबकान सोसायटी के जनसंस्थान में होने वाले इस सम्मेलन में भारत सहित विदेशों से भी चिकित्सक विशेषज्ञ शामिल होंगे। इस दौरान हार्ट, डायबिटीज और किडनी रोगों के टुकड़ में आधुनिक चोप और नई तकनीक पर चर्चा होगी। दुर्गाकुंड



काशीनगर में अहोमजित प्रेम वार्मा में सोसायटी की राष्ट्रीय अध्यक्ष डॉ. पार्वती मिश्रा और राष्ट्रीय परिचय डॉ. आरुणोप मिश्रा ने बताया कि यह कॉन्फ्रेंस डायबिटीज के कारण हटन, मुई और अंग्रेजों पर चढ़ने वाले 17भागों पर केंद्रित

### हार्ट, शुगर और गुर्दा रोग पर विशेषज्ञ करेगे मंथन

रोगों। विशेषज्ञ आधुनिक और उच्चतम उपचार पद्धतियों पर अपने विचार साझा करेंगे। कॉन्फ्रेंस के दूसरे दिन 8 मार्च को अंतर्राष्ट्रीय महिला दिवस के उपलक्ष्य में 11 दिवसीय महिलाओं और 11 स्वयंसेवक महिलाओं को उनके उच्चतम सामाजिक योगदान के लिए सम्मानित किया जाएगा। प्रेस वार्ता में मुख्य सलाहकार डॉ. उत्तम शेट्टी, डॉ. नमुर शोभा और सराफ अहमद को उल्लेखित रही।

