nature medicine

Perspective

https://doi.org/10.1038/s41591-024-03223-z

Integrating liver endpoints in clinical trials of cardiovascular and kidney disease

Received: 12 April 2024

Accepted: 30 July 2024

Published online: 03 September 2024

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The intersection of cardiovascular disease, metabolic disorders and chronic kidney disease represents a complex clinical picture challenging healthcare systems worldwide. Metabolic-dysfunction-associated steatotic liver disease (MASLD) often manifests sequentially or concomitantly with these diseases, and may share underlying mechanisms and risk factors. Growing evidence suggests that new therapies could have benefits across these diseases, but trial sponsors and investigators tend to be reluctant to include patients with comorbidities—particularly liver diseases—in clinical trials. In this Perspective, we call for inclusion of patients with MASLD and measurement of liver outcomes in cardio–kidney–metabolic trials, when data suggest mechanistically plausible benefits and liver and cardiovascular safety. We discuss the implications of this new paradigm for clinical trial design and considerations for regulatory approval. Finally, we outline the challenges to implementing such an approach and provide recommendations for future clinical trial conduct.

The intersection of cardiovascular disease (CVD), metabolic disorders and chronic kidney disease (CKD) represents a complex clinical matrix that presents major challenges for healthcare systems worldwide. In recognition of this, the American Heart Association in 2023 issued a scientific statement describing the evidence for cardiovascular–kidney–metabolic (CKM) syndrome[1]. This syndrome generally originates from excess or dysfunctional adipose tissue, from which multiple pathological processes (including inflammation, oxidative stress, insulin resistance and vascular dysfunction) lead to the development of metabolic dysfunction and the progression of kidney disease and CVD (Fig. 1). Clinically, these diseases often manifest sequentially or concomitantly with MASLD, which is not unexpected given that they share many risk factors, progress through similar mechanisms dominated by inflammation and fibrosis and exacerbate each other[1–6]. A large body of evidence shows that patients with MASLD are at increased risk for subclinical CVD as well as for clinical cardiovascular events and cardiovascular-related death[6]. Steatosis itself adds to CVD risk and is pathogenetically linked to atherosclerosis as a consequence of atherogenic lipids. Other mechanisms, some involving prothrombotic and inflammatory mediators and angiogenetic factors, also mediate links between MASLD and atherosclerosis[7].

In support of this concept of shared drivers and mechanisms, there is evidence that new and emerging therapies, both in development and on the market, could have benefits across these diseases (Fig. 2)—helping to mitigate CVD risk and metabolic diseases and/or metabolic disturbances, preserving kidney function and reducing liver inflammation[8–13]. Data from 2016–2019 suggest that approximately 38% of the global population had MASLD, and the rates of both MASLD and its more advanced form, metabolic-dysfunction-associated steatohepatitis (MASH), are increasing[14]. Yet, clinically significant liver disease is under-represented and under-reported in CVD trials. For example, in the SELECT trial—which evaluated cardiovascular effects of the GLP-1 receptor agonist semaglutide in individuals who are overweight or obese—only 8.2% of patients had MASLD, and only 0.7% had MASH[15].

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https://doi.org/10.1038/s41591-024-03223-z

