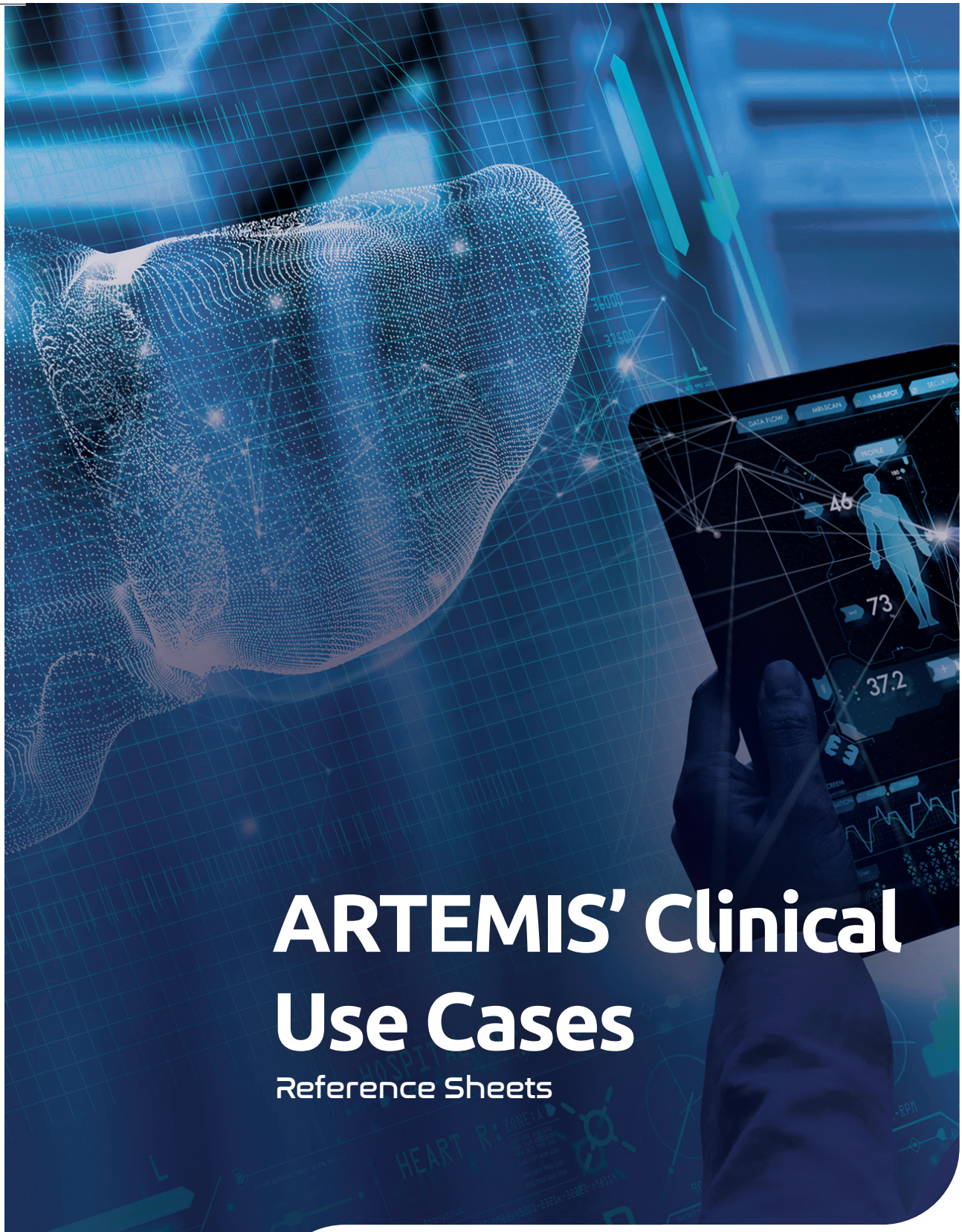


ARTEMIS' Clinical Use Cases

Reference Sheets

ARTEMIS

The Power of Virtual Twins to Fight MAFLD

#1

CLINICAL CASE #1

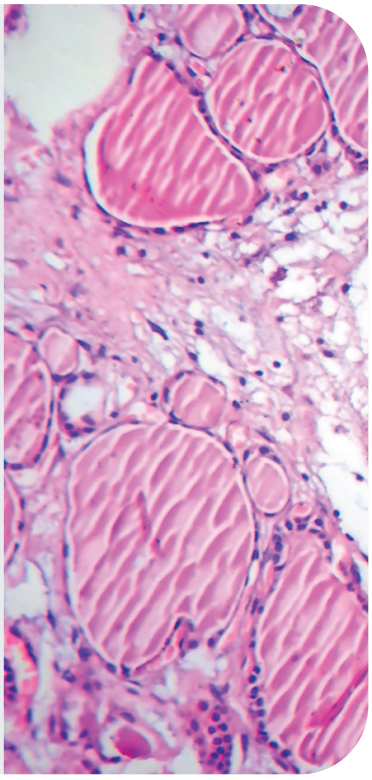
Fibrosis progression in MAFLD patients

PRIMARY OBJECTIVE

Distinguish “fast” VS “non-fast” progressing patients

SECONDARY OBJECTIVE

Evaluate the model’s ability to distinguish patients based on time to mortality and to different endpoints (transplantation, liver decomposition, HCC)



#2

CLINICAL CASE #2

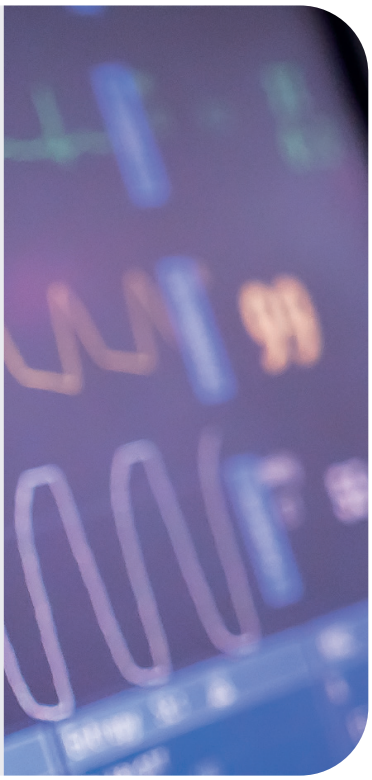
Fibrosis-associated heart failure patients

