Stratifying Cardiovascular–Kidney–Metabolic Syndrome by Metabolic Dysfunction-Associated Steatotic Liver Disease: A Pathophysiology-Anchored, India-Contextualised Framework for Node-Directed Pharmacotherapy

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Abstract

The same drug can protect the heart, the kidney and the liver at once—not by coincidence, but because these organs share a small set of molecular failure points. Cardiovascular–kidney–metabolic (CKM) syndrome, formalised by the American Heart Association in 2023[1,2] and codified in the first-ever 2026 AHA/ACC/ADA/ASN multisociety guideline[3], describes the progression from dysfunctional adiposity through cardiorenal and metabolic injury. Its staging construct, however, incorporates the liver only implicitly, despite metabolic dysfunction-associated steatotic liver disease (MASLD)[4] being both a near-universal companion of CKM and an independent, pharmacologically actionable amplifier of its trajectory. This review advances a pathophysiology-anchored framework positioning MASLD as the hepatic node of CKM and liver fibrosis stage as a quantitative modifier that reclassifies cardiorenal-metabolic risk. We first deconstruct the shared molecular nodes linking liver, heart, kidney and adipose tissue—adipose lipotoxicity, hepatic de novo lipogenesis and the thyroid/ATP-citrate lyase axis, stellate-cell fibrosis, NLRP3-inflammasome inflammation, the mineralocorticoid–fibrotic axis, the cardiorenal hemodynamic–tubular axis, and the gut–liver axis. We then map the contemporary pharmacopoeia—incretin and multi-agonists, sodium–glucose cotransporter-2 (SGLT2) inhibitors, pioglitazone, the thyroid hormone receptor-β agonist resmetirom, fibroblast growth factor 21 (FGF21) analogues, the nonsteroidal mineralocorticoid antagonist finerenone, bempedoic acid, low-dose colchicine, and microbiome-directed strategies—onto these nodes rather than onto organ silos; two agents (resmetirom[36] and semaglutide[24]) now carry regulatory approval for steatohepatitis with fibrosis. Because the epidemiology, phenotype, genetics, diet and drug-access realities of South Asia materially alter how the framework applies, we integrate an India-specific analysis throughout[59,62]. Synthesising the evidence into a CKM-stage × fibrosis-stage selection matrix (rendered as an India-adapted therapeutic ladder) and a tiered evidence appraisal, we argue that fibrosis stage, not organ label, should guide individualised pharmacotherapy across the CKM spectrum.

Keywords: cardiovascular–kidney–metabolic syndrome; MASLD; MASH; liver fibrosis; resmetirom; GLP-1 receptor agonist; FGF21; finerenone; SGLT2 inhibitor; India; lean NAFLD; saroglitazar

Abbreviations

ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; AHA, American Heart Association; AMPK, AMP-activated protein kinase; ASCVD, atherosclerotic cardiovascular disease; ChREBP, carbohydrate-response element-binding protein; CKD, chronic kidney disease; CKM, cardiovascular–kidney–metabolic; CKLM, cardiovascular–kidney–liver–metabolic; DAG, diacylglycerol; DCGI, Drugs Controller General of India; DNL, de novo lipogenesis; FASN, fatty-acid synthase; FGF19/21, fibroblast growth factor 19/21; FXR, farnesoid X receptor; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HFpEF, heart failure with preserved ejection fraction; HSC, hepatic stellate cell; IL, interleukin; INASL, Indian National Association for Study of the Liver; IRS-1, insulin-receptor substrate-1; LPS, lipopolysaccharide; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MR(A), mineralocorticoid receptor (antagonist); NLRP3, NLR family pyrin domain containing 3; PKCε, protein kinase C-epsilon; PNPLA3, patatin-like phospholipase domain-containing 3; PPAR, peroxisome proliferator-activated receptor; RSSDI, Research Society for the Study of Diabetes in India; SCFA, short-chain fatty acid; SGLT2, sodium–glucose cotransporter-2; SREBP-1c, sterol regulatory element-binding protein 1c; T2D, type 2 diabetes; TGF-β, transforming growth factor beta; THR-β, thyroid hormone receptor beta; TM6SF2, transmembrane 6 superfamily member 2; TMAO, trimethylamine-N-oxide.

1. Introduction

The 2023 American Heart Association Presidential Advisory on cardiovascular–kidney–metabolic (CKM) health reframed a cluster of previously siloed conditions—obesity, type 2 diabetes (T2D), chronic kidney disease (CKD), and the atherosclerotic and heart-failure phenotypes of cardiovascular disease—as a single, staged continuum driven by shared upstream biology[1]. The construct assigns individuals to stages 0 through 4, from the absence of risk factors, through excess or dysfunctional adiposity and metabolic risk factors, to subclinical and then clinical cardiovascular–renal disease[2]. In June 2026 the first-ever AHA/ACC/ADA/ASN multisociety guideline operationalised this staging for practice, embedding routine cardiorenal-metabolic risk assessment and prioritising cardioprotective antihyperglycaemic therapy[3].

Conspicuously, the liver occupies an ambiguous place in this schema. MASLD—renamed from non-alcoholic fatty liver disease in the 2023 multisociety Delphi nomenclature statement to foreground its metabolic aetiology[4]—appears in CKM guidance chiefly as a screening consideration rather than as a staging axis, even though it shares every upstream driver of the syndrome and affects an estimated quarter to a third of the global adult population. This omission is increasingly untenable. Advancing MASLD, and specifically the transition from simple steatosis through metabolic dysfunction-associated steatohepatitis (MASH) to fibrosis, independently predicts incident heart failure (particularly the preserved-ejection-fraction phenotype), CKD progression, and atherosclerotic events over and above conventional risk factors. A 2026 roadmap in the *Journal of the American College of Cardiology* went so

far as to argue for expanding the construct to a cardiovascular–kidney–liver–metabolic (CKLM) syndrome and redesigning trials around multiorgan endpoints[5].

The clinical consequence of leaving the liver implicit is that pharmacotherapy is selected by organ label—a cardiologist's, nephrologist's, or hepatologist's remit—rather than by the shared mechanism a given drug actually engages. Yet the therapeutic landscape has shifted decisively: within twenty-four months, two agents earned regulatory approval for MASH with fibrosis[36,24], an entire class of direct antifibrotics entered phase 3, and several cardiorenal-outcome drugs were shown to act on nodes common to liver, heart, and kidney. This review therefore proposes a deliberately simple reorganisation. We treat MASLD as the **hepatic node** superimposed on the four-organ CKM construct, and liver **fibrosis stage (F0–F4)** as a quantitative **modifier** that reclassifies cardiorenal-metabolic risk and should inform drug choice. We then map the contemporary pharmacopoeia onto the pathophysiological nodes these drugs share, contextualise the framework for the Indian population in which the author practises, and translate the result into a stage-by-fibrosis selection matrix. Our thesis is that fibrosis stage, not organ label, is the axis along which CKM pharmacotherapy should be individualised.