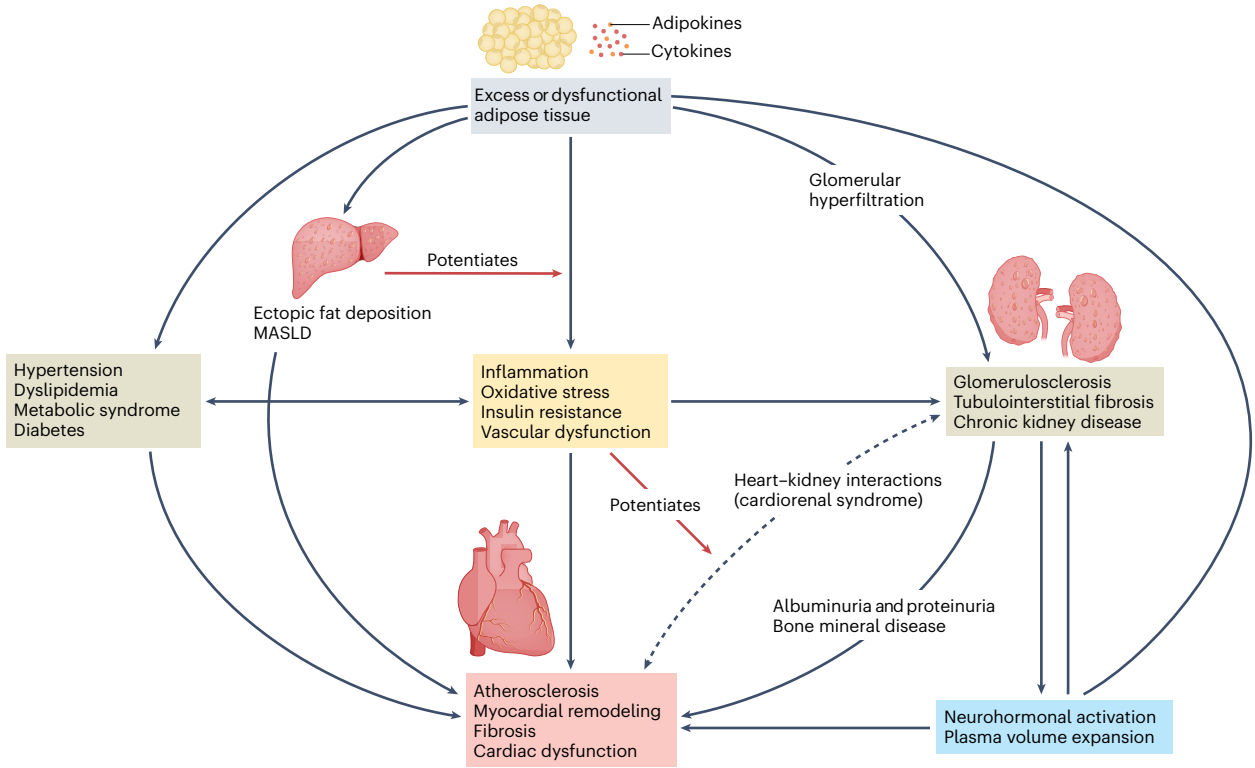

Fig. 1 | Conceptual diagram for CKM syndrome from the American Heart Association. Reprinted with permission from ref. 1, American Heart Association. The pathophysiology underlying CKM syndrome is shown. CKM syndrome most commonly originates from excess adipose tissue, dysfunctional adipose tissue or both. Multiple pathological processes related to dysfunctional adipose tissue result in insulin resistance and eventually hyperglycemia. Inflammation, oxidative stress, insulin resistance and vascular dysfunction are highlighted as central processes that lead to the development of metabolic risk factors, progression of kidney disease, potentiation of heart–kidney interactions and development of cardiovascular diseases. Metabolic risk factors and chronic kidney disease further predispose individuals to cardiovascular diseases through multiple direct and indirect pathways.

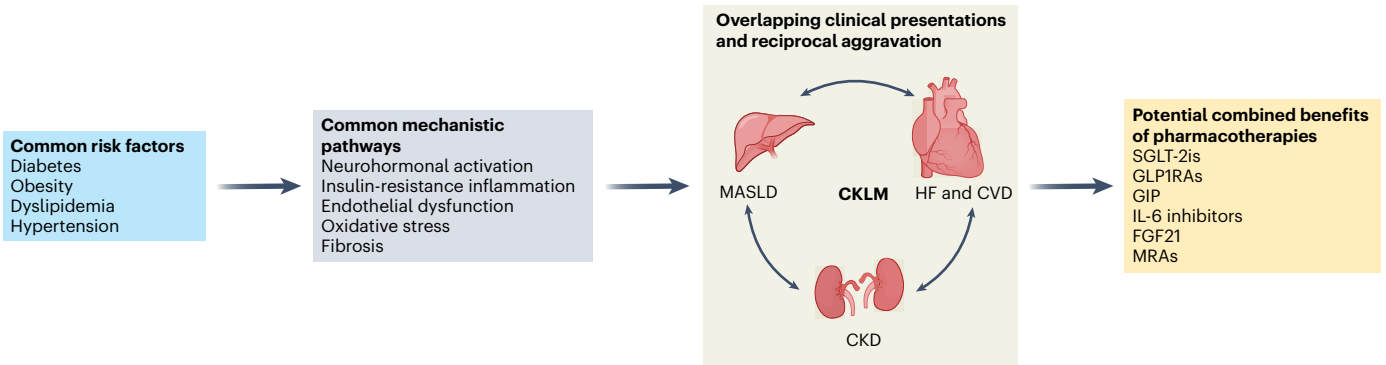

Fig. 2 | The intersection of CVD, metabolic disorders and CKD provides support for designing cross-organ clinical trials. Common risk factors, common pathology, overlapping clinical presentations and cross-organ benefits of pharmacotherapies provide support for a new paradigm for clinical trial design and consideration of a single cardiovascular–kidney–liver–metabolic disorder. CKLM, cardiovascular–kidney–liver–metabolic disorder; FGF21, fibroblast growth factor 21; GIP, glucose-dependent insulinotropic polypeptide; GLP1RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; IL-6, interleukin-6; MRAs, non-steroidal mineralocorticoid receptor antagonists; SGLT-2is, sodium-glucose cotransporter-2 inhibitors.

Thus, the prevalence of these liver conditions in SELECT was very low compared with the reported rates among individuals who are obese or overweight (MASLD, 70–75%; MASH, 34%)[16]. This could be related to the under-diagnosis of these conditions, or individuals with elevated alanine transaminase (ALT) or aspartate transaminase (AST) levels might not be referred to the trial by clinicians owing to safety concerns. Similarly, individuals with diagnosed CVD or CKD might be excluded from MASLD trials. It is advisable, therefore, for sponsors to revise commonly proposed exclusion criteria as the evidence evolves, to improve trial inclusivity and relevance of trial results to real-world populations. Conducting kidney and hepatic-impairment studies in phase 2 studies could help minimize exclusion of participants from phase 3 studies.