PRIMARY OBJECTIVE

Prediction of incidence of any cardiovascular event in MAFLD patients

SECONDARY OBJECTIVE

Evaluate the impact of hepatic fibrosis and NASH on early cardiovascular risk and the degree of cardiac dysfunction



#3

CLINICAL CASE #3

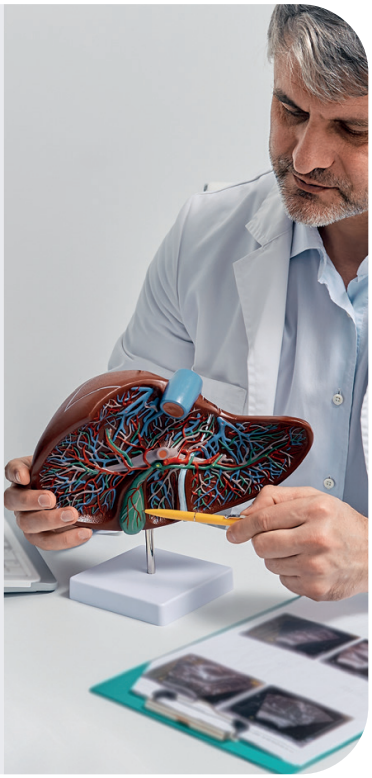
Cardiovascular complications after TIPS placement *(Portal Hypertension)*

PRIMARY OBJECTIVE

Predict cardiovascular events after placement of TIPS

SECONDARY OBJECTIVE

Evaluation of overall survival, prediction of further decompensation of cirrhosis, evaluation of TIPS patency