2. MASLD as the hepatic node: a conceptual framework

The CKM construct is usefully understood as four interacting organ systems—dysfunctional adipose tissue, the heart, the kidney, and systemic metabolism—connected by bidirectional crosstalk. MASLD is best positioned not as a fifth silo but as a hepatic node that both receives and amplifies signals from the other four. The liver is simultaneously a victim of ectopic lipid overflow from failing adipose tissue and a driver of systemic dyslipidaemia, insulin resistance, and low-grade inflammation that feed cardiac and renal injury[6,10].

Two features make the hepatic node uniquely informative for stratification. First, it is **stageable**. Unlike the more continuous adipose or vascular contributions, hepatic disease progresses through histologically and non-invasively definable steps—steatosis, steatohepatitis, and progressive fibrosis (F0–F4)—that can be tracked with elastography and serum indices. Second, fibrosis stage carries **prognostic weight that extends beyond the liver**: it is the hepatic variable most tightly linked to extrahepatic cardiovascular and renal outcomes. A patient at CKM stage 2 who harbours F3 fibrosis is, functionally, closer to the cardiorenal risk of a stage-3 patient than the staging label alone conveys.

We therefore propose that fibrosis stage operate as a **risk-reclassifying modifier** layered onto CKM staging (Figure 1). This is not merely descriptive. It has direct therapeutic implications, because the drugs available to a clinician differ sharply depending on whether the dominant problem is steatosis in a metabolically active but fibrosis-free liver, established MASH with F2–F3 fibrosis, or compensated cirrhosis—and depending on whether the coexisting cardiorenal burden is subclinical or overt. The remainder of this review builds the mechanistic and pharmacological content required to act on that principle.

3. Shared pathophysiological nodes: a molecular deconstruction

Rather than catalogue drugs by organ, we first identify the molecular nodes on which CKM injury converges. These nodes are the targets that the pharmacopoeia in Section 4 engages, and their annotated mapping to drug classes is depicted in Figure 2.

3.1 Adipose failure and lipotoxicity — the upstream driver

The initiating lesion in CKM is arguably not hepatic but adipose. Hypertrophic, inflamed subcutaneous adipose tissue that has exhausted its capacity to safely store surplus energy permits free fatty acids to spill over ectopically into liver, myocardium, skeletal muscle, and kidney[6]. Two consequences dominate. First, the adipokine profile shifts adversely: adiponectin falls while leptin and resistin rise. Because adiponectin normally activates hepatic AMP-activated protein kinase and peroxisome proliferator-activated receptor-α (PPARα) through the AdipoR1/R2 receptors to promote fatty-acid oxidation and restrain lipogenesis, its loss directly de-represses hepatic steatosis—which is why adiponectin recurs throughout this review as a therapeutic hub[7]. Second, intrahepatic fatty acids are esterified to sn-1,2-diacylglycerol, which recruits and activates protein kinase C-ε (PKCε) at the plasma membrane; activated PKCε phosphorylates threonine-1160 of the insulin receptor kinase domain and serine residues on insulin-receptor substrate-1, uncoupling proximal insulin signalling—the molecular basis of hepatic insulin resistance[8,9]. Accumulating ceramides independently impair Akt2 activation and activate protein phosphatase 2A, providing a parallel lipotoxic route. The clinical corollary is mechanistically precise: the culprit is not stored triglyceride per se—an inert sink—but the flux of bioactive lipid intermediates (diacylglycerol, ceramide) through the hepatocyte, which is why steatosis and insulin resistance can dissociate, and why therapies that lower substrate flux outperform those that merely redistribute fat.

A defining feature is the *selectivity* of the resulting insulin resistance. Insulin fails to suppress FoxO1-driven gluconeogenesis yet continues to stimulate sterol regulatory element-binding protein-1c (SREBP-1c)-driven lipogenesis, so hyperglycaemia and hepatic fat accumulate together rather than trading off[10]. This paradox explains why simply improving glycaemia does not resolve steatosis, and why effective therapy must reduce the lipotoxic substrate load itself.

3.2 Hepatic de novo lipogenesis and the thyroid/ACLY axis

De novo lipogenesis (DNL) contributes disproportionately—on the order of a quarter to a third—to the hepatic triglyceride pool in MASLD, far above its contribution in health[11,12]. It is transcriptionally driven by insulin, via SREBP-1c, and by glucose, via carbohydrate-response element-binding protein (ChREBP), converging on acetyl-CoA carboxylase, fatty-acid synthase, and stearoyl-CoA desaturase-1. The pivotal upstream metabolite is cytosolic acetyl-CoA, generated by ATP-citrate lyase (ACLY)—a node that sits above both cholesterol synthesis and fatty-acid synthesis and thereby mechanistically links hepatic steatosis to atherogenic dyslipidaemia[13]. The thyroid axis provides a parallel lever: hepatic thyroid hormone receptor-β (THR-β) signalling upregulates mitochondrial β-oxidation, mitochondrial biogenesis, lipophagy, and low-density lipoprotein-receptor expression[14]. This node is therapeutically privileged

because it can be engaged in a liver-selective manner, sparing systemic thyroid and cardiac THR-α effects (Sections 4.4 and 4.7).

3.3 Hepatic stellate-cell activation — the final common fibrotic pathway

Whatever the proximal injury, hepatic fibrosis proceeds through transdifferentiation of quiescent, vitamin-A-storing hepatic stellate cells (HSCs) into collagen-secreting myofibroblasts. This activation is driven by transforming growth factor-β (TGF-β)/SMAD2/3 signalling, platelet-derived growth factor-BB, mechanotransduction through matrix stiffness (YAP/TAZ), and paracrine signals from injured hepatocytes and activated macrophages[15]. Two points matter for the framework. First, because fibrosis is the convergence point of otherwise distinct upstream injuries, it is the rational endpoint on which to stratify. Second, fibrosis regression is intrinsically slow, which shapes both trial design and clinical expectation: antifibrotic effects may require many months to a year or more to declare themselves, a caveat that recurs in the FGF21 data (Section 4.5).

