



PARIS
MASH
MEETING

Integrated Trial Design - challenges and opportunities for MASLD to be included in CRM trials

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Disclosures

Steering committees and DSMB and Advisory boards: Alnylam, Bayer, Biopeutics, Boehringer, Cellprothera, Cereno, Corteria, CVRx, Merck, Owkin, Ribocure, Roche.

Equities, Stock options: Polygon, Cereno pharmaceutical and CVCT

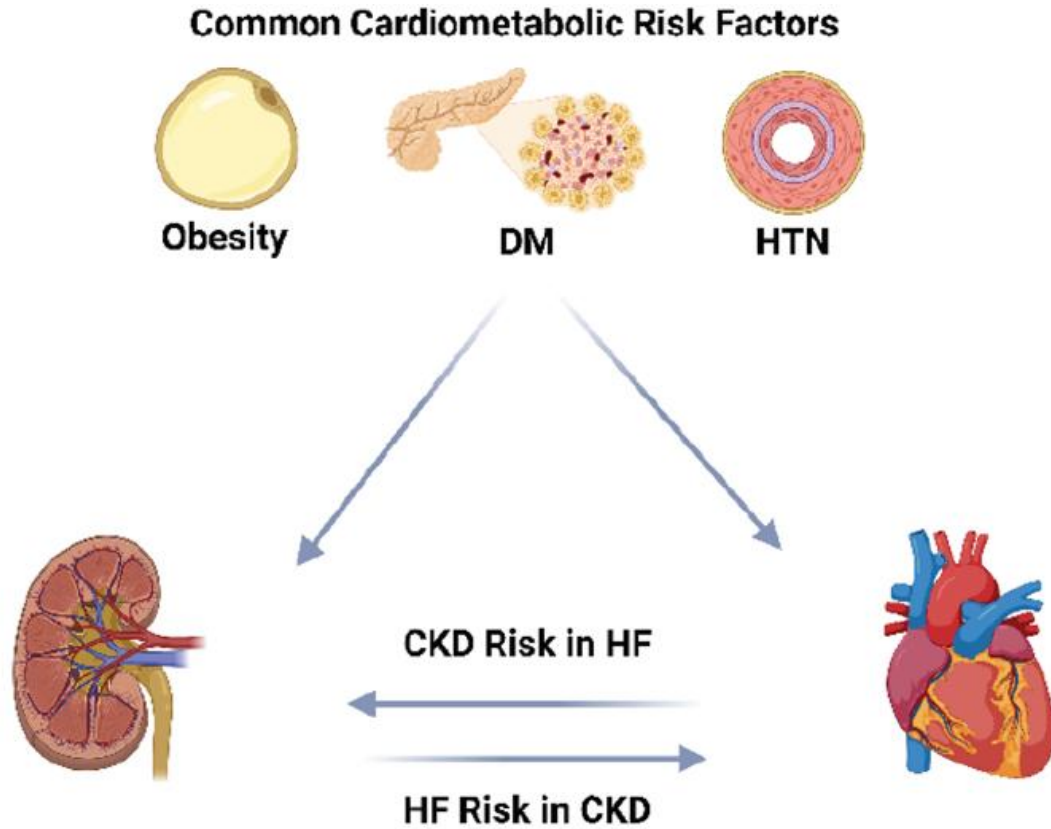
Lectures, Speakers' bureau, Bayer, Boehringer, Centrix, CVRx, Lupin, Opalia Recordati, Merck, NovoNordisk, Viatris.

What is a difference between god
and cardiologist?