#4

CLINICAL CASE #4

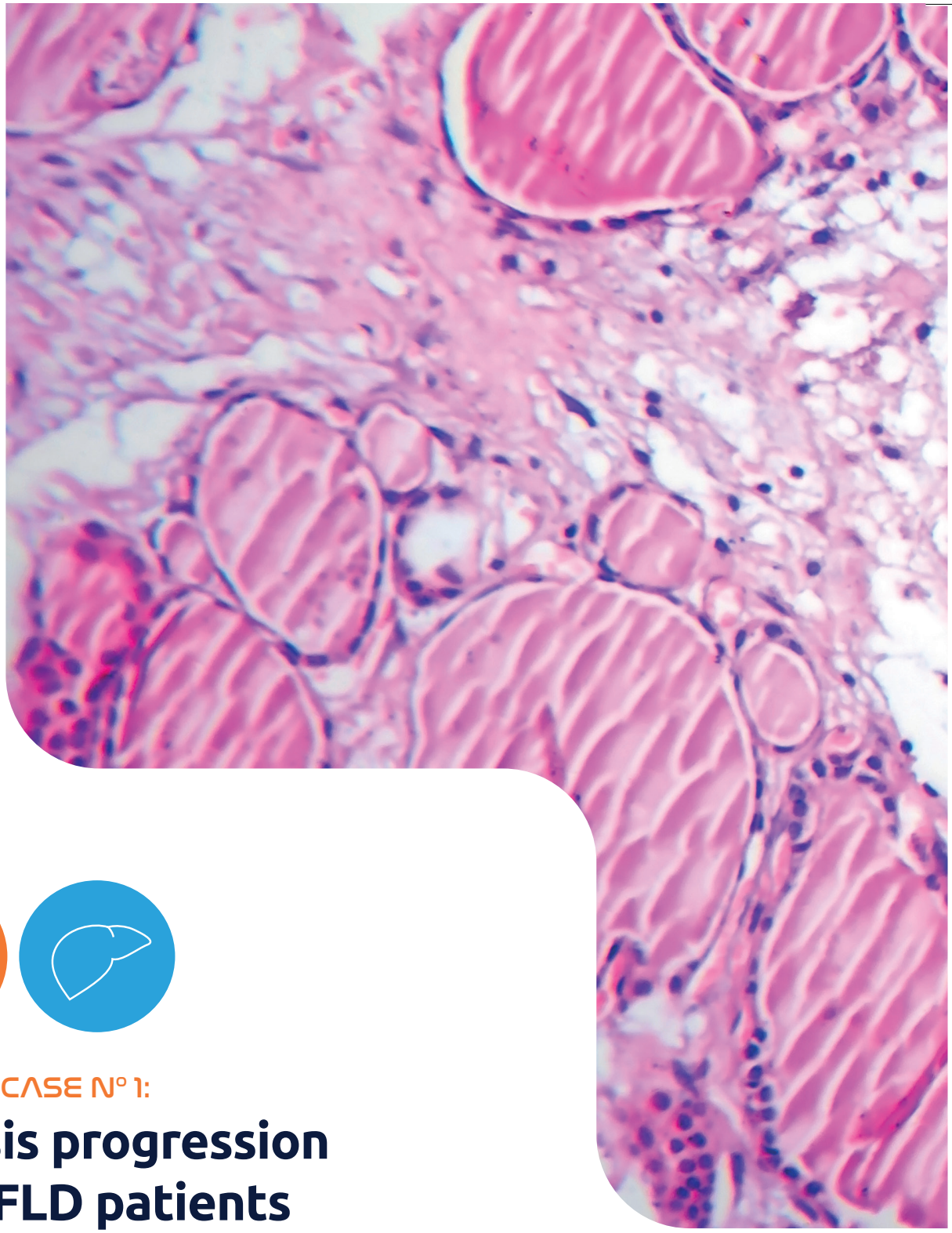
Prediction of cardiac complications due to HCC treatments