3.4 The NLRP3 inflammasome — where metabolism becomes inflammation

The NLR family pyrin domain containing 3 (NLRP3) inflammasome is the mechanistic hinge converting metabolic stress into sterile inflammation. Lipotoxic danger signals—free-cholesterol crystals, palmitate, mitochondrial reactive oxygen species, extracellular ATP, and mitochondrial DNA—provide the activation signal, while gut-derived lipopolysaccharide (LPS) provides the nuclear factor-κB priming signal[16]. Two distinct signals are required, and this two-hit logic is therapeutically instructive: signal one (priming) transcriptionally upregulates NLRP3 and pro-IL-1β via nuclear factor-κB, whereas signal two (activation) triggers inflammasome assembly—so interventions that lower either the metabolic danger load or the gut-derived priming tone can both dampen the output. Assembled NLRP3 recruits ASC and activates caspase-1, which matures interleukin-1β (IL-1β) and IL-18 and cleaves gasdermin-D to form membrane pores, driving pyroptotic hepatocyte death and Kupffer-cell activation; recruited monocyte-derived macrophages in turn activate HSCs, closing a self-amplifying loop between the inflammatory (Section 3.4) and fibrotic (Section 3.3) nodes. This same IL-1β axis is a validated *cardiovascular* target: canakinumab, a monoclonal antibody to IL-1β, reduced recurrent cardiovascular events independently of lipid lowering in the CANTOS trial, establishing a mechanistic bridge between hepatic inflammation and residual atherosclerotic risk[17]. The node is therapeutically accessible both directly (Section 4.8) and indirectly through mineralocorticoid blockade (Section 4.6).

3.5 The mineralocorticoid–fibrotic axis

Volume-independent overactivation of the mineralocorticoid receptor (MR) in heart, kidney, vasculature, adipose tissue and—importantly for the hepatic node—HSCs and macrophages, drives nuclear factor-κB inflammation, galectin-3 induction, and TGF-β/connective-tissue growth factor-mediated collagen deposition[18]. Because MR-driven fibro-inflammation is a mechanism shared almost verbatim across the CKM organs, its pharmacological blockade offers a “one axis, three organs” rationale that is directly relevant to fibrosis-stratified therapy (Section 4.6).

3.6 The cardiorenal hemodynamic–tubular node

Distinct from the fibro-inflammatory nodes above is a hemodynamic and tubular axis best exemplified by renal tubuloglomerular feedback. Restoration of sodium and glucose sensing at the macula densa—achieved pharmacologically by SGLT2 inhibition, which increases distal sodium delivery—triggers adenosine-mediated afferent arteriolar constriction, lowering intraglomerular pressure and pathological hyperfiltration[19]. Coupled effects include a shift of myocardial and renal substrate use toward ketones and free fatty acids, reductions in preload and afterload, contraction of epicardial adipose tissue, and attenuation of oxidative stress. This node governs hard cardiorenal outcomes and is the pharmacological backbone of advanced CKM stages, largely independent of hepatic status (Section 4.2).

3.7 The gut–liver axis — the integrating node

Intestinal dysbiosis and barrier failure permit portal translocation of microbial products; LPS engages Kupffer-cell Toll-like receptor-4 and feeds directly into the NLRP3 node of Section 3.4[20]. The bile-acid/farnesoid X receptor (FXR)–FGF19 loop constitutes a second, therapeutically important limb: ileal FXR activation releases FGF19, which signals to the liver to repress bile-acid synthesis and improve metabolic tone, and is the endogenous relative of the FGF21 analogues discussed below[21]. Short-chain fatty acids (SCFAs) generated by fibre fermentation stimulate enteroendocrine secretion of glucagon-like peptide-1 (GLP-1) and peptide YY through free fatty-acid receptors FFAR2/3, mechanistically linking the microbiome to the incretin node[22], while microbial choline metabolism to trimethylamine-N-oxide (TMAO) contributes an independent atherogenic vector[23]. The gut–liver axis thus functions as the connective tissue of the whole framework, integrating hepatic, cardiac, and renal signals.

Read together, these seven nodes are not a list but a circuit (Figure 2). Adipose lipotoxicity (3.1) supplies the substrate; de novo lipogenesis (3.2) amplifies it; stellate-cell activation (3.3) is the fibrotic sink into which the inflammatory (3.4), mineralocorticoid (3.5), and gut-derived (3.7) inputs all drain; and the cardiorenal haemodynamic node (3.6) governs the hard outcomes that make the whole syndrome lethal. The single most important consequence for therapy is that a drug engaging any one node exerts effects that radiate across the circuit—which is precisely why, as the next section shows, agents developed for one organ repeatedly prove beneficial in another. We therefore turn from mechanism to pharmacology, mapping each contemporary agent onto the node it engages rather than the specialty that owns it.

4. Pharmacotherapy mapped to nodes

We now map available and emerging agents onto the nodes above. For each, we state the node engaged, the mechanism, the key evidence with quantified effect sizes, and the CKM/fibrosis positioning. Table 1 summarises this node-to-drug mapping; Sections 4.1–4.9 provide the supporting evidence.

Table 1. Mechanistic nodes of CKM syndrome and the drug classes that engage them. Each node is a convergence point on which liver, heart, kidney and adipose injury act; the right-hand column lists the agents whose primary or secondary mechanism engages that node.

Molecular node	Core mechanism	Engaging drug class(es)
Adipose failure / lipotoxicity (§3.1)	FFA overflow → hepatic DAG–PKCε and ceramide-mediated insulin resistance; low adiponectin	GLP-1 RA & multi-agonists; pioglitazone; FGF21 analogues
Hepatic DNL / thyroid–ACLY (§3.2)	SREBP-1c/ChREBP-driven lipogenesis via ACLY; THR-β β-oxidation deficit	Resmetirom (THR-β); bempedoic acid (ACLY); FGF21 analogues; pioglitazone
Hepatic stellate-cell fibrosis (§3.3)	TGF-β/SMAD, PDGF, YAP/TAZ → myofibroblast collagen deposition	FGF21 analogues; resmetirom; incretins (indirect)
NLRP3 inflammasome (§3.4)	Caspase-1 → IL-1β/IL-18, gasdermin-D pyroptosis	Low-dose colchicine; finerenone (indirect); canakinumab (proof-of-concept)
Mineralocorticoid–fibrotic axis (§3.5)	MR overactivation → NF-κB, galectin-3, CTGF fibrosis	Finerenone (nonsteroidal MRA)
Cardiorenal hemodynamic–tubular (§3.6)	Tubuloglomerular feedback, ketone substrate shift, preload/afterload	SGLT2 inhibitors
Gut–liver axis (§3.7)	LPS translocation, FXR–FGF19 loop, SCFA–incretin link, TMAO	Microbiome-directed strategies; FXR/FGF19 agents; incretins (indirect)