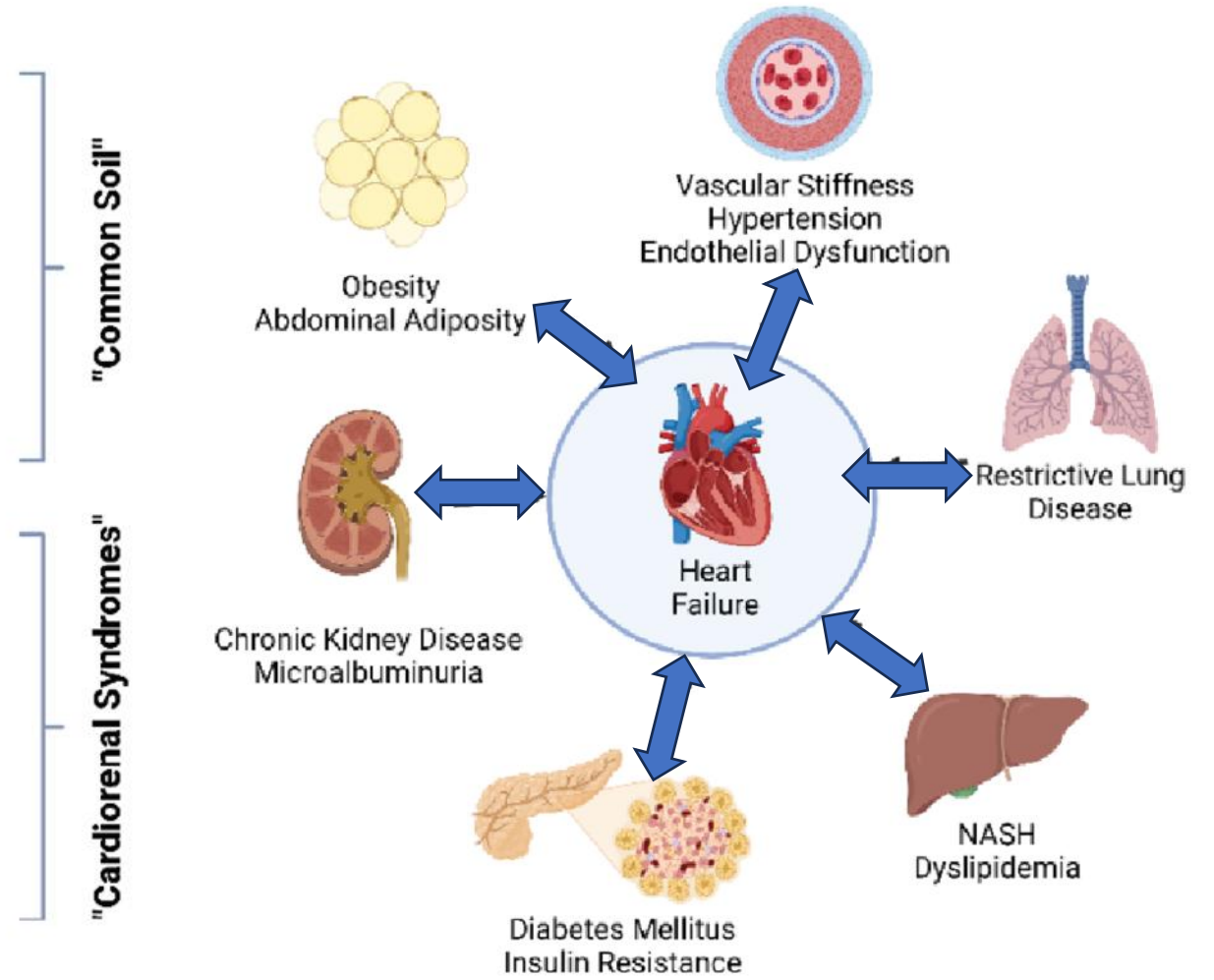
Cardiologist says he is god but god never
says he is cardiologist....