We suggest that a holistic approach should be taken in future trials, in which enrolled patients are representative of the confluence of CKM diseases, and that cardiology and nephrology trialists work with endocrinology, diabetology and hepatology trialists to develop common protocols when relevant. Specifically, we call for inclusion of patients with MASLD in cardio–kidney–metabolic trials (along with

Table 1 | Key considerations when including liver outcomes in CKM trials

Phase 2 trials	Phase 3 trials
• Establish biological rationale for testing drug for multiple end organ diseases. • Establish the recommended phase 2 dose before starting the trial. The dose needs to be adequate to impact all end-organs of interest. • In short-term phase 2 studies, measure disease activity or other outcomes that can show changes within the duration of the trial. • Establish safety profile across end-organ disease states, including those that are likely to be comorbidities. • Positive studies will support integrated CKLM phase 3 trials. • Be wary of over-interpretation of post hoc analyses of efficacy in subpopulations.	**Study population:** • Include subpopulations with enough disease to warrant drug intervention. • Use NIT or other routinely available methods to identify patient populations so that trial concepts can be translated into practice. **Design:** • Ensure adequate sample size providing sufficient statistical power for individual outcome measures that will go into product labeling. • Consider post-randomization events that can modify the outcomes of subpopulations. **Endpoints:** • Consider NIT-based versus composite outcomes to capture holistic benefits. • Minimize burden on participants.

measurement of liver outcomes) and vice versa—that is, inclusion of patients with CKD and CVD in MASLD trials, when data suggest mechanistically plausible, multiple-organ benefits. In this Perspective, we discuss the implications of this new paradigm for clinical trial design, with a focus on target patient populations and liver endpoints. We outline considerations for regulatory approval, priorities for implementing this more-inclusive approach and recommendations for conducting future clinical trials.

Clinical trial design considerations

The goal of including multi-organ outcomes in clinical trials is to increase the efficiency of drug development by using studies targeting one disease state to collect data on related conditions, to potentially pursue multiple efficacy or safety claims and approval for multiple indications and, ultimately, to facilitate early patient access to new and improved treatments.

This new integrative paradigm brings some challenges that need to be recognized and addressed. These involve defining the right target patient population with multi-organ disease, considerations for the sample size of the trial population, issues with the execution of multi-specialty trials, agreement on appropriate and clinically meaningful organ-specific efficacy and safety endpoints, validation of multi-organ composite endpoints and progression through multiple regulatory approval departments. Key considerations relating to these topics are discussed below and summarized in Table 1.

Lessons from kidney-disease trials

Just as patients with MASLD and/or MASH (MASLD/MASH) are currently excluded from many CKD and/or CVD (CKD/CVD) trials, patients with poor baseline kidney function were historically excluded from CVD trials (a phenomenon known as 'renalism'). Over the past decade, however, risk stratification and trial inclusion with respect to kidney disease have evolved substantially. Since 2015, an increasing number of CVD trials showed kidney benefits as key primary or secondary outcomes[10,17–20], leading to the design of kidney outcomes trials with sodium-glucose cotransporter-2 (SGLT-2) inhibitors, non-steroidal mineralocorticoid receptor antagonists (MRAs) and glucagon-like peptide 1 (GLP-1) receptor agonists.

These trials prioritized enrollment of patients with high-risk CKD on the basis of a low estimated glomerular filtration rate and albuminuria levels, as defined by the Kidney Disease Improving Global Outcomes (KDIGO) risk categorization, which meticulously maps baseline risk across 10 cardiovascular and kidney outcomes, including death[21]. The KDIGO risk map offers a framework to design combined cardio–kidney endpoints, including timeframes of when these occur, and event rates by baseline KDIGO risk category[21]. Designing trials such as FIGARO and FIDELIO, which assessed cardiovascular and kidney outcomes as primary endpoints, in patients with CKD and diabetes thus became an organic and logical next step[19,20].

Therefore, the increased enrollment of CKD patients and the addition of kidney endpoints in CVD trials facilitated the emergence and success of cardio–kidney trials. Similarly, we anticipate that the improved enrollment of patients with MASLD/MASH and addition of liver endpoints in CVD/CKD trials could help the emergence of integrated cardiovascular–kidney–liver–metabolic disorder trials. This can be done progressively, for example by initially evaluating liver endpoints as secondary outcomes in CVD/CKD trials, while continuing to refine feasibility as well as patient phenotyping and risk scoring,

Target patient populations

Trial sponsors and investigators tend to be particularly reluctant to include patients with liver diseases in clinical trials, because many drugs are metabolized in the liver, raising the potential for adverse effects[22,23]. This highlights the need for hepatic-impairment studies in phase 2 trials to justify inclusion criteria and dosing adjustments in phase 3 trials. Rather than excluding those with liver conditions, CKM trial populations should in fact be enriched for these patients, owing to the shared mechanisms and the potential for multi-organ benefits mentioned above.

Patients should be screened for MASLD but not excluded without a compelling rationale, such as a known hepatic safety risk associated with the intervention. Depending on the context, screening and trial enrollment can be based on a MASLD risk score, such as the Fibrosis-4 index (FIB-4)—which uses standard, widely available laboratory variables and is inexpensive compared with transient elastography[24,25]. We contend that those with MASLD fibrosis scores of F0 or F1/2, who are not at a high risk for adverse liver outcomes, should be included in CKM trials. There is a need to reconsider the routine practice of excluding patients on the basis of ALT and AST values greater than two times the upper limit of normal (ULN). Such exclusion criteria should be used only if there is a compelling pharmacological reason to do so, on the basis of early phase 1 and phase 2 studies with the investigational treatment. In MASH trials, a serum ALT level of ≥200 IU l^{-1} is routinely used as an exclusion criterion, given that higher levels can be indicative of another disease process. It is worth exploring whether MASLD comorbidity (similar to CKD) interacts with the cardiovascular benefit of a drug, by stratifying patients at enrollment according to presence or absence of MASLD, or running MASLD subgroup analysis.

