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Review Article

Assessment and management of cardiovascular–kidney–liver metabolic-syndrome in the primary care setting: A multidisciplinary consensus statement

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ABSTRACT

The recently introduced cardiovascular–kidney–metabolic (CKM) syndrome captures the close interplay between metabolic risk factors, chronic kidney disease, and cardiovascular disease, but insufficiently reflects the important additional role of the liver. Metabolic dysfunction–associated steatotic liver disease (MASLD), the most prevalent chronic liver disease worldwide, is strongly associated with cardiovascular events, kidney disease progression, and all-cause mortality, yet remains frequently under-recognized in routine clinical practice. We propose the concept of a cardiovascular–kidney–liver–metabolic syndrome (CKLMS) and present a multidisciplinary, primary care–centered framework for its assessment and management. Based on expert consensus and current evidence, the framework integrates cardiovascular, renal, hepatic, and metabolic risk stratification using accessible, validated tools feasible in primary care, including blood pressure and lipid profiling, assessment of kidney function and albuminuria, non-invasive liver fibrosis testing, and systematic screening for diabetes and obesity. Management emphasizes early lifestyle intervention, use of pharmacological therapies with multi-organ benefit, and clearly defined referral pathways to specialist care. Primary care professionals are positioned as coordinators of longitudinal, patient-centered, multidisciplinary management. Early, integrated identification and treatment of CKLMS in primary care represents a pragmatic and effective strategy to prevent disease progression, reduce cardiovascular and kidney events, and improve long-term outcomes.

1. Introduction

Recently, the Cardiovascular–kidney–metabolic (CKM) syndrome was introduced to describe the pathophysiological interplay between metabolic risk factors, such as obesity and diabetes, with chronic kidney disease (CKD) and cardiovascular disease (CVD), leading to multiorgan dysfunction and high rates of adverse cardiovascular outcomes [1]. The CKM syndrome manifests through various forms of end-organ injury that reflect the multidirectional relationships among metabolic risk factors, CKD, and the cardiovascular system.

The role of the liver, and in particular the association of non-alcoholic fatty liver disease (NAFLD) with CVD [2,3] and CKD [4] has been recognized for several years. A case in point is a large analysis of the US NHANES database demonstrating that NAFLD is highly prevalent in individuals with hypertension, with a progressive increase in steatosis and advanced fibrosis across blood pressure categories [5].

More recently, metabolic dysfunction–associated steatotic liver disease (MASLD), has been acknowledged in the context of CKM, but remains absent from its title and definition. MASLD, the most common liver disease worldwide [6], is defined as steatotic liver disease (SLD) in the presence of one or more cardiometabolic risk factors without harmful alcohol intake [7,8]. It is often described as the hepatic

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manifestation of metabolic syndrome [9]. Genetic, epigenetic, environmental, and lifestyle factors influence progression from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), advanced fibrosis, cirrhosis, or hepatocellular carcinoma [10].

Type 2 diabetes and abdominal obesity are the metabolic conditions with the strongest impact on MASLD progression [11]. MASLD is associated with increased risk of CKD and cardiovascular events [11,12]. In a German primary care study, MASLD independently predicted myocardial infarction, coronary artery disease, atrial fibrillation, or stroke [13]. In patients with heart failure, liver fibrosis (FIB-4 index) predicted all-cause mortality and was associated with structural and functional cardiac changes [14]. Combining the FIB-4 index with a high fatty liver index further improved prognostic prediction for liver events, CVD, and mortality [15]. Despite this, awareness of the importance of liver health in CKM management remains low; incorporating hepatic assessment into routine cardiovascular–kidney–liver–metabolic (CKLM) care is essential for improving outcomes (Fig. 1).

These associations are underpinned by shared risk factors including established and novel (e.g. environmental) cardiovascular risk factors [16,17], and pathophysiological processes linking insulin resistance, hyperglycemia, dyslipidemia, and hypertension with visceral and ectopic adiposity as a central upstream driver (Fig. 2) [3,18–23]. The severity of disease increases with the number of affected CKLM phenotypes [24,25].

Recognition of the liver's central role in systemic metabolic dysfunction is growing. The European Atherosclerosis Society consensus on systemic metabolic disorders (SMD) includes the liver alongside the cardiovascular system, kidneys, and pancreas, emphasizing early detection [26].

The aim of this article is to develop a multidisciplinary consensus framework for assessing and managing CKLM-syndrome (CKLMS) in primary care (Fig. 3). This framework focuses on early identification of at-risk individuals, prevention of MASLD progression, and integration of hepatic assessment into existing CKLMS protocols (Fig. 3). Risk stratification incorporates cardiovascular, kidney, liver, and metabolic indicators to guide timely referrals and coordinated care among cardiologists, endocrinologists, hepatologists, hypertensiologists, and nephrologists. Given the multifactorial nature of CKLMS, effective management must integrate lifestyle, psychosocial, socioeconomic, and pharmacological interventions [27].