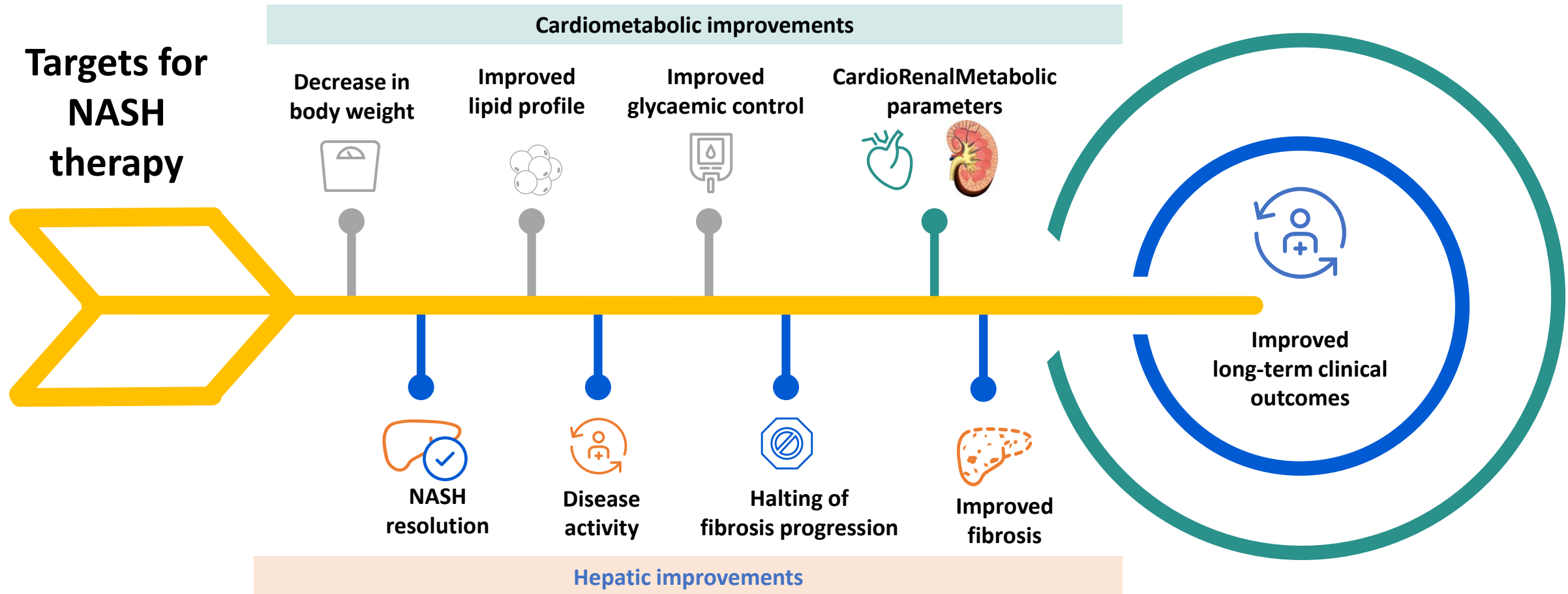
Siloed Cardiocentric



Holistic



Pharmacological management of NASH should aim to stabilise liver disease activity and address cardiometabolic comorbidities



Exclusion of Liver Disease and Underutilization of Liver-Specific Endpoints in Heart Failure Trials

Liver disease and liver-specific endpoints remain underexplored in major heart failure trials

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Nicolas Girerd, MD, PhD,^{f,g} Nicholas W.S. Chew, MBBS,^{h,i} Michael L. Volk, MD,^j Javed Butler, MD, MPH, MBA,^{a,k}
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- 43 trials were included (N . 128,773; mean age: 68.5 years; women: 35.8%).
- 32/43 reported liver-related exclusion criteria
- 19/43 Nineteen trials excluded patients based on abnormal LFTs (AST, ALT, or ALP, bilirubin)
- 10/43 trials excluded patients with any evidence of known significant liver disease.
- One/43 trial reported the proportion of MASLD.
- 8/43 trials reported baseline LFTs (Most were normal)
- 8/43 Eight trials reported liverspecific data
- None reported them as key secondary or prespecified exploratory endpoints,
- 4/43 trials examined the association between composite cardiovascular outcomes and liver markers
- One single trial/43 examined the association between in-hospital mortality, worsening of HF, or kidney function and baseline LFTs.
- One trial/43 evaluated the association between NITs (NFS and FIB-4 score) and composite cardiovascular outcomes.
- 4/43 trials reported effects of HF therapy on liver-specific markers.

CVD and related endpoints remain underrepresented in MASLD trials

- 19 MASLD trials
- N: 11,689 patients; mean age: 49.4 years; women: 49.9%.
- 4/19 trials reported baseline CV assessment.
- 6/19 trials reported proportion of patients with hypertension
- 2/19 trials reported ASCVD.
- no trial assigned hard outcomes such as CV death, HF hospitalization, or new-onset HF as key secondary endpoints.
- MACE was the most commonly reported safety/exploratory endpoint.