Several classes of drugs indicated for obesity, dyslipidemia, type 2 diabetes, CVD and CKD—such as SGLT-2 inhibitors, GLP-1 receptor antagonists, lipid-lowering agents and non-steroidal MRAs—have also been shown to have beneficial effects on liver parameters[8–13,26,27], and are becoming standard of care in CKM conditions (Fig. 3). These drugs are likely to be prescribed as background therapies in patients with CKM comorbidities enrolled in future MASLD/MASH trials. The residual risk and event rate associated with modern background therapy needs to be re-evaluated in real-world data and/or in ongoing trials, because it could have important consequences for trial sample-size calculations. Also, the potential interaction between background therapy and any MASLD/MASH investigational agent should be considered, which could necessitate stratification of patients according to background therapy.

Liver endpoints in cardiovascular–kidney–metabolic syndrome trials

The particular strategy for embedding liver endpoints in CKM trials depends on the target patient population. Enriching CKM trials with MASLD inclusion criteria might not allow for collection of liver outcomes, unless the trial size is large enough and the duration is sufficient.

https://doi.org/10.1038/s41591-024-03223-z

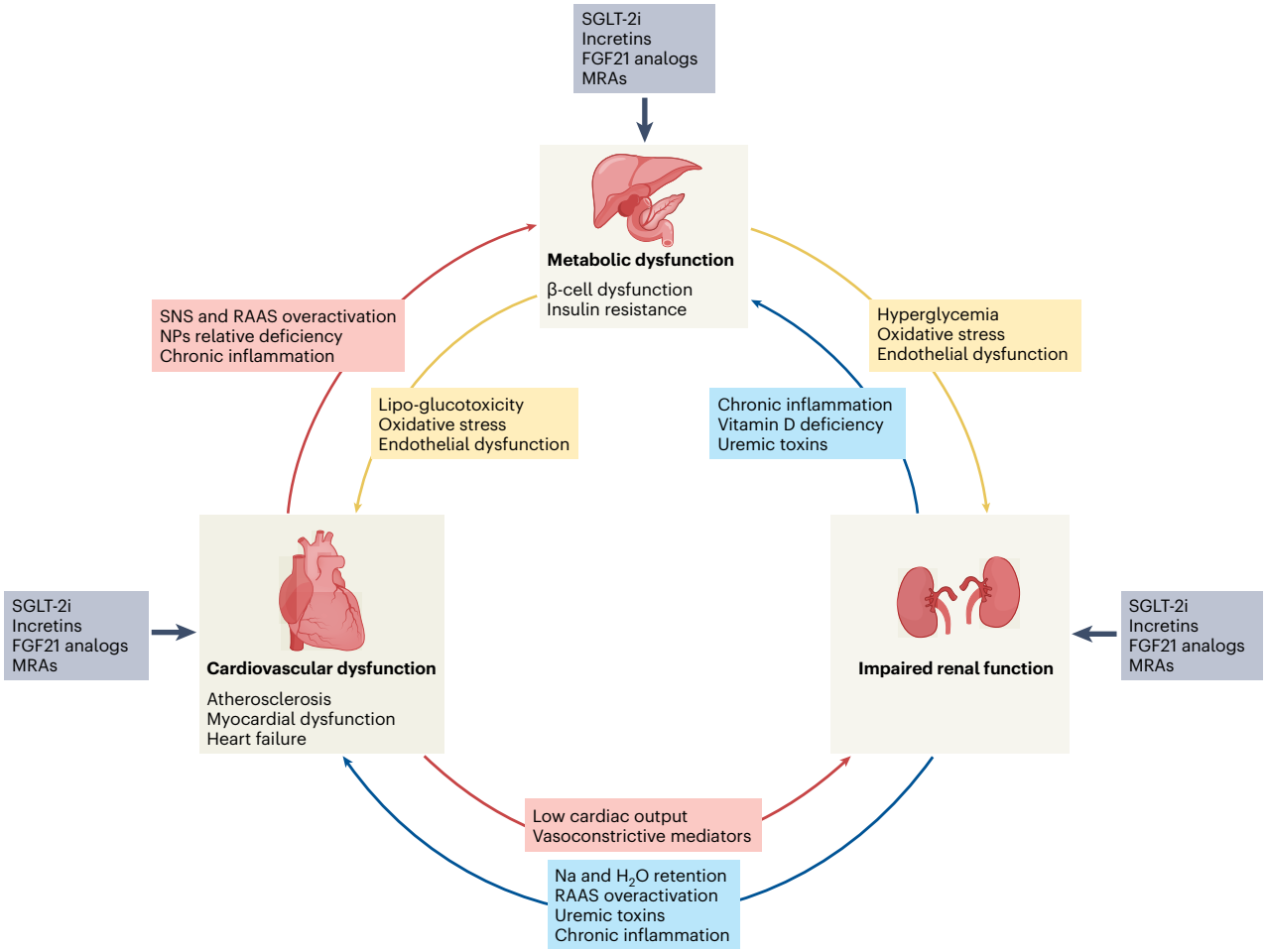

Fig. 3 | Cardio–metabolic–renal interconnections and therapeutic options. Reprinted with permission from ref. 54, BioMed Central. Data have shown that the beneficial effects of drugs such as SGLT-2, incretins, MRAs and FGF21 analogs extend beyond single organ systems. SNS, sympathetic nervous system; RAAS, renin–angiotensin–aldosterone system; NPs, natriuretic peptides.