PRIMARY OBJECTIVE

Prediction of cardiovascular events related to therapeutic responses in HCC patients

SECONDARY OBJECTIVE

Assess interventions that could prevent the onset of HCC



#1

CLINICAL CASE N° 1:

Fibrosis progression in MAFLD patients

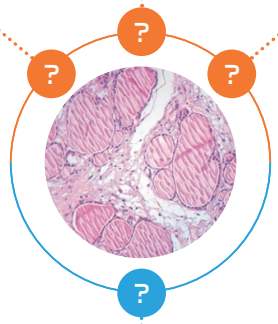
Prediction model designed to distinguish between fast and non-fast fibrosis progression among MAFLD patients

CLINICAL QUESTIONS & EXPECTATIONS

Will statins / SGLT2 inhibitors / Metformin be effective in slowing fibrosis progression in this patient (of a rapid fibrosis progression phenotype)?

Is this patient at a high risk of rapid fibrosis progression?

Are there further possible targets for a successful therapy approach?



Can one infer systematic relationships by multi-level mechanistic Virtual twins and/or AI-based models between certain signatures at the histological level and blood biomarkers or / and medical imaging that permit to predict patient specific disease scenarios and to follow-up patients longitudinally?

MODELING QUESTIONS & EXPECTATIONS

PRIMARY OBJECTIVE

Evaluate the model's ability to distinguish patients based on their time to progression between subsequent phases of liver fibrosis and clinical phenotypes

SECONDARY OBJECTIVES

- Evaluate the model's ability to distinguish patients based on their **time to mortality**
- Evaluate the model's ability to distinguish patients based on their **time to liver transplantation**
- Evaluate the model's ability to distinguish patients based on their **time to liver decompensation**
- Evaluate the model's ability to distinguish patients based on their **time to hepatocellular carcinoma**

EXPLORATORY OBJECTIVES

- Better understanding of **mechanism of actions of specific therapeutic interventions for obesity,** T2DM or cardiovascular diseases prevention and their impact on liver fibrosis
- Evaluation of the **impact of lifestyle modifications** and **treatments on fibrosis stage progression**
- **Measurement of demographic, clinical, biochemical** (fibrosis stage assessment: fibroscan, liver histology, sheerwave elastography, validated biomarquers scores such as FIB4 (https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4) associated to progression of liver fibrosis in a large cohort of patients with MAFLD

PRIMARY OUTCOME MEASURE

Time to progression between subsequent phases of liver fibrosis, based on the Fib-4 algorithm
| *Time frame: 5-7 years*

SECONDARY OUTCOME MEASURES

- Measurement of median mortality rate | *Time frame: 5 years*
- Measurement of time to liver transplantation | *Time frame: 5 years*
- Measurement of time to liver decompensation | *Time frame: 5 years*
- Measurement of time to diagnosis of hepatocellular carcinoma | *Time frame: 5 years*
- Occurrence of non-liver cancer events | *Time frame: 5-7 years*

EXPLORATORY ENDPOINT

- Time to progression between subsequent phases of liver fibrosis, based on the Fib-4 algorithm
- Non-invasive biomarkers of the presence of and severity of cardiac fibrosis through metabolomics and/other analytical biomarkers | *Time frame: 5 years* - liquid biopsy

INCLUSION CRITERIA

- Age ≥18 years
- Diagnosis of MAFLD confirmed by radiology or histology (gold standard, following NASH CRN recommendation)
- Diagnosed with fatty liver by ultrasound
- Subjects having a platelet count of at least 50 × 109/L and prothrombin activity of ≥50%

EXCLUSION CRITERIA

- Missing data on Ultrasound, blood glucose, BMI and metabolic status
- Patients who have received systemic chemotherapy
- Patients with hepatitis B (HBV) and hepatitis C (HCV), alcoholic liver disease (more than 5 years of drinking history, equivalent to alcohol volume ≥ 40g / D in male and ≥ 20g / D in female), drug-induced liver disease or autoimmune hepatitis
- Subjects having a significant risk of bleeding (platelet < 50x109 / L, prothrombin activity < 50%)
- Presence of any other form of chronic liver disease except MAFLD