Cardiovascular-Kidney-Liver Metabolic (CKLM) Interactions in Heart Failure: Breaking Down Silos

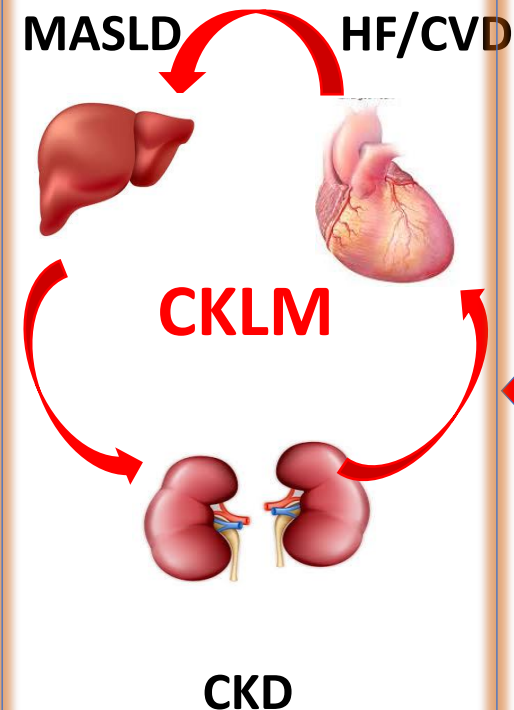
**Common
risk factors**

Diabetes
Obesity
Dyslipidemia
Hypertension

**Common
mechanistic
pathways**

**Neurohormonal
activation**
Insulin resistance
Inflammation
**Endothelial
dysfunction**
Fibrosis
Oxidative stress

**Overlapping
clinical
presentations**



**Potential combinatorial
benefits
of pharmacotherapies**

SGLT2is
GLP1RAs
GIP




IL6 inhibitors
FGF21
MRAs
.../...

<https://doi.org/10.1038/s41581-023-00789-8>

Chronic cardiovascular–kidney disorder: a new conceptual framework

Carmine Zoccali, Francesca Mallamaci, Jean-Michel Halimi, Patrick Rossignol, Pantelis Sarafidis, Raffaele De Caterina, Robert Giugliano & Faiez Zannad

 Check for updates

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EDITORIAL COMMENT

Heart Failure and Kidney Disease in Type 2 Diabetes 2 Sides of the Same Coin*

Faiez Zannad, MD, PhD

Perspective

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

Integrating liver endpoints in clinical trials of cardiovascular and kidney disease

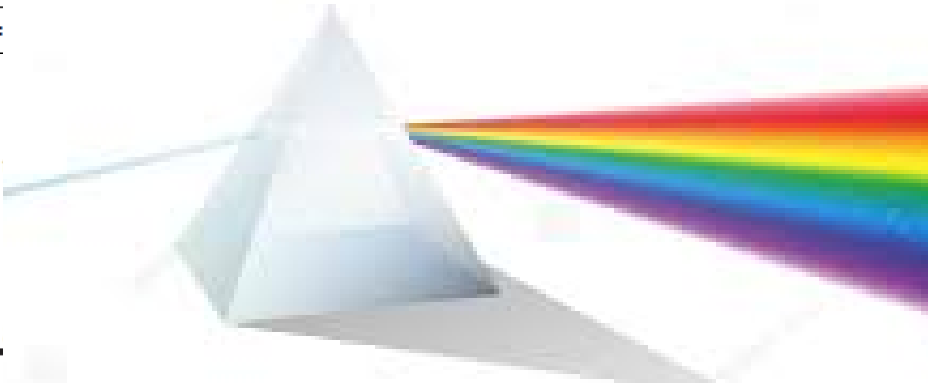
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ca Miller⁵ &

Accepted:

VOL. 80, NO.