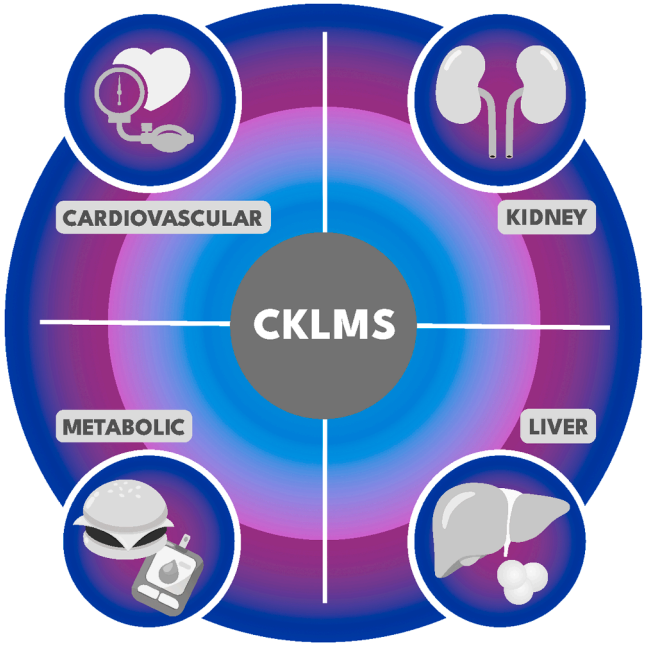

Fig. 1. CKLMS overview.

2. Management of CKLMS at the primary care level: unlocking the untapped potential

Given the high prevalence of CKLMS phenotypes, these conditions are usually first identified in the primary care setting. General practitioners or internists routinely manage interconnected conditions, such as hypertension, diabetes, dyslipidemia, and obesity, which frequently coexist in the same patient.

Primary care professionals occupy a pivotal position in the patient pathway by delivering holistic, person-centered, longitudinal care that integrates health promotion, prevention, risk assessment, and the management of both acute and chronic disease. This makes them well-placed to participate in a shared-care framework with specialists, supported by other health-care professionals, including nurses, dieticians, nutritionists, and pharmacists.

Because primary care builds on personal knowledge of patients, continuity, and bio-psycho-social understanding, it is also central to motivating lifestyle change. However, achieving this is challenging. Time constraints, competing priorities, and limited resources may hinder optimal care for patients with CKLMS [28]. These barriers highlight the need for targeted tools, training, and easy to access pathways that enable effective early detection, intervention, and long-term follow-up across cardiovascular, kidney, liver, and metabolic domains aiming at reducing mortality and societal costs.

When well-integrated into care pathways, primary healthcare providers can foster patient empowerment through raised awareness, prevention, and shared decision-making. In our proposed framework, the primary care professional remains at the center of patient-focused, interdisciplinary care, coordinating with secondary specialists to tailor management according to individual CKLMS risk profiles and needs.

3. Assessment of CKLMS phenotypes in primary care

We propose a longitudinal framework for assessing patient risk based on cardiovascular, kidney, liver, and metabolic indicators to identify individuals at increased risk in the context of CKLMS (Fig. 3). The framework incorporates a screening panel for the continuous evaluation of all CKLMS phenotypes, which is initiated following a detailed medical history and clinical examination. All the recommended investigations are feasible within primary care, and were selected for their accessibility, validity, and cost-effectiveness. To leverage the continuity of care and detailed patient knowledge inherent in the primary care setting, such screening should integrate cardiovascular, renal, hepatic, and metabolic risk profiles into a single, patient-centered assessment.

3.1. Cardiovascular risk estimation

Cardiovascular risk can be estimated based on the overall burden of risk factors, presence of hypertension-mediated organ damage, diabetes, CKD, or CVD. Considering these elements together allows classification of patients into different risk categories without the use of formal risk-scoring tools [16,29](Fig. 4). In patients not already clinically classified as high or very-high risk, 10-year cardiovascular risk can be formally estimated using the Systematic Coronary Risk Estimation 2 (SCORE2) algorithm, recommended for adults aged 40–69 years [29]. For individuals aged ≥70 years, the SCORE2-OP algorithm can be applied. Both are region-specific prediction models with calibration models tailored to European risk regions (i.e. low-, moderate, high, and very-high-risk regions). They incorporate sex, age, smoking status, systolic blood pressure, and non–high-density lipoprotein (HDL) cholesterol levels, to estimate the 10-year risk of fatal and non-fatal cardiovascular events in individuals with untreated or stable risk factors. Thus, SCORE2 or SCORE2-OP appear useful in individuals who are not