#2

CLINICAL CASE N° 2:

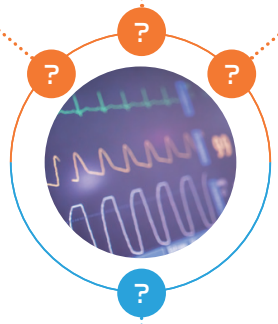
Fibrosis-associated heart failure patients

CLINICAL QUESTIONS & EXPECTATIONS

Is this patient with advanced liver fibrosis at a higher risk of developing cardiac fibrosis?

Is this patient at a high risk of cardiac events?

How does the evolution of hepatic steatosis and fibrosis affect the development of cardiac complications, such as coronary artery calcium scores, myocardial flow deficit, etc?



Can one infer a systematic coupling between progression of MAFLD and heart fibrosis / cardiac events by multi-level mechanistic Virtual twins and/or AI-based models that can be detected and followed-up by blood biomarkers or/and medical imaging?

MODELING QUESTIONS & EXPECTATIONS

PRIMARY OBJECTIVE

Assessment of a computational model to predict the incidence of major fibrosis-associated heart failure including syndromic, metabolic, and multicellular (heart) diseases. | *Time Frame: Patients will be followed for an expected mean time of 5 years*

SECONDARY OBJECTIVES

- Evaluate the impact of hepatic fibrosis and NASH (inflammation) on **early cardiovascular risk and the degree of cardiac dysfunction**

EXPLORATORY OBJECTIVES

- Evaluation of the impact of fibrosis **in immunological system**
- Identification of **therapeutic targets**
- Evaluation of **response to treatment**

PRIMARY OUTCOME MEASURE

Any cardiovascular events (myocardial infarction, stroke; atrial fibrilation) or comorbidities

SECONDARY OUTCOME MEASURES

- Framingham Cardiovascular risk score | *Time frame: 36 months*
- Liver stiffness measured by vibration controlled transient elastography (VCTE)
- Measurement of clinical, biochemical (fibrosis stage assessment: fibroscan, liver histology, sheerwave elastography, validated biomarquers scores such as FIB4
- Systemic Coronary Risk Estimation (SCORE) ranging from <1% very low risk to >15% very high risk of cardiovascular mortality
- Coronary calcium score
- Coronary heart disease | *Time Frame: 3 months* | Diagnosis of coronary heart disease

INCLUSION CRITERIA

- Age ≥18 years
- MAFLD patients regardless of disease stage of severity (from simple steatosis to cirrhosis)
- Patient without known heart disease
- Cardiovascular assessment available
- Subjects presenting cardiac fibrosis, without a known MAFLD diagnosis

EXCLUSION CRITERIA

- Association with another cause of liver disease
- History of hepatitis B or C
- Already known coronary artery disease

#3

CLINICAL CASE N° 3:

Cardiovascular complications after TIPS placement
(Portal Hypertension)

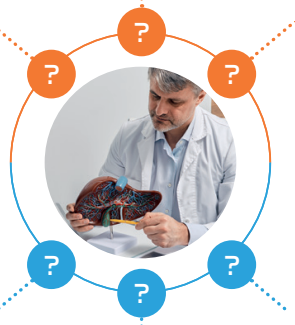
Cirrhosis patients/Portal Hypertension

CLINICAL QUESTIONS & EXPECTATIONS

Is this cirrhosis patient at a higher risk of developing HF post TIPS intervention?

Which TIPS intervention would benefit most this cirrhotic patient?

Is this cirrhosis patient at a higher risk of developing "ischemic hepatitis" post TIPS intervention?

