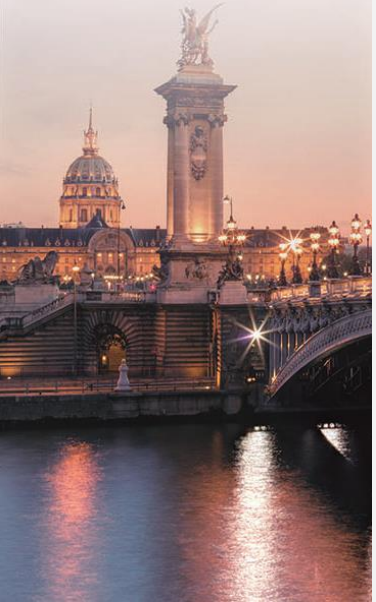
Paris NASH Meeting

International Think Tank

STANDARD OF CARE COMORBIDITIES MANAGEMENT



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THE FORUM For Collaborative Research℠

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STANDARD OF CARE COMORBIDITIES MANAGEMENT

BEFORE THE TRIAL

INTRODUCTION - COMORBIDITIES TO BE ADRESSED:

- The most prevalent co-morbidities
- Comorbidities where treatment might impact on NAFLD/NASH histology
    - Weight
    - Diabetes
    - Dyslipidemia
    - Hypertension
- Other comorbidities to be eventually mentioned:
    - Sleep Apnea – adds complexity to the trial (long to diagnose/manage)
    - Renal function impairment
        - Rather an exclusion criteria
        - No specific treatment

DURING THE TRIAL

TERM DEFINITION

- **Unstable medical condition** – life expectancy should exceed the trial duration (ex. CV events, recent history of cancer, etc.)
- **Uncontrolled comorbidities** - might impact the course of the liver disease or require hospitalization, discontinuation of study drug or use of "forbidden" medication
- **Optimal control of comorbidities** - all patients should have an *optimal* and *acceptable*, even if not a perfect control of their main cardio-metabolic comorbidities and must be as much as possible in a *stable* condition.
  - The optimal control of comorbidities before the trial starts should consider the *accepted boundaries and the best strategies allowed to optimize them without delaying the trial and without a significant interaction with the drug tested*.

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TYPE 2 DIABETES:

Individualized glycemic targets: <6.5% for patients with short duration diabetes, long life expectancy, no CV comorbidities, to <8% for patients with multiple comorbid conditions, long-standing type 2 diabetes and multiple glucose lowering agents

1. **Newly diagnosed T2DM**
    1. *Start treatment before inclusion*:
        1. Lifestyle recommendation during the screening period
        2. Treatment decision left up to local/national guideline
        3. Start treatment before/after LB?
    2. *Start trial without treatment for diabetes*
2. **Already known but uncontrolled T2DM:** ➔ follow diabetes guidelines
    1. Adjust treatment if HbA1c ≥ 1.5% above the glycemic target
    2. The choice of diabetic medication:
        1. non-insulin agents lowers the HbA1c levels of 0.7% to 1%.
        2. Insulin therapy is recommended if HbA1c levels ≥ 11% or ≥ 2% above target (guidelines)
            1. Some drug interfere with LFC as measured by MRI PDFF (GLP1, glitazone, SGLT2 inhibitors) or might induce significant weight loss (GLP1) – **particularly in phase 2 trials**

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Arterial Hypertension :

- ✓ Uncontrolled BP if ≥ 160/100 mmHG
- ✓ Uncontrolled BP is rather a safety issue than a confounder – particularly in Phase 3 trials assessing on-term CV outcomes
- ✓ Treatment to be adjust according to local guideline – dose escalation of an already existing drug or introducing a new drug
  - Antihypertensive drugs have no established effect on liver histology

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Dyslipidemia and CV risk :