4.1 Incretin-based therapies: GLP-1 receptor agonists and multi-agonists

Nodes: adipose/lipotoxicity (3.1), inflammation (3.4), gut–liver (3.7). Incretin-based agents are the most cross-cutting class in CKM because they act on weight, glycaemia, and cardiorenal outcomes simultaneously. In the phase 3 ESSENCE trial, once-weekly subcutaneous semaglutide 2.4 mg produced resolution of steatohepatitis without worsening of fibrosis in 62.9% of patients versus 34.3% with placebo at 72 weeks, with a significant advantage in fibrosis improvement as well; on this interim histological evidence the agent received FDA accelerated approval for MASH with moderate-to-advanced (F2–F3) fibrosis in August 2025[24]. A mechanistically important observation is that liver-health benefits appeared even at low levels of weight reduction, implying weight-independent anti-inflammatory and immunometabolic effects—relevant because the GLP-1 receptor is minimally expressed on hepatocytes and the hepatic benefit is therefore largely indirect. Dual and triple agonists extend the mechanism: GIP agonism enhances adipose lipid-buffering and glucagon agonism directly augments hepatic fat oxidation and energy expenditure. Survodutide (glucagon/GLP-1) achieved MASH resolution in 62% versus 14% with placebo at 48 weeks[28]; tirzepatide (GIP/GLP-1) achieved MASH resolution in up to 62% versus 10% in SYNERGY-NASH[29]; and the triple agonist retatrutide reduced MRI-PDFF liver fat substantially in its MASLD substudy[52]. A 2025 network meta-analysis of 29 trials ranked these agents highly for MASH resolution, with the FGF21 analogue pegozafermin and survodutide at the top, followed by tirzepatide and semaglutide[30]. Given independent cardiovascular and renal outcome benefit for GLP-1 receptor agonists

(SUSTAIN-6, SELECT, and the kidney-outcome FLOW trial)[25,27,26], this class is appropriate across CKM stages wherever MASH is present, and is the natural backbone of combination regimens.

4.2 SGLT2 inhibitors

Node: cardiorenal hemodynamic–tubular (3.6). Sodium–glucose cotransporter-2 (SGLT2) inhibitors are the archetypal cardiorenal-outcome drugs, with benefit established across heart failure with reduced ejection fraction (DAPA-HF), preserved and mildly-reduced ejection fraction (EMPEROR-Preserved, DELIVER), and CKD (DAPA-CKD, EMPA-KIDNEY) populations irrespective of diabetes status[31,32,33,34,35]. Their hepatic effect is real but modest—steatosis reduction mediated largely through weight loss and reduced lipogenesis—with weak direct fibrosis evidence. They should therefore be positioned as the CKM-stage-driven backbone for stages 3–4 (established CKD or heart failure), selected for their cardiorenal protection rather than as a MASLD-directed therapy.

4.3 Pioglitazone

Nodes: adipose/lipotoxicity (3.1), DNL (3.2). Pioglitazone, a PPARγ agonist, remains the prototypical adipose insulin-sensitiser, redistributing lipid to subcutaneous depots and restoring adiponectin. It demonstrated steatohepatitis resolution and modest antifibrotic benefit in dedicated biopsy trials in patients with and without diabetes (PIVENS; Cusi et al.)[39,38], and reduced ischaemic events in insulin-resistant patients after stroke or transient ischaemic attack (IRIS)[40]. The caveat that governs its place in the framework is fluid retention and heart-failure risk: pioglitazone is contraindicated in the very stage-4 patients with reduced-ejection-fraction heart failure in whom volume overload is dangerous. It therefore belongs in earlier-stage, MASH-dominant, heart-failure-free patients, particularly those with T2D or prediabetes—a group especially large in India (Section 5).

4.4 Resmetirom

Nodes: DNL/thyroid (3.2), fibrosis (3.3). Resmetirom is a liver-selective THR-β agonist that increases hepatic fatty-acid oxidation and mitochondrial biogenesis while sparing THR-α-mediated cardiac effects, and it lowers atherogenic lipids as a consequence of upregulated LDL-receptor expression[37]. It became the first agent approved for noncirrhotic MASH with F2–F3 fibrosis—FDA accelerated approval on 14 March 2024—on the basis of the phase 3 MAESTRO-NASH biopsy trial, in which it met both fibrosis-improvement and MASH-resolution endpoints[36]. Its dual liver-directed and lipid-lowering profile makes it a disease-modifying option for the MASH-dominant patient, with a secondary CKM-lipid rationale. As detailed in Section 5, resmetirom is not yet commercially registered in India, which materially constrains its role there.

4.5 FGF21 analogues

Nodes: adipose/lipotoxicity (3.1), DNL (3.2), fibrosis (3.3). Fibroblast growth factor 21 (FGF21) analogues are the class with the most direct combination of antifibrotic and cardiometabolic activity. Signalling through FGFR1c/2c/3c with the β-klotho co-receptor concentrated in liver and adipose tissue, they raise

adiponectin, suppress DNL, promote fatty-acid oxidation, lower triglycerides and LDL cholesterol, and exert direct antifibrotic effects by attenuating HSC activation. Pegozafermin achieved ≥1-stage fibrosis improvement without MASH worsening in 27% versus 7% with placebo in ENLIVEN[42], and efruxifermin reached 49% versus 19% at 96 weeks in the phase 2b HARMONY trial[41]. Two nuances matter for the framework. First, the antifibrotic effect is genuine but slow: efruxifermin missed its 36-week primary endpoint in the SYMMETRY compensated-cirrhosis trial yet showed a dose-dependent fibrosis benefit on exploratory 96-week analysis, consistent with the biology of Section 3.3[43]. Second, the intensity of commercial interest is striking: during 2025 the three leading FGF21 assets were acquired in quick succession—GSK acquired efimosfermin (up to $2.0 billion), Roche acquired 89bio/pegozafermin (up to $3.5 billion), and Novo Nordisk acquired Akero/efruxifermin (up to $5.2 billion)—signalling high expectation for this class as the next antifibrotic frontier. FGF21 analogues are best positioned for the fibrosis-dominant, longer-horizon patient.

4.6 Finerenone

Nodes: mineralocorticoid–fibrotic (3.5), inflammation (3.4). Finerenone is a nonsteroidal MR antagonist with balanced cardiac–renal tissue distribution and substantially less hyperkalaemia than steroidal agents. It demonstrated cardiorenal outcome benefit in CKD with T2D (FIDELIO-DKD, FIGARO-DKD) and in heart failure with mildly reduced and preserved ejection fraction (FINEARTS-HF)[44,45,46]. Although it carries no MASLD indication, hepatic MR expression on HSCs and macrophages gives it a mechanistically coherent antifibrotic rationale, allowing a unifying “one axis, three organs” argument. It is the rational choice for CKM stages 3–4—CKD and the preserved-ejection-fraction heart-failure phenotype—where MASLD coexists.