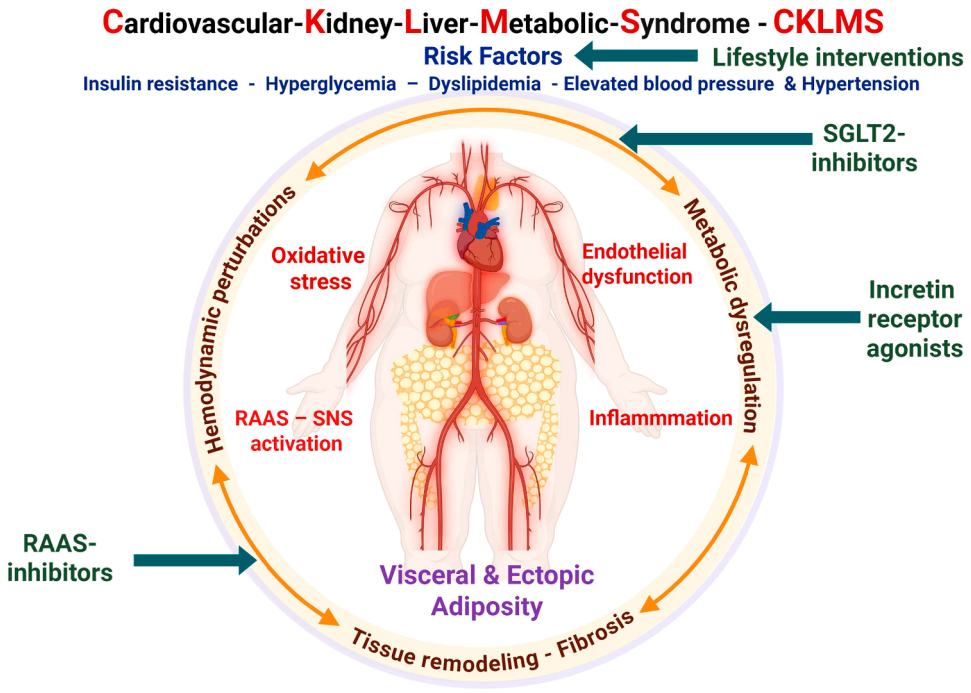

Fig. 2. Shared pathophysiologic pathways in cardiovascular–kidney–liver–metabolic syndrome (CKLMS) and convergent therapeutic targets.
This figure illustrates visceral and ectopic adiposity as a central upstream driver of cardiovascular–kidney–liver–metabolic syndrome (CKLMS), linking insulin resistance, hyperglycemia, dyslipidemia, and hypertension. These factors converge on shared pathophysiologic mechanisms, including activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system, chronic inflammation, oxidative stress, and endothelial dysfunction. These processes interact through hemodynamic perturbations and metabolic dysregulation, forming a self-amplifying cycle that promotes tissue remodeling and fibrosis, leading to parallel injury in the vasculature, heart, kidney, and liver. Therapeutic interventions act at complementary points within this network. Lifestyle measures target upstream drivers (risk factors). SGLT2 inhibitors, incretin receptor agonists (including GLP-1 receptor agonists, dual GLP-1 plus glucose-dependent insulinotropic polypeptide [GIP], and emerging triple agonists) [68,69], and RAAS inhibitors (ACE inhibitors, ARBs, mineralocorticoid receptor antagonists (steroidal, e.g. spironolactone/eplerenon and non-steroidal, e.g. finerenone), and emerging aldosterone synthase inhibitors) [66,67] are depicted according to their predominant mechanisms; however, all exert pleiotropic effects across multiple pathways, contributing to integrated multi-organ protection. Figure created with BioRender.com.

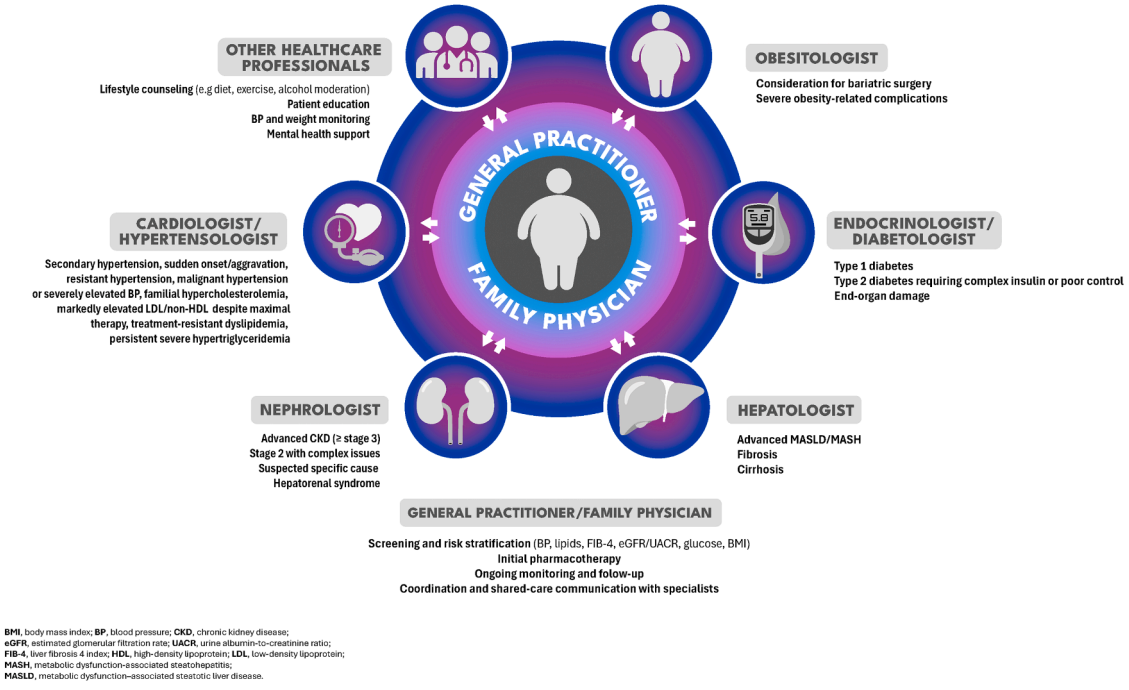

Fig. 3. Multidisciplinary approach for CKLMS management in primary care.

already at high or very-high risk due to established CVD, CKD, long-standing or complicated diabetes, or severe hypertension-mediated organ damage (e.g. left ventricular hypertrophy) [16]. Alternatively, the PREVENT risk assessment tool (developed by the American Heart