Circulation



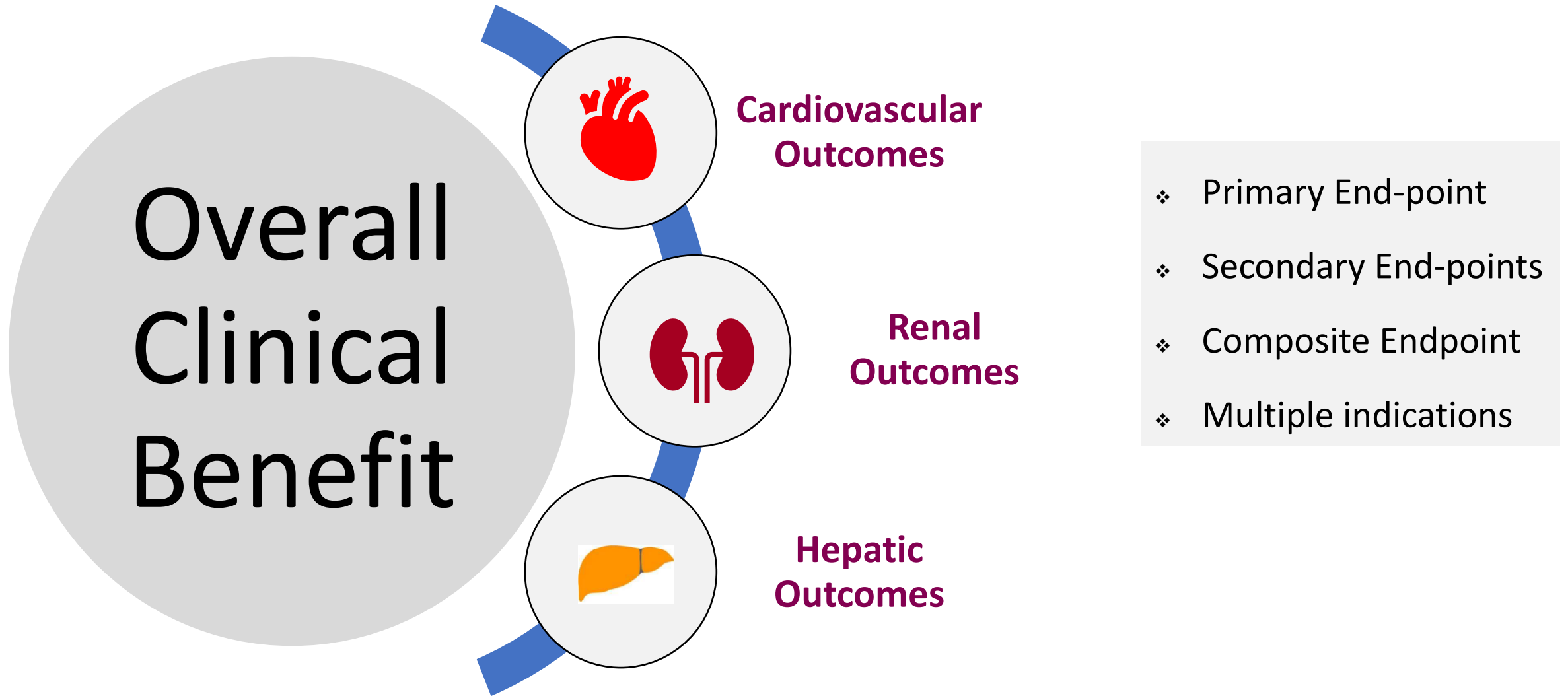
INTERORGAN CROSSTALK IN HEART FAILURE AND CARDIOMETABOLIC DISEASES COMPENDIUM

Cardiovascular, Kidney, Liver, and Metabolic Interactions in Heart Failure: Breaking Down Silos

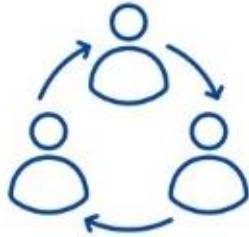
Chang Jie Mick Lee¹, Leah B. Kosyakovsky², Muhammad Shahzeb Khan³, Feng Wu⁴, Guo Chen, Joseph A. Hill⁵, Jennifer E. Ho⁶, Roger S.-Y. Fook⁷, Faiez Zannad⁸

CKM → CKLM

Multiple endpoints Trial Design



PRIORITIES OF MULTI-ORGAN CLINICAL TRIALS



Multidisciplinary Collaboration

Synergistic efforts between cardiologists, nephrologists and hepatologists to design holistic trial frameworks



Enriched Patient Selection

Utilization of non-invasive biomarkers as to target high risk populations, thereby reducing invasive procedures and improving stratification



Inclusion of Comprehensive Endpoints

Incorporating multi-organ endpoints, and linking NITs to hard clinical outcomes



Data Sharing

Better data-sharing standards and regulatory acceptance enhance trust, collaboration, and rigor in trials



Inclusivity and Equity

Addressing underrepresentation of ethnic minorities, women and socioeconomically disadvantaged groups



External Placebo Database

These databases reduce burden on patients and sponsors by reducing the need for large placebo groups



Integration of Advanced Technologies

Leveraging AI/ML for improved patient selection, endpoint predicting and risk stratification

Challenges of Multi-organ Clinical Trials



Identifying appropriate patients with multi-organ disease is inherently complex as traditional risk assessment tools do not account for the presence and severity of liver disease