4.7 Bempedoic acid

Nodes: DNL (3.2), inflammation (3.4). Bempedoic acid inhibits ATP-citrate lyase, the node upstream of both cholesterol and lipogenic acetyl-CoA. It is a prodrug activated by very-long-chain acyl-CoA synthetase-1, an enzyme expressed in liver but not muscle, conferring liver selectivity and sparing patients the myalgia that limits statins[13]. Beyond its established LDL-lowering and cardiovascular-event benefit in statin-intolerant patients (CLEAR Outcomes), it reduces high-sensitivity C-reactive protein, and its position upstream of hepatic DNL provides a plausible—though still hypothesis-level—steatosis rationale[47]. It is useful for residual atherogenic and inflammatory risk in MASLD-CKM, particularly in statin-intolerant patients.

4.8 Low-dose colchicine

Node: NLRP3 inflammation (3.4). Low-dose colchicine disrupts microtubule-dependent NLRP3 inflammasome assembly and leukocyte trafficking, lowering IL-1β, and has established secondary-prevention cardiovascular benefit in chronic coronary disease (LoDoCo2) and after myocardial infarction (COLCOT)[48,49]. Direct steatohepatitis-fibrosis data remain limited, so it is best framed as a residual-

inflammatory-risk modifier in patients with established atherosclerotic disease within the CKM spectrum, rather than as a liver-directed therapy.

4.9 Microbiome-directed strategies

Node: gut–liver (3.7). Interventions targeting the gut–liver axis span dietary modification, prebiotic and synbiotic approaches, experimental faecal microbiota transplantation (FMT), and bile-acid/FXR pharmacology. Mechanistic and clinical reviews document reduced Akkermansia and Faecalibacterium prausnitzii, expansion of Proteobacteria, LPS-driven inflammation, SCFA depletion, and secondary bile-acid dysmetabolism in MASLD[53,54]. Proof-of-concept RCTs show that lean-donor microbiota transfer improves peripheral insulin sensitivity in metabolic syndrome[55], and that allogenic FMT reduces intestinal permeability in NAFLD[56], while the microbial TMAO pathway is an independent clinical cardiovascular risk marker[57]. The FXR-agonist obeticholic acid failed regulatory review for MASH on account of pruritus and LDL elevation[50], but engineered FGF19 analogues such as aldafermin remain in development (positive in compensated cirrhosis by ELF score)[51], and the SCFA–incretin link offers an indirect route to the incretin node. Hard outcome data lag, but this node is conceptually indispensable as the integrator of the framework.

5. The Indian context: why the framework must be tailored

The framework above is derived largely from trials conducted in predominantly White, higher-body-mass-index populations. India—home to the world's largest burden of diabetes and a distinctive metabolic phenotype—illustrates why fibrosis-anchored, node-directed reasoning must be adapted to local epidemiology, genetics, diet, guidelines, and drug access rather than transplanted wholesale.

5.1 Epidemiology and the "thin-fat" phenotype

The ICMR-INDIAB national cross-sectional study (n = 113,043; all 31 states and union territories) estimated that India has approximately 101 million people with diabetes and a further 136 million with prediabetes, 315 million with hypertension, 254 million with generalised obesity, and 351 million with abdominal obesity, with dyslipidaemia (predominantly low HDL cholesterol) present in 81.2% of adults[59]. Against this metabolic backdrop, a systematic review and meta-analysis estimated the pooled prevalence of MASLD/NAFLD in Indian adults at roughly 38%—about 28% in community settings and 41% in hospital settings—so that approximately one in three Indian adults harbours the hepatic node of CKM[61]. Rural–urban gradients are pronounced (29.6% urban versus 16.0% rural in a large North Indian survey), with diabetes, central obesity and insulin resistance the dominant independent correlates[69].

Critically, this burden accrues at lower body-mass indices than in Western cohorts. The "thin-fat Indian" phenotype, crystallised in the Yajnik–Yudkin (Y-Y) paradox, describes the observation that South Asians carry substantially higher body-fat percentage and visceral/truncal adiposity than White Europeans at identical BMI[60]. The clinical corollary is a high prevalence of **lean MASLD**—significant hepatic steatosis and even steatohepatitis in individuals whose BMI would be classified as normal. This means BMI-triggered

screening thresholds derived from Western guidance will systematically under-detect the hepatic node in Indians, and that the adipose-lipotoxicity node of Section 3.1 is engaged at deceptively "normal" anthropometry.

5.2 Genetic susceptibility

The genetic architecture of MASLD in India adds a further layer of heterogeneity. In one of the few India-specific studies to genotype both major risk variants stratified by ancestry, PNPLA3 (rs2281135, linked to the I148M variant) was significantly associated with NAFLD in North-East Indians, whereas TM6SF2 (rs58542926) conferred a 2.7-fold higher risk specifically in Ancestral South Indians, with transheterozygosity amplifying risk in both groups[64]. Because PNPLA3-driven steatohepatitis is characteristically lipogenesis- and fibrosis-prone but relatively lipid-neutral, this genetic profile reinforces the rationale for DNL- and fibrosis-directed agents (resmetirom, FGF21 analogues, pioglitazone) in genetically susceptible Indian patients, and cautions against assuming that every steatotic Indian liver reflects the same mechanistic mix seen in Western trials[63].

5.3 Diet and the gut–liver axis in India

Indian dietary patterns interact directly with the gut–liver node of Section 3.7. In a large South Indian case-control study, patients with NAFLD consumed significantly more refined rice, animal fat, red meat, refined sugar and fried foods than controls[67], and a longitudinal Kerala cohort found that a "rice–meat–refined-wheat" pattern was independently associated with higher HbA1c and central obesity, while a "sweets–snacks" pattern raised triglycerides[68]. The high-glycaemic, refined-carbohydrate-dominant staple diet of much of India is thus a potent driver of hepatic DNL (Section 3.2) and of the dysbiosis that feeds the NLRP3 and TMAO pathways. Dietary carbohydrate quality is, in this population, not an adjunct but arguably a first-line, node-directed intervention.

5.4 Guidelines and clinical practice

Indian practice is shaped by dedicated national guidance rather than by direct extrapolation from Western documents. The INASL guidance paper on NAFLD explicitly incorporates the lean phenotype—recommending waist circumference, not BMI alone, to define lean NAFLD in Asian Indians—and, importantly for pharmacotherapy, notes that saroglitazar (a dual PPAR-α/γ agonist) is approved by the Drugs Controller General of India for MASH/NASH, a therapy not approved in the United States or Europe[62]. The RSSDI-ESI clinical practice recommendations for T2D situate SGLT2 inhibitors, GLP-1 receptor agonists and pioglitazone within the Indian cardiometabolic context[65]. The renal limb of CKM is also substantial: the SEEK-India study found a 17.2% prevalence of CKD, rising to 28.9% among those with diabetes[66]. Together these documents argue for an India-adapted CKM pathway in which the hepatic node is screened by waist-circumference-inclusive criteria and treated with regionally available, evidence-supported agents.