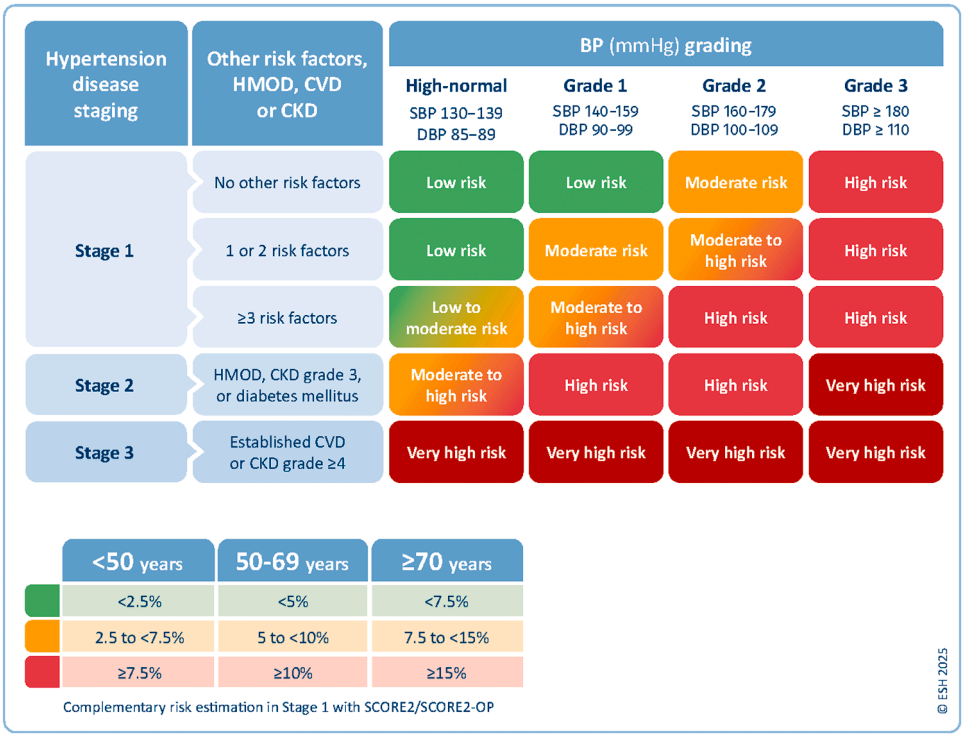

Fig. 4. Risk stratification according to grade and stage of hypertension[39].
CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HMOD, hypertension-mediated-organ damage; SBP, systolic blood pressure; SCORE2/SCORE2-OP, Systematic Coronary Risk Evaluation 2-Older Persons. Alternatively, to SCORE2/SCORE2-OP, the PREVENT risk assessment tool may be considered [30].

Association for the United States) may be considered [30]. This tool provides a framework for risk-based cardiovascular prevention by integrating quantitative risk estimation with CKM health staging, including CKM-related variables (e.g. eGFR, albuminuria, and glycaemic parameters).

3.2. Hypertension

Most international guidelines agree on the diagnostic cut-off for hypertension as an office systolic blood pressure (BP) reading ≥140 mmHg and/or diastolic BP ≥90 mmHg, with the notable exception of the US guidelines, which adopt lower thresholds [16,31–35]. Although cardiovascular and all-cause mortality risk rises continuously from BP levels as low as 115/75 mmHg [36], most guidelines recommend initiating treatment at ≥140/90 mmHg. For primary prevention of atherosclerotic cardiovascular disease, a BP target below 120/80 mmHg has been proposed when considered alongside other risk factors [37]. For cardiovascular risk estimation in hypertensive patients, the use of the SCORE2 or SCORE2-OP algorithms may be considered [16,31]. However, diastolic blood pressure is not incorporated into these tools, which represents a limitation.

For the initial diagnosis and screening, office BP measurement remains the basic evaluation [38]. Whenever deemed feasible and necessary, out-of-office BP monitoring, (either 24-hour ambulatory BP monitoring or home BP monitoring) should be performed [31,39]. A home BP reading ≥135/≥85 mmHg is equivalent to an office reading ≥140/≥90 mmHg for diagnosing hypertension, while readings below 130/80 mmHg are considered equivalent for both settings [39].

3.3. Lipids

For cardiovascular-risk estimation with SCORE2 or SCORE2-OP, all patients should have total cholesterol and HDL cholesterol measured, enabling calculation of non–HDL cholesterol, the lipid parameter required for SCORE2 algorithms [29]. Low-density lipoprotein (LDL) cholesterol measurement is strongly recommended to guide broader cardiovascular and metabolic risk management [40], even though it is not directly used in the SCORE2 calculations. Triglycerides should be measured in selected situations, such as suspected hypertriglyceridemia, evaluation of metabolic syndrome, or suspected secondary dyslipidemia. In addition, the European Society of Hypertension (ESH) recommend total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides as part of the standard laboratory work-up for patients with hypertension [16].

3.4. Kidney function and chronic kidney disease (CKD)

Assessment of kidney function and damage should follow the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines [41]. This includes measurement of serum creatinine to calculate the estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR) in a spot urine sample. In young healthy adults, eGFR is typically 90–125 ml/min/1.73m^2 and UACR <30 mg/g (A1, normoalbuminuria).

CKD is diagnosed when eGFR is <60 ml/min/1.73m^2 for >3 months, regardless of UACR, or when UACR is >30 mg/g (A2, moderately elevated albuminuria) or >300 mg/g (A3, severely elevated albuminuria) for >3 months, regardless of eGFR [42]. Individuals with eGFR ≥60 ml/min/1.73m^2 and normoalbuminuria are not classified as having CKD.

3.5. Steatotic liver disease

Currently, SLD is diagnosed non-invasively using novel biomarkers. Although liver biopsy remains the gold standard for diagnosing hepatic fibrosis, it is not feasible in most clinical settings. In adults with MASLD, blood-based non-invasive tests (NITs)—by themselves or in combination with imaging—are the preferential method to stratify risk this large

patient population. NITs outperform classical liver tests, e.g. liver enzyme tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), in detecting patients with significant disease [11]. In the primary care setting, the FIB-4 index is recommended by current guidelines as validated tool [43,44]. It is calculated using age, ALT, AST, and platelet count [45]. Similar to the eGFR mentioned above, FIB-4 can often be generated automatically by laboratories, providing categorical results for risk stratification with the following **FIB-4 categories:** low risk <1.30; indeterminate risk 1.30–2.67; high risk >2.67 [45,46].