However, by selecting high-risk patients for inclusion, it might be feasible to measure clinical (hard) liver outcomes, because endpoints in CKM trials might be enriched for MASH.

The gold standard for MASH diagnosis, as well as for monitoring progression, is still liver biopsy. But it is invasive and cannot be used for exploratory purposes, as an enrichment or inclusion criterion or as the basis for endpoints in CKM trials. Instead, non-invasive tests (NITs) can be sufficient to detect possible signals of liver improvement in CKM trials.

Non-invasive tests. Patients in CKM trials should be assessed at baseline and follow-up visits for underlying liver disease. The FIB-4 index is a useful, validated measure based on age, AST and ALT levels and platelet counts[28]. The sensitivity and specificity for identifying advanced fibrosis with a rule-in cut-off point of >2.67 were 33% and 98%, respectively, and for a rule-out cut-off of <1.3 were 74% and 71%, respectively. The fibrosis score is a strong predictor of cardiovascular events[29,30], and although clinically meaningful fibrosis is uncommon in early-stage liver disease, it may develop over long-term follow-up. From a practical perspective, using combinations of tests for liver outcomes, which are readily available, should not place a high burden on patients. Box 1 summarizes useful NITs and their potential roles in phase 2 and 3 clinical trials[25,31–38]; liver biopsy should not be necessary in CKM trials to detect signals of hepatic efficacy and safety.

It is important to agree on liver endpoints (including NITs) with regulatory authorities during the early stages of trial design. Data from the Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) project suggested that none of the currently available single markers or multi-marker scores were acceptable replacements for biopsy in detecting MASH and clinically significant fibrosis, although many would be useful for trial enrichment[39]. The Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBLE) consortium is conducting research to facilitate qualification of biomarkers for MASH diagnosis and disease monitoring through the US Food and Drug Administration (FDA) Biomarker Qualification Program (BQP), and has published data on diagnostic biomarkers as a step toward qualification[35,36].

Clinical outcomes. Liver-specific clinical events (including liver transplant, ascites, hepatic encephalopathy and variceal hemorrhage) are rare, unless the trial population is enriched for such outcomes. Current MASLD trials do not include hard liver outcomes as endpoints and have an insufficient follow-up duration to capture them. Only MASH trials including high-risk patients, such as those with grade F2–F4 fibrosis, can accrue liver outcomes and thus can be designed as event-driven trials. CKM trials are usually large and have long follow-up periods. If the trials are enriched with patients with MASLD at risk of liver outcomes, these hard outcomes can occur with sufficient frequency as to be worth embedding in a multi-organ composite endpoint. Collecting hard liver endpoints in ongoing or future CKM trials could help estimate effect sizes and concordance patterns with cardiovascular and kidney events. There is growing interest in composite cardio–kidney endpoints in

https://doi.org/10.1038/s41591-024-03223-z

BOX 1

Potential roles of non-invasive tests in CKM trials

(i) Useful NITs

ALT:

- Strong predictor of hepatic benefit in active NASH

FIB-4:

- Predictive of histological fibrosis stage in NASH
- Predictive of hepatic benefit in fibrosis
- Significant association with heart failure
- Predictive of liver-related events in NAFLD

Enhanced liver fibrosis (ELF) score:

- Classifies risk of disease progression
- Predictive of histological fibrosis stage in NASH
- Predictive of hepatic benefit in fibrosis
- Associated with progression to cirrhosis in NASH

Pro-C3 (propeptide of type III collagen):

- Biomarker of fibrogenesis
- Correlates with severity of steatohepatitis and fibrosis stage

Liver stiffness measured by vibration-controlled transient elastography:

- Predictive of histological fibrosis stage in NASH
- Increased baseline score associated with NAFLD progression
- Predictive of hepatic benefit in fibrosis
- Predictive of liver-related events in NAFLD

(ii) Potential roles of NITs in CKM trials

Phase 2:

- Exclude patients with FIB-4>2.6, or perform hepatic-impairment studies for investigational therapies without established safety profiles
- Report FIB-4 distribution in baseline demographics
- Assess changes in activity markers including NIS4, liver fat content and liver enzymes

Phase 3:

- Stratify for FIB-4 in advanced phase trial, if safety is not an issue
- Enrich a subpopulation for liver outcomes: ELF test, vibration-controlled transient elastography (possibly consider Pro-C3)

CKM trials[40]. It may be worth considering an additional step, to explore the feasibility and regulatory acceptability of composite cardio–kidney–liver endpoints.