5.5 Drug access, cost, and the pragmatic Indian formulary

The single greatest divergence between the global framework and Indian practice is drug access. Several node-directed agents are inexpensive and ubiquitous in India, whereas the two globally approved MASH drugs are, respectively, unavailable or very costly. Table 2 summarises the practical picture as of mid-2026, drawn from Indian regulatory and market sources rather than from the trial literature.

Table 2. Access and approximate cost of node-directed CKM–MASLD agents in India (mid-2026). Prices are indicative retail figures from Indian market and regulatory sources and vary by brand, dose and state; they are provided for pragmatic orientation, not procurement.

Agent / class	India status	Practical / cost note
Pioglitazone	Off-patent generic, ubiquitous	Branded generics ~₹68–124 per 10-tab strip; Jan Aushadhi ~₹1.20/tab. Widely used for MASH with T2D/insulin resistance.
Saroglitazar (PPAR-α/γ)	DCGI-approved for MASH/NASH	India-specific option not approved in the US/EU; positioned in INASL guidance for the hepatic node.
Empagliflozin (SGLT2i)	Patent expired Mar 2025; generics	Domestic generics from Mar–Apr 2025 at ~₹5.49–11/tab versus ~₹53–60/tab branded; NPPA-regulated.
Dapagliflozin (SGLT2i)	Available; generic combos	Branded ~₹330 per 14-tab strip; NPPA-fixed generic fixed-dose combinations lower per-tablet cost.
Semaglutide (GLP-1 RA)	Wegovy Jun 2025; Ozempic Dec 2025	Wegovy ~₹17,345–26,015/month; generic semaglutide (Sun Pharma, Dr Reddy's) expected after Mar 2026 patent expiry.
Finerenone	Available (branded)	Registered nonsteroidal MRA; cost higher than generic spironolactone, which is a lower-cost though less-selective alternative.
Resmetirom	NOT commercially registered	No CDSCO marketing authorisation; access only via Rule 36 personal-import pathway with specialist prescription—effectively out of reach for most patients.
FGF21 analogues	Investigational (not marketed)	No Indian availability; phase 3 assets recently acquired by large pharma; future access and pricing unknown.

The pragmatic consequence is a partial inversion of the global hierarchy. In India, the **affordable** node-directed backbone—pioglitazone for the adipose/DNL node, saroglitazar for the hepatic node, generic empagliflozin or dapagliflozin for the cardiorenal node, and dietary carbohydrate-quality intervention for the gut–liver node—will treat the great majority of MASLD-CKM patients, while resmetirom and FGF21 analogues remain, for now, largely aspirational. A framework that ranks drugs purely by trial-grade evidence, ignoring access, would be clinically unusable for most of the Indian population; node-directed reasoning, by contrast, identifies affordable substitutes that engage the same mechanism.

6. A MASLD-stratified selection matrix

Synthesising Sections 3–5, Table 3 maps CKM stage, modified by MASLD/fibrosis stage, onto preferred and mechanistically rational agents, with an India-adapted note in each row; Figure 3 renders the same

logic as a therapeutic ladder, shaded by real-world access in India. The organising principle is simple: the dominant node—and therefore the priority agent—shifts predictably as one climbs the ladder, from the adipose–lipogenic nodes of early disease, through the fibrotic and cardiorenal nodes of advanced CKM, to the limited disease-modifying options of established cirrhosis.

Table 3. MASLD-stratified pharmacotherapy across CKM stages, with India-adapted options. The "dominant node" column links each clinical scenario to Sections 3.1–3.7; the India column reflects the access realities of Table 2.

CKM stage (+ MASLD/fibrosis)	Dominant node	Preferred / rational agents	India-adapted option
Stage 1–2, steatosis–early MASH (F0–F1)	Adipose insulin resistance, DNL	GLP-1 RA; pioglitazone (if T2D/prediabetes, no HF); lifestyle & microbiome-directed measures	Pioglitazone (low-cost); carbohydrate-quality diet; saroglitazar where hepatic node dominant
Stage 2, MASH with F2–F3 fibrosis	Hepatic injury and fibrosis	Semaglutide or resmetirom (both approved); FGF21 analogues (trials); pioglitazone	Semaglutide (rising access) or saroglitazar + pioglitazone; resmetirom via Rule 36 only
Stage 3, CKD / subclinical CVD with MASH	Cardiorenal-fibrotic plus hepatic	SGLT2i + GLP-1 RA backbone; finerenone (CKD with T2D); resmetirom for hepatic node	Generic empagliflozin/dapagliflozin + finerenone; add pioglitazone/saroglitazar for liver
Stage 4, HF / ASCVD with MASH-fibrosis	Multi-organ fibro-inflammation	SGLT2i + GLP-1 RA; finerenone (esp. HFpEF); bempedoic acid or colchicine for residual risk; avoid pioglitazone in reduced-EF HF	Generic SGLT2i + finerenone; low-dose colchicine for residual ASCVD risk; avoid pioglitazone if reduced-EF HF
Any stage, F4 compensated cirrhosis	Portal / fibrotic	Resmetirom (F4 data emerging, outcomes pending); FGF21 analogues (slow antifibrotic); GLP-1 RA with caution	Limited disease-modifying options in India; focus on cardiorenal backbone, surveillance and specialist referral

7. Evidence tiers and regulatory status

The agents above occupy a clear evidence gradient, which we make explicit to prevent overstatement (Table 4). Only resmetirom and semaglutide are regulatory-approved for steatohepatitis with fibrosis. A second tier comprises drugs with proven cardiometabolic outcomes that act on shared nodes but lack direct hepatic validation. A third tier is investigational. Recognising this gradient is itself a stratification tool: it tells the clinician where efficacy for the hepatic node is established, where it is inferred, and where it remains a hypothesis.

Table 4. Evidence tiers and regulatory status of CKM–MASLD agents. Approval status refers to steatohepatitis with fibrosis specifically; several tier-2 agents are approved for cardiorenal or metabolic indications.

Tier	Agents
Approved for MASH with fibrosis	Resmetirom (F2–F3); semaglutide (F2–F3). Saroglitazar is DCGI-approved for MASH in India specifically.
Cardiometabolic-outcome-proven, hepatically unvalidated	SGLT2 inhibitors; finerenone; bempedoic acid; low-dose colchicine; pioglitazone (hepatic benefit shown but not a MASH label).
Investigational	FGF21 analogues (efruxifermin, pegozafermin, efimosfermin); survodutide, tirzepatide and retatrutide for MASH; FGF19 analogues (aldafermin); microbiome-directed strategies.