In addition to its diagnostic utility, FIB-4 also carries prognostic value for all-cause mortality in obesity/type 2 diabetes and predicts liver, cardiovascular, and mortality outcomes independently of baseline cardiovascular risk [15]. Clinical guidelines recommend FIB-4 screening in individuals with MASLD or metabolic risk factors, with low-risk patients continuing management in primary care [47–49].

Recommended approach:

1. FIB-4 calculation in at-risk patients.
2. If indeterminate/high risk, confirm with imaging (e.g., liver elastography). Manage metabolic comorbidity and provide liver-specific therapies as available.
3. Reassess every 1–3 years to monitor progression [11,50].

3.6. Diabetes

Screening for type 2 diabetes mellitus and prediabetes can be integrated into regular preventive primary care visits, using the American Diabetes Association (ADA) criteria [51]:

- **Fasting plasma glucose (FPG):** normal <5.6 mmol/L (<100 mg/dL); prediabetes 5.6–6.9 mmol/L (100–125 mg/dL); diabetes ≥7.0 mmol/L (≥126 mg/dL).
- **Oral glucose tolerance test (OGTT), 2h value:** normal <7.8 mmol/L (<140 mg/dL); pre-diabetes 7.8–11.0 mmol/L (140–199 mg/dL); diabetes ≥11.1 mmol/L (≥200 mg/dL).
- **HbA1c:** normal <39 mmol/mol (<5.7 %); prediabetes 39–47 mmol/mol (5.7–6.4 %); diabetes ≥48 mmol/mol (≥6.5 %).

In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal results from different tests, which may be obtained at the same time (e.g., HbA1C and FPG), or the same test at two different time points.

3.7. Obesity

Visceral adipose tissue is metabolically active, producing pro-inflammatory and pro-oxidative mediators that promote vascular, cardiac, renal, and hepatic injury [52–57] . Obesity contributes to insulin resistance, impaired glucose tolerance, elevated cardiovascular risk, and CKD progression [58,59].

The most commonly used index to diagnose obesity if the body mass index **(BMI) classification (WHO):** normal weight 18.5–24.9 kg/m^2; overweight 25.0–29.9 kg/m^2; obesity class I 30.0–34.9 kg/m^2; obesity class II 35.0–39.9 kg/m^2; obesity class III ≥40.0 kg/m^2 [60].

Diagnosis of obesity is based on BMI combined with waist circumference, to assess fat distribution and related health risks. While BMI has limitations, it remains a robust, low-cost, and widely applicable index in primary care [27]. An abnormal BMI should prompt early intervention (lifestyle changes, risk reduction, pharmacotherapy, as needed) to prevent further metabolic deterioration or end-organ damage, especially in those with personal or family history of cardio-metabolic diseases and events.

4. Management in the primary care setting

In this section, we propose recommendations for long-term management of CKLMS in primary care, combining lifestyle and behavioral strategies with evidence-based pharmacological interventions, following the guidance of selected professional societies (Fig. 5). The approach should be individualized, risk-stratified, and coordinated with secondary care as needed.

4.1. Lifestyle and behavioral interventions

Primary care is often the ideal setting to implement behavioral and lifestyle interventions, including: weight loss support; smoking cessation; adoption of a healthy diet rich in vegetables, fruits, and whole grains; avoidance of high-salt processed foods; regular physical activity; reduction of sugar-sweetened beverages; and moderation of alcohol intake (including “low-alcohol” options with hidden sugar). Team-based care involving nurses, dieticians, nutritionists, physical therapists and other health care professionals can play a central role in patient management and long-term follow-up.

4.2. Pharmacological interventions

4.2.1. Hypertension

The current European hypertension guidelines emphasize a stepwise, combination-based strategy for effective blood pressure (BP) control [16,31,35,39].

The recommendations by ESH include:

- **Life-style interventions** for all hypertensive patients.
- **Initiate pharmacological treatment** at an office BP ≥140/90 mmHg (or home BP ≥135/85 mmHg) for most hypertensive patients.
- **Consider** treatment in very-high cardiovascular-risk patients with high–normal BP (130–139/85–89 mmHg).
- **BP targets for most patients:** 120–129 mmHg systolic and 70–79 mmHg diastolic.

In most patients, initial therapy should begin with a low-dose dual combination of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) plus either a calcium channel blocker (CCB) or a thiazide/thiazide-like diuretic, preferably as a single-pill combination to improve adherence. If BP remains uncontrolled after 1–3 months, two pathways are proposed: the ESH 2023 approach [16] recommends increasing the doses of the initial two-drug combination to the maximum tolerated levels before adding a third agent, while the European Society of Cardiology (ESC) 2024 approach [31] advocates adding a third drug (low-dose triple combination) earlier in the treatment course. The preferred triple regimen combines an ACE inhibitor or ARB with a CCB and a thiazide/thiazide-like diuretic. Beta-blockers may be added at any stage for compelling indications, such as ischemic heart disease, heart failure, or arrhythmia. Regular follow-up every 1–3 months is advised until the target BP (<140/80 mmHg, and <130/80 mmHg if tolerated) is achieved, with subsequent annual reviews to ensure long-term control and adherence.