Composite cardio–kidney and liver outcome endpoints. When enriched for MASLD criteria at enrollment, follow-up in CKM outcome trials should be of adequate duration to observe the development of liver outcomes, and the sample size should be large enough and sufficiently powered to assess these outcomes—although not necessarily in isolation. This is because liver outcomes occur at a relatively low annual rate in patients with MASLD, so that assessment of individual outcomes often lacks statistical power—although they could be included as part of a composite cardio–kidney–liver outcomes endpoint. Analysis of appropriate current and future epidemiological and trial data could help estimate the rates of CVD, kidney and liver outcomes—alone and in combination—to inform sample-size calculations and duration of trials with cardio–kidney and liver outcome endpoints.

Conditions for a valid composite endpoint could be difficult to meet. Indeed, composite endpoints might oversimplify a more complex pattern. In addition, components vary in their clinical importance, and treatment effect can vary across components. Ideally, in a reasonable composite endpoint, individual components should be relatively similar in their clinical importance to patients; they should be biologically and mechanistically related; and they should be influenced in a concordant way by the therapy[41]. Endpoints within an ordered cardio–kidney–liver composite endpoint can be ranked from highest to lowest priority and analyzed hierarchically in this order. Although challenging, composite cardio–kidney–liver endpoints should be evaluated in future trials, because they might help improve the design of CKM–MASLD/MASH trials. As well as making sense clinically, by treating patients in a more holistic way, composite endpoints might help accrue more events and therefore decrease the required trial sample size.

Patient-reported outcomes. Disease-specific patient-reported outcomes (PROs), both physical and mental, can capture clinical impairment in patients with CKM disease as well as in patients with MASLD[42]. Improvements in fibrosis or liver biomarkers have been correlated with improvements in PRO domains[43,44], which represent clinically meaningful outcomes. Improvements in quality-of-life indicators are valued by regulators and can facilitate approval for CKM drugs[45]. Therefore, PROs should be considered in CKM trials that also enroll patients with MASLD. In addition to generic instruments such as the EuroQol-5D (a standardized quality-of-life measure), there are disease-specific tools that have been validated in patients with liver diseases—such as the Chronic Liver Disease Questionnaire and NASH CHECK[46,47].

Importantly, when analyzing PRO (or, indeed, NIT) endpoints in patients with multiple comorbidities in CKM trials, it is important to take into consideration the competing risks of mortality and cardiovascular outcomes. The risk of missing data related to mortality in long-term trials can be mitigated by imputation methods, which have well-known limitations. The safest way to get interpretable PRO results is to examine the data before there is excessive data loss. However, if treatment effects take time to manifest (for example, mediated by weight loss), effects on PROs might be hard to demonstrate at early timepoints.

Regulatory approval considerations

Regulatory pathways in Europe and the United States segment pre-cirrhotic and cirrhotic MASH, with full approval requiring demonstration of clinical benefit on a liver composite outcome (Table 2)[48–51]. From a regulatory perspective, approved drugs for MASH with fibrosis still represent an unmet need, and biopsy is required for accelerated approval in this indication—with full approval relying on demonstration of clinical benefit. MASH should be considered separately from MASLD, and trials should be dedicated specifically to MASH. Accelerated approval pathways are available, but these require liver-biopsy-based outcomes. Approving a MASH drug does not necessitate demonstration of cardiovascular benefits; however, cardiovascular safety must be monitored. Also, MASH trials are generally underpowered to assess cardiovascular outcomes and, even when there are observed differences in cardiovascular safety outcomes, these are unlikely to reach statistical significance.

In March 2024, the US FDA approved resmetirom, the first drug for the treatment of MASH, under the accelerated approval pathway[52]. Using baseline and 12-month biopsies, the MAESTRO-NASH trial showed greater rates of MASH resolution and an improvement in liver scarring with resmetirom compared with placebo[53]. Although biopsies were used in the study, the FDA's prescribing information does not require a liver biopsy for diagnosis. The drug was approved on the basis of a surrogate endpoint that is likely to predict clinical benefit; however, a postapproval study to verify clinical benefits is required, which is underway in the ongoing MAESTRO-NASH trial.

Table 2 | FDA and EMA guidance for MASH drug development

	Pre-cirrhotic MASH	Cirrhotic MASH
Population	• NAS score ≥ 4 • Fibrosis stage F2, F3 • EMA: F1 could be included for exploratory purposes	• No minimum NAS score requirement • Fibrosis stage F4
Requirement for full approval	• Clinical benefit on composite outcome • Progression to fibrosis stage F4 • Reduction in hepatic decompensation events (for example, ascites, variceal bleeding, encephalopathy) • Change in MELD score to >15 • Liver-transplant rate • All-cause mortality rate	• Clinical benefit on composite outcome • Complications of ascites (for example, spontaneous bacterial peritonitis, diuretic-resistant ascites, hepatic pleural effusion) • Change in MELD score to >15 • Liver-transplant rate • All-cause mortality rate
Accelerated or conditional approval pathway	• Yes • US FDA: NASH resolution *or* improvement in fibrosis • EMA: NASH resolution *and* improvement in fibrosis	• No
Cardiovascular impact	• US FDA: cardiovascular safety should be adequately monitored • EMA: focus cardiovascular safety evaluation on MACE and on cardiovascular risk factors	

Adapted from refs. 48–51. EMA, European Medicines Agency; MACE, major adverse cardiovascular events; MELD, Model for End-Stage Liver Disease; NAS, NAFLD activity score.