Drug metabolism and safety issues typically prevent liver disease patients from participating in cardiovascular and kidney trials



Lack of standardized clinical guidelines for managing patients with overlapping conditions introduces heterogeneity into clinical trials



Difficult to enroll and retain patients in trials with traditional biopsy-based approaches for diagnosing and staging liver disease

Challenges of Multi-organ Clinical Trials



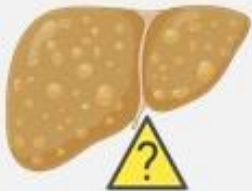
Establishing consensus on developing and validating clinically meaningful organ-specific efficacy and safety endpoints remains a contentious issue



Defining the optimal combination of biomarkers, imaging modalities, and hard clinical outcomes remains a significant challenge

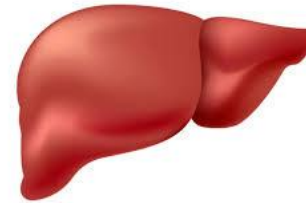
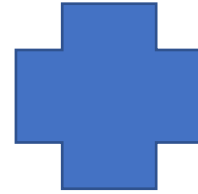
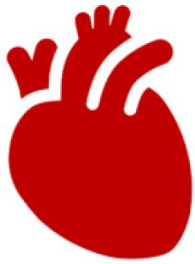


The regulatory approval processes can be complex in multi-organ trials because these trials span various medical specialties and require the green light from multiple regulatory bodies



Uncertainty in enriching trials like including patients with advanced cardio-kidney-metabolic disease may make it difficult to observe liver reversibility

The case for composite endpoints



Frequent coexistence of CKD and cardiovascular disease



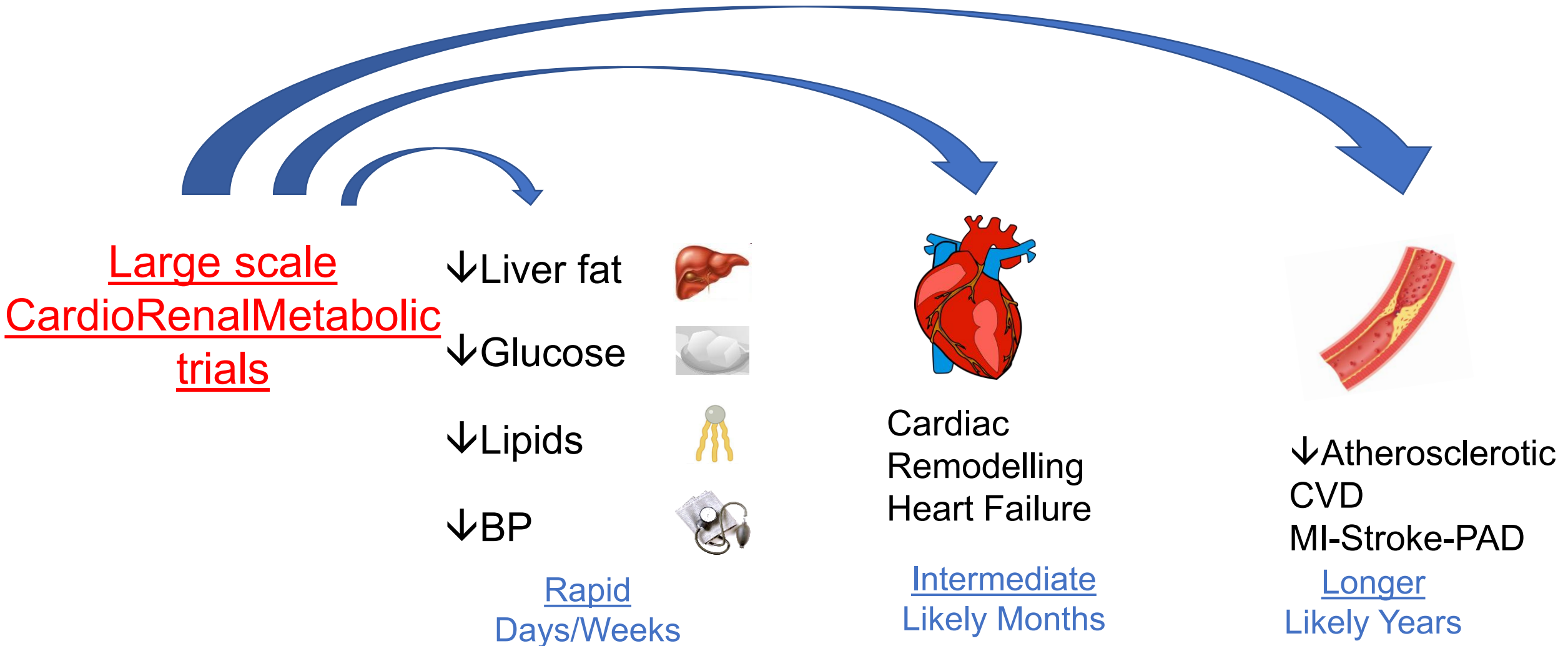
Overlapping clinical presentations in the setting of comorbid CKD and HF