4.2.2. Lipids

The treatment targets for LDL-cholesterol depend on the patient’s total **cardiovascular risk** classification, defined by clinical factors as mentioned above or formal estimation with the SCORE2/SCORE2-OP tools [16,29]. The current recommendations according to the ESC/EAS guidelines [40] are as follows:

- **Low risk (SCORE2 <2 %)**: LDL cholesterol goal <3.0 mmol/L (<116 mg/dL).
- **Moderate risk (SCORE2 2–<10 %)**: LDL cholesterol goal <2.6 mmol/L (<100 mg/dL).
- **High risk (SCORE2 10–<20 %, or markedly elevated single risk factors)**: LDL cholesterol goal <1.8 mmol/L (<70 mg/dL) and ≥50 % reduction from baseline.

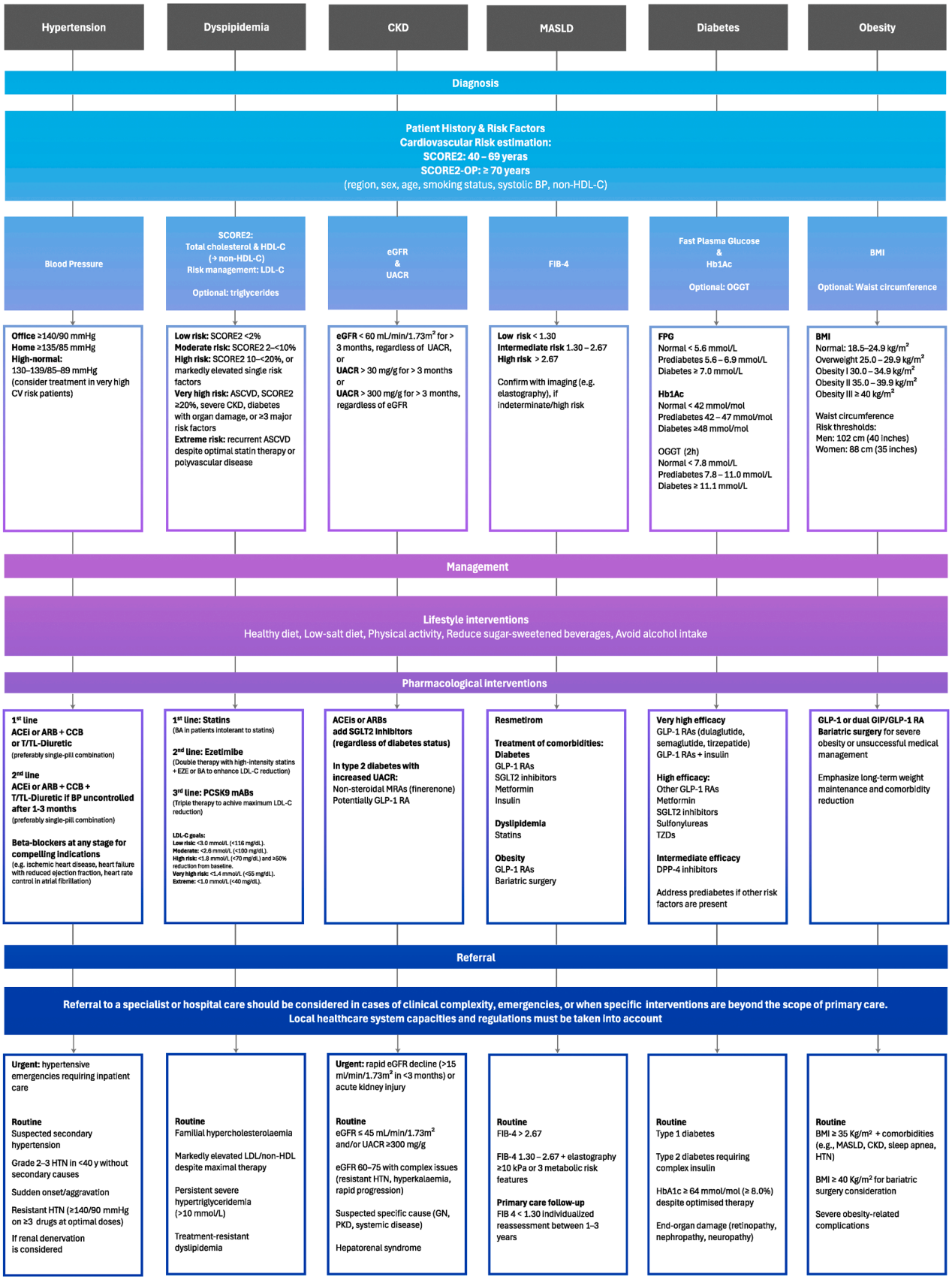

Fig. 5. Management algorithm.
Alternatively, to SCORE2/SCORE2-OP, the PREVENT risk assessment tool may be considered [30].

- **Very high risk (atherosclerotic cardiovascular disease [ASCVD], SCORE2 ≥20 %, severe CKD, diabetes with organ damage, or ≥3 major risk factors)**: LDL cholesterol goal <1.4 mmol/L (<55 mg/dL).
- **Extreme risk (recurrent ASCVD despite optimal statin therapy or polyvascular disease)**: LDL cholesterol goal <1.0 mmol/L (<40 mg/dL).

In summary, the intensity of LDL cholesterol-lowering therapy increases progressively with cardiovascular risk, combining both **absolute LDL-cholesterol targets** and **relative reductions (≥50 %)** from baseline to optimize cardiovascular prevention. Pharmacological LDL cholesterol lowering follows a stepwise intensification [40], with statins representing the first-line therapy, providing an average LDL cholesterol reduction of about 30 % with moderate-intensity and 50 % with high-intensity statins.