Although biopsy is the gold standard for accelerated approval of treatments for a MASH indication, NITs could play a larger role in clinical trials in the MASLD population in the future, not just for trial enrichment but also for marketing approval. However, there is a need for further validation of NITs in patients with MASLD, for treatment response across multiple mechanisms of action and timeframes. As mentioned above, work is underway to validate single and combined NITs for this use[35,36,39]. In addition, prevention of MASH with fibrosis is likely to be an approvable outcome, as is the case for drugs for prediabetes that delay the onset of type 2 diabetes.

Investigators designing MASLD trials can learn from the adjudication methodology used for cardiovascular outcomes in CKM trials, ensuring that best practices are followed and key data are collected to allow robust adjudication. A priori definition-based adjudication of cases is most likely to be acceptable to regulators. In CKM trials, composite cardiovascular and kidney outcomes are often used. Ideally, cut-offs for events are well-defined in the study protocol, and the same should be true for liver outcomes.

Priorities and challenges for implementation of multi-organ clinical trials

Currently, regulatory approval of MASH drugs still requires liver biopsy data. It might be challenging to have a treatment approved for MASH on the basis of liver biopsy data collected in a CKM trial, even if the trial is enriched for patients with MASH, because of the extra burden imposed by liver biopsy on patients.

For treatments with the potential for cardio–kidney, metabolic and liver benefits, pragmatic multi-organ trials have the advantage of addressing the confluence of commonly coexisting diseases. However, to assess the feasibility of running a MASLD or MASH trial embedded in a CKM trial (that is enriched for patients with liver disease), further research is needed to assess the timing and rate of MASLD or MASH endpoints relative to CKM endpoints. Collaborative research with multiple specialists, including cardiologists, nephrologists, endocrinologists, diabetologists and hepatologists, is crucial to characterize patients with coexisting CKM and MASLD or MASH in prospective, longitudinal cohorts with sufficient duration of follow-up. Further, in ongoing and future CKM trials, stakeholders should be encouraged not to exclude patients with MASLD/MASH. Appropriate liver data, including NITs and other outcomes, should be prospectively collected—in consultation with regulatory agencies regarding what evidence is needed for approvals.

Existing informative trials and biorepositories can be harnessed to generate data on the confluence of cardio–kidney metabolism and MASLD/MASH, their common risk factors and underlying mechanisms, and the progression and interplay of the respective cardiac, kidney and liver component diseases and corresponding respective outcomes. Data-mining and artificial intelligence are powerful tools for analyzing the vast amount of such data across specialties.

In most instances so far, drug development—as driven by the current regulatory framework—has pursued approval for single indications. Guidance from regulatory agencies might need to evolve to consider multi-disease and/or multi-organ endpoint trials in the case of single drugs with potentially multiple indications. Regulatory agencies may consider increasing communication between internal subdivisions dedicated to distinct diseases, to encourage investigation of liver benefits in CKM trials and to facilitate consideration of MASLD/MASH approval on the basis of convincing liver benefits in CKM trials.

Conclusion

To date, many indications have been studied in unique development programs, with separate trials for MASH, glucose control, lipid lowering, major adverse cardiac events, weight loss, heart failure, CKD and other indications—with ad hoc design, inclusion criteria, allowable background therapy, trial duration and endpoints. Such was the case for SGLT-2 inhibitors and GLP-1 receptor agonists, which were initially approved to lower glucose levels, and were subsequently approved for cardiac and kidney benefits or for weight loss. We suggest that, as science and our understanding of underlying pathogenic mechanisms evolve, the clinical trial landscape for chronic diseases must also evolve to allow treatments to be tested for more than one disease at a time, in unique development programs aiming to evaluate multi-organ benefits for regulatory approval purposes based on appropriate endpoints.

Data availability

No new data were generated or analyzed in support of this research.

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Acknowledgements

This article was generated from discussions at the second annual MOSAIC (Metabolic multi-Organ Science Accelerating Innovation in Clinical Trials) meeting held in October 2023 (https://mosaic-nash.tmacademy.org/). MOSAIC is a strategic workshop for high-level dialog between clinical trialists, industry representatives, regulatory authorities and patients. We thank P. Lavigne and S. Portelance for medical writing and editing services (funded by the MOSAIC group). The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organizations with which the author(s) is/are employed/affiliated. MOSAIC meetings are supported by unrestricted educational grants from 89Bio, AstraZeneca, Boehringer Ingelheim, Echosens, Gilead, Inventive, Kowa, Madrigal Pharmaceuticals, Merck, Novo Nordisk, Northsea Therapeutics and Olink, with no allocation for speakers' fees.