Concordant benefits of certain pharmacotherapies upon cardiovascular and kidney outcomes

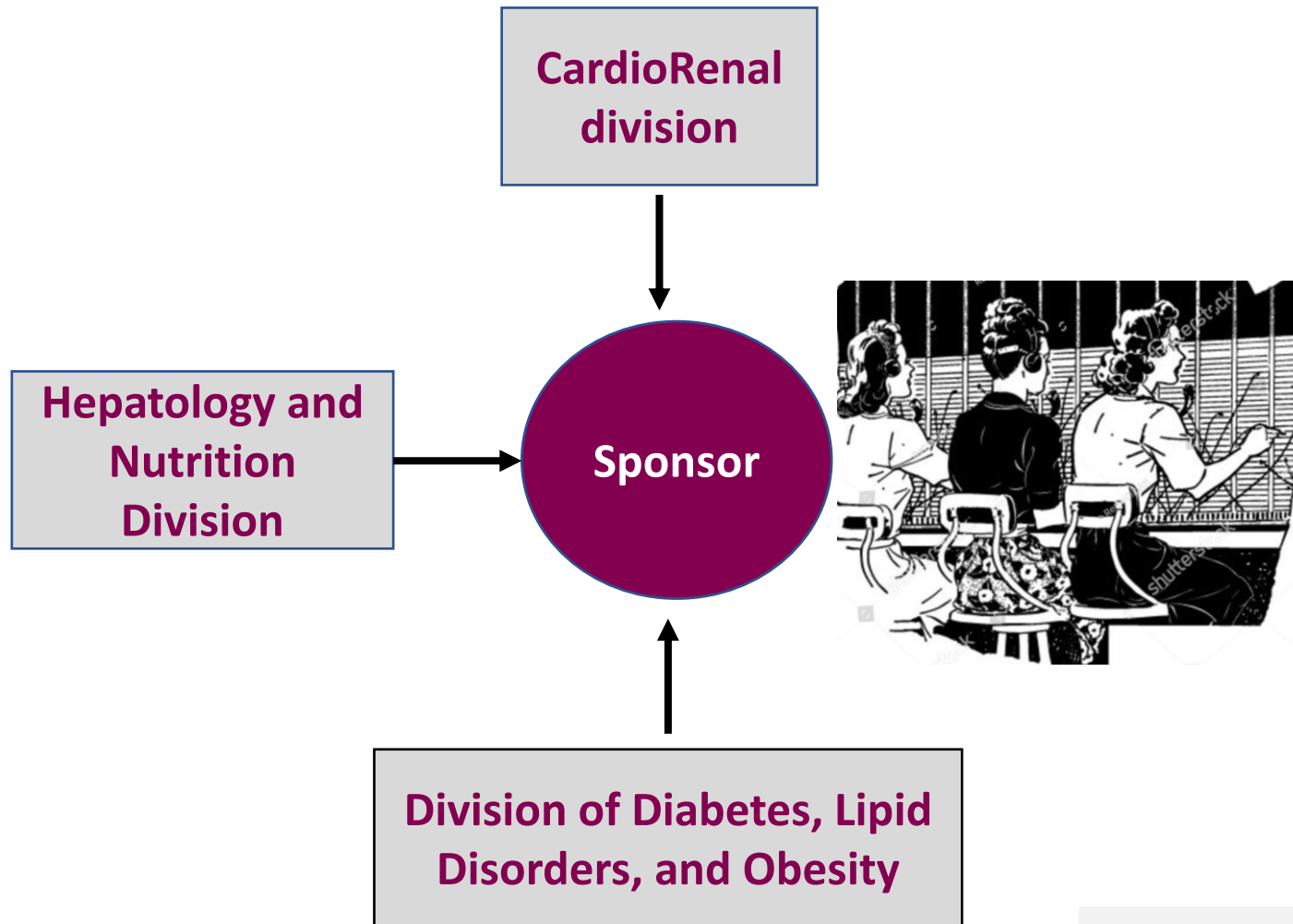
Hitting multiple birds with a single stone