8. Combination therapy and future directions

The node framework predicts that the most effective regimens will pair agents acting on complementary nodes: an incretin to reduce the lipotoxic substrate load together with an FGF21 analogue for direct antifibrosis; or a liver-directed agent such as resmetirom layered onto a cardiorenal backbone of SGLT2 inhibitor and finerenone[58]. Several ongoing outcome trials will define this space, including the compensated-cirrhosis programmes for resmetirom and FGF21 analogues and the completion of ESSENCE. The principal unmet need is trial architecture: as the 2026 CKLM roadmap argued, endpoints must move beyond single-organ histology or event counts toward integrated multiorgan outcomes that reflect the syndrome as a whole[5]. Fibrosis-stratified enrolment—rather than organ-defined enrolment—would be the natural design correlate of the framework advanced here. For India and similar settings, a parallel priority is pragmatic, cost-aware trials of affordable node-directed combinations (for example pioglitazone or saroglitazar with a generic SGLT2 inhibitor) that reflect the drugs patients can actually obtain.

9. Conclusion

CKM syndrome is unified by a small set of molecular nodes on which liver, heart, kidney, and adipose injury converge. MASLD is the hepatic expression of that shared biology, and fibrosis stage is the single most informative modifier of extrahepatic risk. Reorganising pharmacotherapy around nodes rather than organs clarifies why the same agent benefits multiple organs, and reframes drug selection as a function of fibrosis stage and cardiorenal burden rather than of specialty. Tailoring the framework to the Indian phenotype—lean MASLD, distinctive genetics, a high-glycaemic diet, and an inverted drug-access hierarchy—shows that node-directed reasoning is not merely elegant but practically necessary, because it identifies affordable, locally available agents that engage the same mechanisms as their costly counterparts. As the pharmacopoeia expands from two approved MASH agents toward a broader antifibrotic and cardiometabolic armamentarium, fibrosis stage—not organ label—should become the

axis along which CKM therapy is individualised. The practical call to action is therefore twofold: stage the liver in every CKM patient, using non-invasive fibrosis markers rather than BMI alone, and let that stage—read against the patient's locally available formulary—drive the choice of node-directed therapy. In settings such as India, doing so converts an expensive, approval-limited framework into an affordable, mechanistically coherent one that can be delivered today.

Key points

- MASLD is best conceptualised as the hepatic node of CKM syndrome, and liver fibrosis stage as a modifier that reclassifies cardiorenal-metabolic risk.
- CKM pharmacotherapy is more coherently organised by shared molecular node than by organ silo, explaining multi-organ benefit of single agents.
- Resmetirom and semaglutide are approved for MASH with F2–F3 fibrosis; SGLT2 inhibitors, finerenone, bempedoic acid and colchicine act on shared nodes without direct hepatic validation; FGF21 analogues are the leading investigational antifibrotics.
- In India, MASLD affects roughly one in three adults, often at normal BMI (lean MASLD), with distinct PNPLA3/TM6SF2 genetics and a refined-carbohydrate diet driving hepatic DNL.
- Drug access inverts the global hierarchy in India: pioglitazone, DCGI-approved saroglitazar, and generic SGLT2 inhibitors are affordable node-directed options, whereas resmetirom is not commercially registered.
- A CKM-stage × fibrosis-stage matrix, with an India-adapted column, operationalises agent selection.
- Antifibrotic effects are intrinsically slow, with implications for both clinical expectation and trial design.

Figures

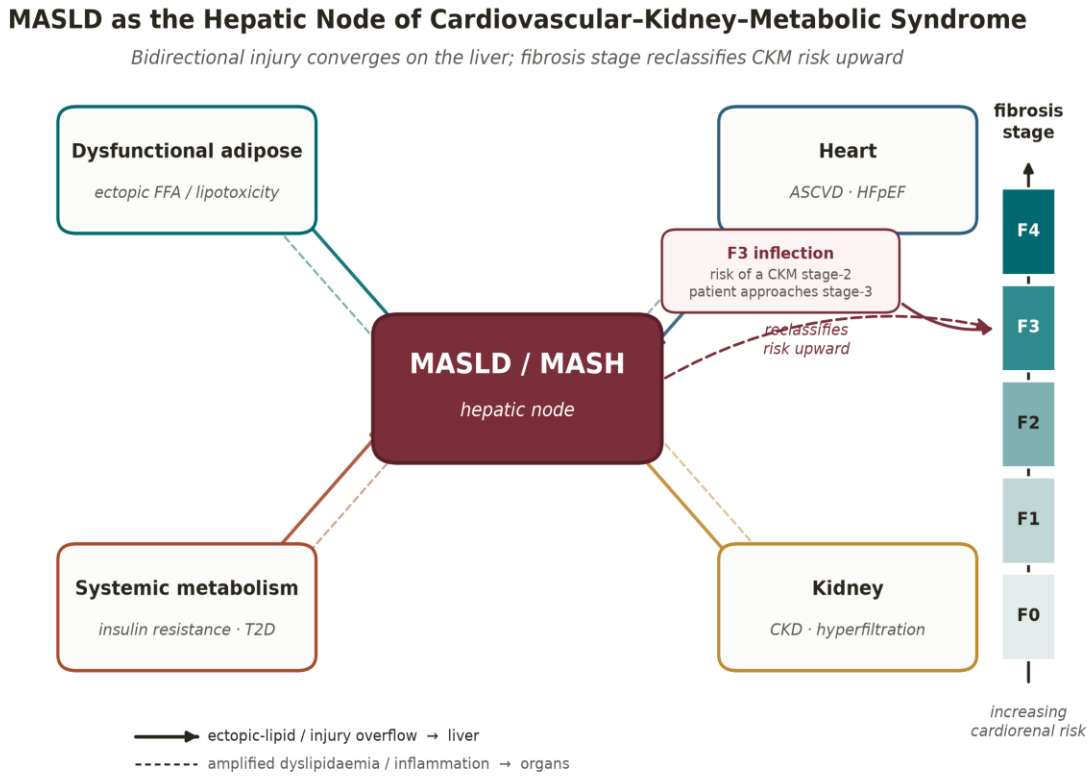

Figure 1. Conceptual framework. The four-organ CKM construct (dysfunctional adipose tissue, heart, kidney, systemic metabolism) with MASLD superimposed as the hepatic node, and fibrosis stage (F0–F4) shown as a modifier axis that reclassifies CKM stage upward.