Author contributions

All co-authors contributed to conceptualization of the MOSAIC meeting, including the aims and selection of the topics. F.Z. drafted the initial manuscript; all authors critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Competing interests

F.Z.: consulting fees from Applied Therapeutics, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Boston Scientific, Cardior Pharmaceuticals, Cereno Scientific, Cellprothera, CVRx, Merck, Novartis, Pfizer and Servier and is the co-founder of cardiorenal and the founder of CVCT. A.J.S.: institutional research grants from Conatus, Gilead, Mallinckrodt, Boehringer Ingelheim, Novartis, Bristol Myers Squibb, Merck, Lilly, Novo Nordisk, Fractyl Health, Madrigal, Inventiva Pharma and Covance; research grants or contracts from Gilead, Mallinckrodt, Salix, Novartis, Galectin, Bristol Myers Squibb and Sequana Medical; royalties or licenses from Elsevier and UpToDate; consulting fees from Genfit, Gilead, Mallinckrodt, Pfizer, Salix, Boehringer Ingelheim, Novartis, Bristol Myers Squibb, Merck, HemoShear Therapeutics, Lilly, Novo Nordisk, Terns, Albireo Pharma, Jansen, Poxel, 89bio, Siemens, NGM Bio, Amgen, Regeneron, Genentech, Alnylam, Roche, Madrigal, Inventiva Pharma, Covance, ProSciento, HistoIndex and Path AI; an unpaid consultancy for Intercept, Sequana, Fractyl Health and AstraZeneca; a leadership role on board of Sanyal Bio (president, unpaid); stock or stock options from Sanyal Bio, Genfit, Exhalenz Bioscience, HemoShear Therapeutics, Durect, Indalo Therapeutics, NorthSea Therapeutics, Tiziana Life Sciences and Rivus Pharmaceuticals; receipt of equipment, materials or drugs from Contaus Pharmaceuticals, Immuron and Echosens-Sandhill; ongoing research collaborations (no direct funding) with Echosens-Sandhill, Owl Pharma, Second Genome, and Siemens; and employment with Sanyal Bio. J.B.: consulting fees from 3ivelabs, Abbott, Amgen, American Regent, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, Cytokinetics, Edwards Life Sciences, Element, Faraday, G3 Pharmaceutical, Imbria, Impulse Dynamics, Innolife, Inventiva, Ionis, Janssen, LivaNova, Lexicon, Medtronic, Merck, Novartis, Novo Nordisk, Otsuka, Occlutech, PharmaCosmos, Roche, Sanofi, Secretome, Sequana, Tricog and Vifor; and payment or honoraria for lectures, presentations or speakers bureaus from Novartis, Boehringer Ingelheim-Lilly, AstraZeneca and Impulse Dynamics. V.M.: received institutional research grants from 89bio, Akero Therapeutics Inc., Albireo Pharma Inc., Aligos Therapeutics, Alimentiv, AlloVir, Altimmune Inc., AMRA Medical AB, Arrowhead Pharmaceuticals, Assembly Biosciences, BioMarin Pharmaceutical Inc., ChemomAb Ltd., Covance Inc., Cymabay Therapeutics, DDL Diagnostic Laboratory, Dynavax Technologies, E-Scopics, EA Pharma Co. LTD, Echosens, Eiger BioPharmaceuticals, Eli Lilly & Company, ENYO Pharma SA, Galectin Therapeutics, Gilead Sciences Inc., GlaxoSmithKline PLC, HepQuant, High Tide Therapeutics, HistoIndex, Icare USA, Immunocore, Intercept Pharmaceuticals, Inventiva Pharma, Janssen, LabCorp, LG Chem Life Sciences, Andos Therapeutics Inc., Merck & Company, Inc., NorthSea Therapeutics, Novartis Pharma AG, Novo Nordisk, Oncoustics, Pharmanest, Pliant Therapeutics, Qiagen Sciences, Regeneron Pharmaceuticals, VBI Vaccines Inc., Vir Biotechnology Inc. and Virion Therapeutics LLC. S.A.H.: grants or contracts from Akero, Altimmune, Axcella, Bristol Myers Squibb, Corcept, CymaBay Therapeutics, Enyo, Galectin, Genentech, Genfit, Gilead, GlaxoSmithKline, Hepion, Hightide, Immuron, Intercept, Inventiva, Ionis, Madrigal, NGM Bio, Novartis, Novo Nordisk, NorthSea Therapeutics, Pfizer, Poxel, Sagimet Biosciences, Terns and Viking; consulting fees from Akero, Aligos, Altimmune, Arrowhead, Boxer Capital, Chronwell, Echosens, Foresite Labs, Galectin, Galecto, Gilead, GlaxoSmithKline, Hepagene, Hepion, Hepta Bio, HistoIndex, Humana, Intercept, Ionis, Inventiva, Madrigal, Medpace, Merck, NeuroBo Pharmaceuticals, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, Sonic Incytes, Sagimet Biosciences, Terns and Viking; and stock or stock options from Akero, Altimmune, Axcella, Bristol Myers Squibb, Corcept, CymaBay Therapeutics, Enyo,

Galectin, Genentech, Genfit, Gilead, GlaxoSmithKline, Hepion, Hightide, Immuron, Intercept, Inventiva, Ionis, Madrigal, NGM Bio, Novartis, Novo Nordisk, NorthSea Therapeutics, Pfizer, Poxel, Sagimet Biosciences, Terns and Viking.

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Peer review information *Nature Medicine* thanks Janani Rangaswami, Aleksander Krag and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Karen O'Leary, in collaboration with the *Nature Medicine* team.