Challenges with varying time-to-endpoint

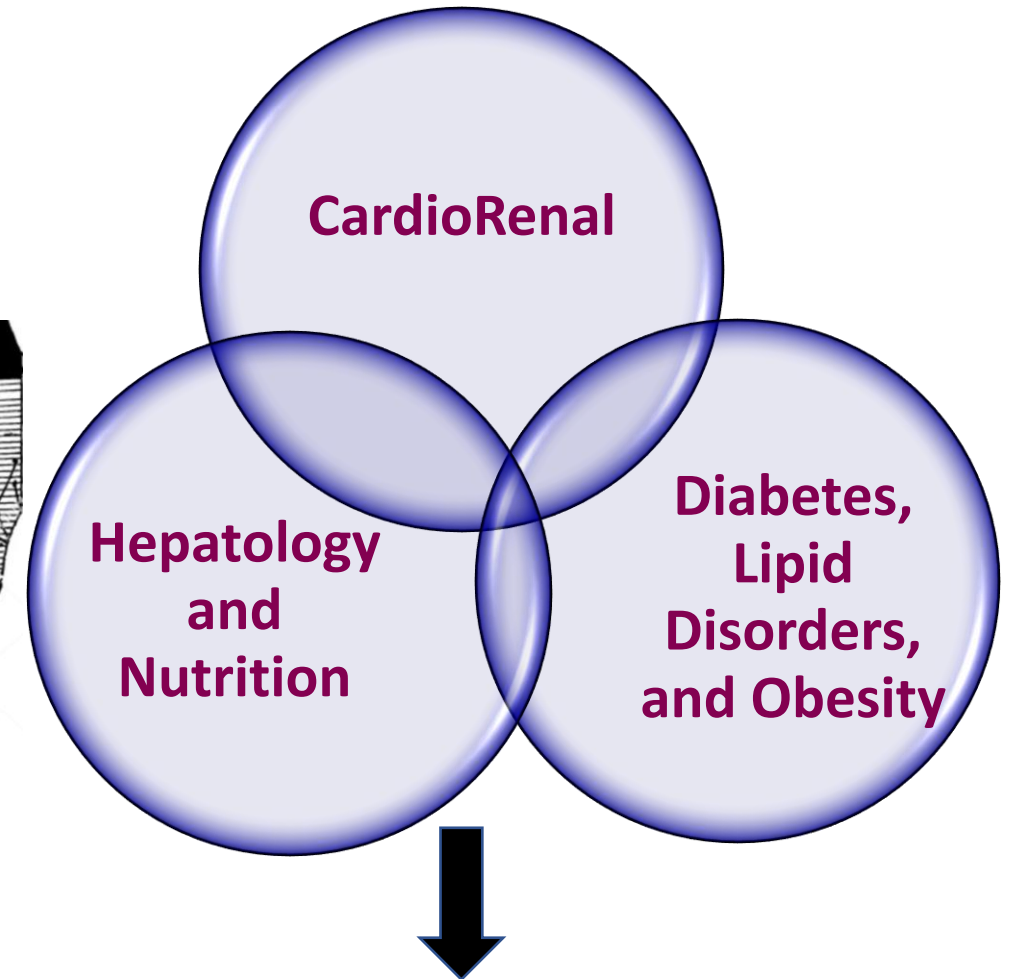


Regulatory Considerations: Paradigm Shift

Current Paradigm



Integrated Paradigm



Integrated Regulatory Guidance on Totality of Benefit

Clinical Trials - Think MultiOrgan

- Enroll patients with MultiOrgan diseases
- Do not exclude CKD or MASLD patients from CV trials
- Characterise and do not exclude MASLD patients in CV trials
- Incorporate cardio-renal-liver-metabolic endpoints into the design of MultiOrgan trials clinical trials
- Aim at multiple (CKLM) indications



A multi-stakeholder multi-specialty NASH/MASH trialists think tank

Metabolic, Hepatology, Nephrology & Cardiovascular cross-talks



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Save the Date