- If LDL cholesterol goals are not achieved, **ezetimibe (EZE)**—which adds about **20 % additional reduction**—should be combined with statins.
- **Bempedoic acid (BA)** is recommended in patients who are unable to take statin therapy to achieve the LDL cholesterol goal. BA provides a similar reduction (~23 %) and can be used alone or together with EZE (~38 % reduction).
- Combining **high-intensity statins with EZE or BA** further enhances LDL cholesterol lowering to around **58–68 %**.
- For patients not reaching these targets or at very high/extreme risk, **proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs)** offer an alternative or additional treatment option, **~60% reduction** when taken alone, and when combined with EZE or statins, can achieve **up to 75–80 % LDL cholesterol reduction**.
- The **maximum LDL cholesterol reduction (~86 %)** is achieved with **triple therapy** (high-intensity statin + EZE + PCSK9 mAb or BA + PCSK9 mAb).

Treatment of elevated triglycerides can be considered in high- or very-high-risk patients, with elevated triglycerides (1.52–5.63 mmol/L or 135–499 mg/dL). **High-dose icosapent ethyl (2 g twice daily)** could be added to statin therapy to reduce cardiovascular risk [40]. In patients with **severe hypertriglyceridaemia (>8.5 mmol/L or >750 mg/dL)** due to familial chylomicronaemia syndrome, **volanesorsen (300 mg weekly)** should be considered to lower triglycerides and prevent pancreatitis.

4.2.3. Chronic kidney disease (CKD)

According to KDIGO 2024 [41] and ESH [16,39], treatment recommendations are as follows:

- **Core nephroprotective therapy:** ACE inhibitors or ARBs; add sodium/glucose cotransporter 2 (SGLT2) inhibitors (regardless of diabetes status when eligible).
- In type 2 diabetes with increased UACR: **Finerenone** (non-steroidal mineralocorticoid receptor antagonists [MRA]) should be prioritized; **glucagon-like peptide 1 (GLP-1) receptor agonists** may be considered.
- Optimal BP and glycemic control in diabetic patients are important to slow progression and improve outcomes.

4.2.4. Diabetes

Diabetes management should follow a **holistic, person-centered approach** that emphasizes individualized glycaemic targets based on age, comorbidities, and treatment goals [61,62]. Individualized glycated hemoglobin (HbA1c) targets should be guided by patient-specific factors, including age, disease duration, comorbidities, risk of hypoglycemia, and treatment burden. For most non-pregnant adults with type 2 diabetes, a target **HbA1c of <7.0 % (53 mmol/mol)** is appropriate to reduce the risk of microvascular complications. More stringent targets, such as **≤6.5 % (48 mmol/mol)**, may be considered for younger individuals, those with shorter disease duration, or those without significant hypoglycemia risk, if these can be achieved safely. Conversely, less-stringent targets, such as **<8.0 % (64 mmol/mol)**, are reasonable for older adults, patients with long-standing diabetes, advanced comorbidities, or a high risk of hypoglycemia. Metformin remains a key initial option; however, combination therapy with additional agents is often necessary to reach targets. In all cases, minimizing hypoglycemia is a priority, especially in high-risk individuals.

The **efficacy of glucose-lowering agents** varies by class:

- **Very-High Efficacy:** Dulaglutide (high dose), semaglutide, and tirzepatide; also insulin and combination injectable therapies (GLP-1 receptor agonist plus insulin).
- **High Efficacy:** Other GLP-1 receptor agonists, metformin, SGLT2 inhibitors, sulfonylureas, and thiazolidinediones (TZDs).
- **Intermediate Efficacy:** dipeptidyl peptidase 4 inhibitors.

Treatment intensification should be guided not only by glycemic targets, but also by the presence of comorbidities and overall cardio–renal risk, supporting the use of GLP-1 receptor agonists, SGLT2 inhibitors or non-steroidal MRAs (finerenone), depending on their approval in patients with type 2 diabetes.

4.2.5. MASLD

Management focuses on lifestyle modification (weight loss, increased physical activity, alcohol moderation) and the treatment of comorbidities using approved therapies: **GLP-1 receptor agonists, SGLT2 inhibitors, metformin and insulin** for type 2 diabetes; **statins** for dyslipidemia; **GLP-1 receptor agonists** or **bariatric surgery** for obesity [63]. **Resmetirom** received FDA approval in 2024, and EMA marketing authorization was granted in August 2025 for non-cirrhotic MASH. Phase 3 data for **semaglutide** suggests MASH resolution and fibrosis improvement. **Efruxifermin** (a fibroblast growth factor 21 analogue) is an emerging novel treatment that showed reversal of cirrhosis in a phase 2 trial [64].

4.3. Obesity / overweight

According to the European Association for the Study of Obesity (EASO) 2024 framework [65], obesity should be recognized and managed as a **chronic, relapsing, multifactorial disease** requiring a long-term, multidisciplinary approach. The adoption of a **sensitive, non-judgmental, and patient-centered approach** is advisable to support engagement, reduce stigma, and foster sustained behavior change. The core pillars of treatment include **behavioral modification** (improved nutrition, increased physical activity, stress management, and sleep optimization), **psychological therapy, pharmacotherapy**, and **metabolic/bariatric procedures** when indicated. Behavioral interventions form the foundation of care for all individuals with obesity. **Anti-obesity medications** should be prescribed according to approved indications—typically for adults with a **BMI ≥30 kg/m²**, or **≥27 kg/m²** in the presence of obesity-related complications. **Metabolic or bariatric surgery** is recommended for individuals with a **BMI ≥40 kg/m²**, or **≥35 kg/m²** with obesity-related disease, and may also be considered for individuals with **BMI ≥ 30 kg/m²** with poorly controlled type 2 diabetes despite optimal medical therapy. Long-term, multidisciplinary follow-up is essential after bariatric surgery to ensure sustained weight loss and manage nutritional or metabolic complications. Management of **obesity-related comorbidities** should be integrated into overall care, prioritizing treatments that do not promote weight gain.