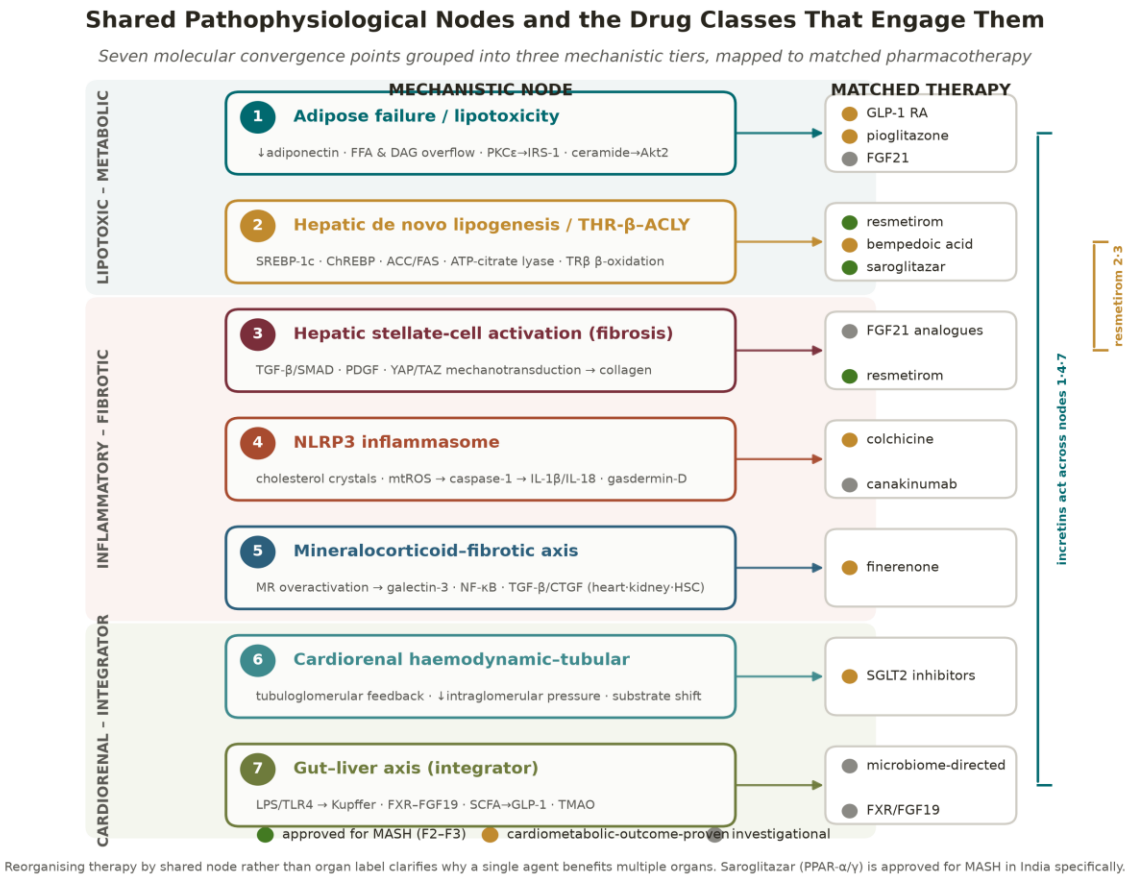

Figure 2. Mechanism-to-node schematic. The seven shared pathophysiological nodes—grouped into three mechanistic tiers (lipotoxic–metabolic; inflammatory–fibrotic; cardiorenal–integrator)—each mapped to matched pharmacotherapy. Coloured badges denote evidence tier (approved for MASH; cardiometabolic-outcome-proven; investigational); brackets mark agents that act across several nodes (e.g. incretins across nodes 1, 4 and 7).

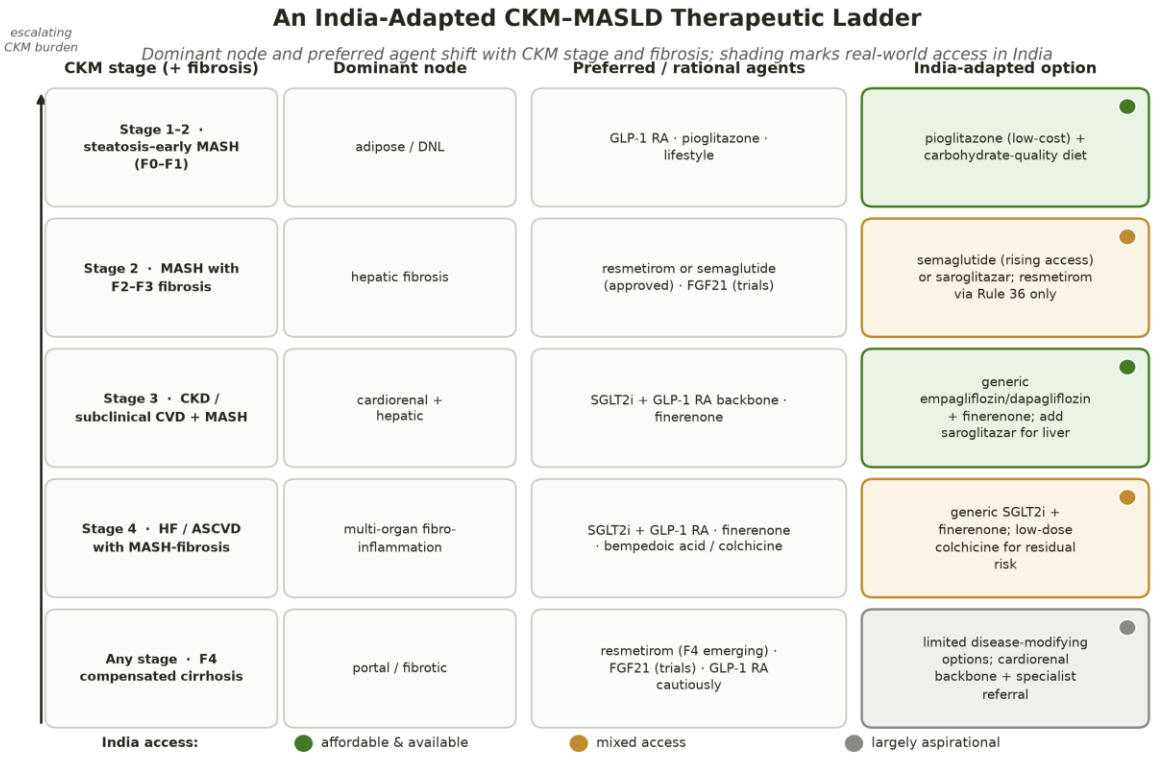

Figure 3. An India-adapted CKM–MASLD therapeutic ladder. Each rung links a CKM stage (with its fibrosis burden) to the dominant molecular node, the mechanistically preferred agents, and the pragmatic India-adapted option. Shading of the final column marks real-world access in India (affordable and available; mixed; largely aspirational), visualising the partial inversion of the global therapeutic hierarchy discussed in Section 5.5.

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All digital object identifiers (DOIs) were verified against publisher pages or PubMed on 2 July 2026. Items 9c and 41 relate to press-release-sourced acquisition figures and conference data where noted in the text; those specific commercial figures are not assigned DOIs.

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