- Lipid lowering therapy is indicated in primary and secondary prevention of CV events and is adapted to individual CV risk
- This apply for most of NAFLD patients and should be initiated before starting the trial – also to avoid/limit excursion in LDL cholesterol induced by some drugs or starting stating during the trial
  - In patients not taking statins, initiate statin therapy/ non statin dyslipidemia therapy if indicated;
  - In patients already taking statin up-titrate the dose if necessary
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- Timing according to liver biopsy ➔ if statins are initiated before the starting the treatment, should this delay the trial? Yes/No/For how long?
- Comments on the use of non statin lipid lowering therapy – ezetimibe, fibrates, bile acid sequestrants, PCSK9 inhibitors.. ?
- Table on the dose equivalence of statins according to LDL target ?
- Distinguish between hydrophilic (pravastatin, rosuvastatin) and lipophilic statins (atorvastatin, fluvastatin, simvastatin, etc) ?
    - Lipophilic statin are more liver specific and are metabolized via P450 .. ; rosuvastatin and pravastatin are excreted largely unchanged
    - Hydrophilic but not lipophilic statins improve insulin sensitivity
    - More side effects (rhabdomyolysis) with lipophilic statins ; Hepatotoxicity?
    - Similar efficacy on CAD
    - Lower risk of incident heart failure with hydrophilic statin ..

METABOLICALLY STABLE CONCEPT

- ✓ No change or minimal changes in comorbidities and their treatment that have no impact on the liver condition or trial outcomes.
- ✓ Some parameters like weight or diabetes control primarily impact on the severity of the histological lesions and therefore on the primary study outcomes; other comorbidities (ex. dyslipidemia or arterial hypertension) are more likely to impact on secondary outcomes and safety evaluation
- ✓ **For how long a patient** is required to be metabolically stable before inclusion in the trial? The same for phase 2 and 3 trials?
- ✓ Stability should refer to the condition (ex weight changes or HbA1c fluctuation) and to treatment (dose, threapeutic class, etc) ..

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WEIGHT CONTROL

- **No specific recommendations to achieve a "target" weight**, ➔ maintain a "stable" weight during the trial
- Weight changes **bi directionally impact the severity of histological lesions** (both progression and regression)
- **5% weight change** (gain or loss) **during the 6 months** prior to LB if histological criteria or prior to screening for biological/imaging criteria
    - Different in trials with histological end-point vs MRI PDFF?
- Should we comment on **upper limit of BMI** (45 kg/m2 in most of the trials)?

  - impact on drug pharmacokinetic and pharmacodynamic – depending upon the drug properties – hydrophilic or lipophilic or route of administration (ex sc injections…)
  - technical difficulties – LB, MRI, etc …
- BMI upper limit should be applied in proof of concept (POC) phase II clinical trials focusing on drug's pharmacokinetics and probably maintained in phase III clinical trials depending on the drug being tested (ex. drugs administered in subcutaneous injection like GLP1 agonists, pegylated FGF21 analogues, etc.) or on the case-by-case individual basis.

RUN-IN PERIOD

- Recommended in diabetes and hypertension trials

- Interest of run-in
  - to stabilize the condition
  -to optimize management
  - to assess adherence

- Interest in NAFLD?

  - Maybe in short-term studies (3 to 4 months) with metabolic endpoints or liver fat content measurement (benefit from a stabilization period and an optimal pre-trial ➔more realistic, efficacy estimates of the active drug over placebo
  - Probably no impact on long-term trial with histological endpoint
  - consider the period between screening and baseline as “run-in”?

ALCOHOL CONSUMPTION

Recommendation on how to document/monitor for alcohol consumption

- The Timeline Follow Back Form seems to be the best and preferred at least by ALD working groups but has not been used in NAFLD – should we recommend it instead of AUDIT? Would this add complexity?
- what about AUDIT? CDT?

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DURING THE TRIAL

- Weight fluctuation during the trial ➔ allow 5 to 10% ?
- Diabetes –
    - If known diabetes already under antidiabetic medication - retest than than adjust treatment if HbA1c ≥ 1.5% above the individualized glycemic target; ≥ 15% increase from baseline; ≥ 9%?
    - If new onset diabetes (define) –retest ➔ if confirmed follow diabetes guidelines to initiate treatment
- Dyslipidemia
- HBP

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- Dyslipidemia: if ≥ 15% increase from baseline ➔ retest and assess CV risk ➔ - if patient not taking statin ➔ initiate statins; if already taking statin ➔ either dose escalation or add a new drug if intolerance or maximal dose already (ezetimibe, etc)
- HBP : repeat measures; if ≥ 160/100 mmHg ➔ dose titration if already treated or start treatment if treatment naïve …