4.4. Cross-condition overlap and convergent therapeutic strategies

Inhibitors of the renin-angiotensin-aldosterone-system (RAAS) [66,67], SGLT2 inhibitors and increctin receptor agonists, e.g. GLP-1 receptor agonists [68,69], provide benefits across multiple CKLMS domains, improving BP control, hemodynamic perturbations, metabolic dysregulation and protect against tissue remodeling and fibrosis, supporting an integrated, rather than siloed, treatment strategy (Fig. 2).

5. Referral pathways

Clear, evidence-based referral pathways are essential to ensure timely specialist care while avoiding unnecessary fragmentation (Fig. 3). Primary-care providers, with their longitudinal understanding of patients' clinical, family, and social context, should act as gatekeepers and coordinators. Referral is not a one-way process—patients may transition back to primary care for shared, ongoing follow-up.

Interdisciplinary models—built on clear communication between primary and secondary care providers—are central to effective CKLMS management [70–73]. Pathways should be adapted to local healthcare structures but remain anchored in objective cut-offs and risk assessment.

5.1. General referral principles

- **Urgent referral** (days–weeks) for unstable clinical status, rapidly progressive disease, or newly detected high-risk features.
- **Routine referral** (planned) for persistent abnormal findings, failure to achieve targets, or complex comorbidities.
- **Specialist coordination** should be phenotype specific but integrated across CKLMS domains, with explicit communication of risk scores, current therapy, and follow-up plans.

5.2. Phenotype-specific recommendations

5.2.1. Hypertension

Follow ESH guidance [16,39]:

- **Urgent:** hypertensive emergencies requiring inpatient care.
- **Routine:** suspected secondary hypertension; Grade 2 or 3 hypertension in patients <40 years without secondary causes; sudden onset or marked worsening of previously controlled BP; resistant hypertension (BP ≥140/90 mmHg despite ≥3 antihypertensive classes at optimal doses).

5.2.2. Lipids

Follow ESC prevention guidance [29,40]. **Routine referral** for familial hypercholesterolemia; markedly elevated non-HDL or LDL cholesterol despite maximal therapy; persistent severe hypertriglyceridemia (>10 mmol/L) or treatment-resistant dyslipidemia.

5.2.3. Kidney function / CKD

Based on KDIGO 2024 [41] and ESH [16,39]:

- **Urgent:** rapid eGFR decline (>15 ml/min/1.73m^2 in <3 months) or acute kidney injury.
- **Routine:** eGFR ≤45 ml/min/1.73 m^2 and/or UACR ≥300 mg/g; eGFR 60–75 ml/min/1.73 m^2 with complex issues (resistant hypertension, hyperkalemia, rapid progression); any suspected specific CKD cause (nephrotic/nephritic syndrome, polycystic kidney disease, systemic immune disease); advanced liver disease with suspected hepato–renal syndrome.

We acknowledge that local criteria may lead to back-referrals when primary care can continue high-quality management; however, conservative thresholds help avoid missing poorly compliant or resistant cases.

5.2.4. MASLD

According to EASL–EASD–EASO 2024 [63]:

- **Routine referral:** FIB-4 > 2.67 to hepatology/gastroenterology for suspected advanced liver disease; FIB-4 1.3–2.67 active management of risk factors and consider referral if elastography ≥10 kPa or three metabolic risk features are present.

Primary care follow-up: FIB-4 < 1.30 individualized reassessment of liver disease severity between 1 and 3 years

5.2.5. Diabetes

Referral depends on the healthcare system structure and complexity of care:

- **Routine:** all patients with type 1 diabetes; type 2 diabetes requiring complex insulin regimens or with poor control (HbA1c ≥64 mmol/mol/≥8.0 %) despite optimized therapy; presence of end-organ damage (retinopathy, nephropathy, neuropathy).

5.2.6. Obesity / overweight

As dedicated obesity referral pathways are not universal, we suggest referral based on comorbidity burden and complexity:

- **Routine:** BMI ≥35 kg/m^2 with major comorbidities (e.g., MASLD, CKD, sleep apnea, hypertension); BMI ≥40 kg/m^2 for bariatric surgery consideration; severe obesity-related complications warranting specialist input.

5.3. Maintaining continuity after referral

Primary care remains central to monitoring lifestyle changes, coordinating multi-specialty recommendations, adjusting pharmacotherapy, and supporting adherence and psychosocial needs.

6. Summary

We present a primary care–centered framework for the early detection, risk stratification, and management of CKLMS. This approach integrates validated screening tools, evidence-based cut-offs, and phenotype-specific management strategies for cardiovascular risk, hypertension, dyslipidemia, CKD, MASLD, diabetes, and obesity. Emphasis is placed on the role of the primary care provider as coordinator of multidisciplinary care, supported by clear referral pathways to specialist services when indicated. Lifestyle modification remains the foundation of management, complemented by pharmacologic therapy targeting both disease control and multi-organ protection.

7. Conclusion

Early, integrated, and coordinated management of CKLMS in primary care offers the best opportunity to prevent progression, reduce cardiovascular and renal events, and improve long-term outcomes. By combining accessible diagnostics, targeted interventions, and seamless referral pathways, primary care can serve as the cornerstone of effective CKLMS care. The adoption of a sensitive, non-judgmental, and patient-centered approach is advisable to promote engagement, adherence, and equitable care delivery.

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