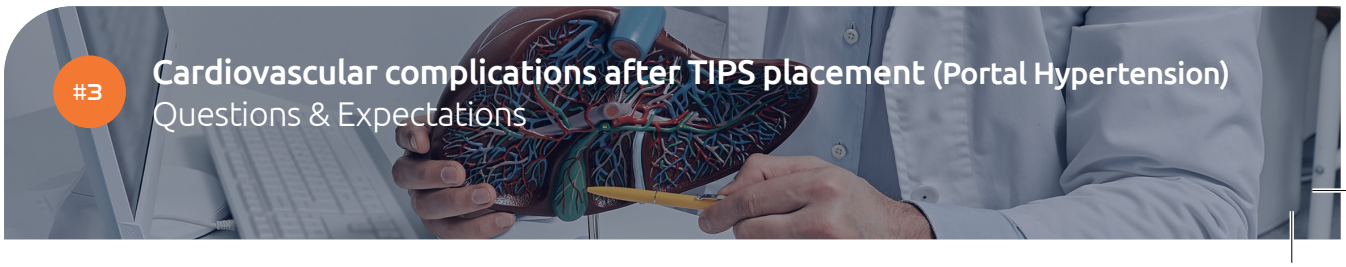


Can a virtual twin predict and optimise TIPS intervention from a hemodynamic point of view for a diversity of cirrhosis patients?

Can a virtual twin of AI, hemodynamics, and metabolism/transport of ammonia and other relevant substances leading to HE, ascites and infection, be generated to understand the cross-talks at play and be predictive?

Can one infer from longitudinal data of portal hypertension patients treated with TIPS with and without HF the possible mechanisms of HF by a combination of AI & mechanistic models?

MODELING QUESTIONS & EXPECTATIONS



#3 **Cardiovascular complications after TIPS placement** (Portal Hypertension)
Questions & Expectations

PRIMARY OBJECTIVE

Evaluate the performance (sensitivity, specificity, positive predictive value and negative predictive value, and likelihood ratios) of a predictive model (association of mechanistic and AI-based models) of cardiovascular complications for patients with cirrhosis undergoing a TIPS placement

SECONDARY OBJECTIVES

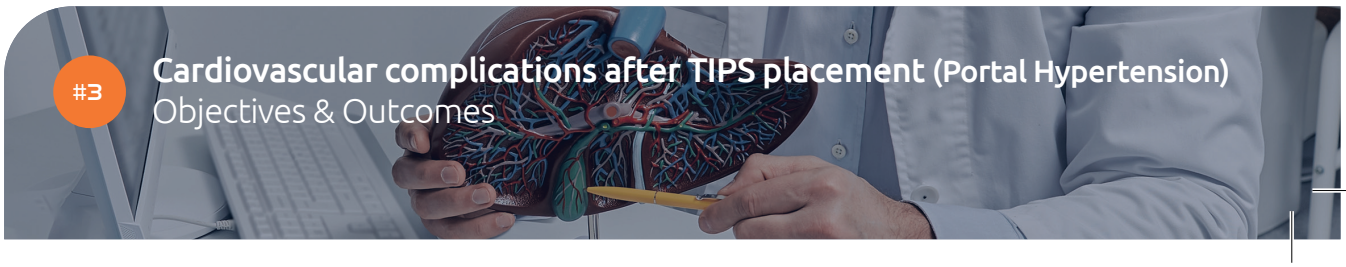
- Evaluation of **overall survival**
- Prediction of **further decompensation of cirrhosis** (hepatic encephalopathy, ascites and infections)
- Evaluation of **TIPS patency**

PRIMARY OUTCOME MEASURE

Incidence rate of cardiac-related events; including heart failure, heart attack
| *Time frame: from insertion of TIPS to 2 years post TIPS*

SECONDARY OUTCOME MEASURES

- Overall survival | *Time frame: all patients will be followed for 4 years after TIPS placement* | evaluation of overall survival from time of TIPS placement to death
- Cirrhosis associated complications | *Time Frame: from insertion of TIPS to 2 years post TIPS* | hepatic encephalopathy, ascites and its complications and infections
- Any post procedural TIPS related events including jaundice and/or acute chronic liver failure
- TIPS patency | *Time Frame: from insertion of TIPS to 2 years post TIPS*

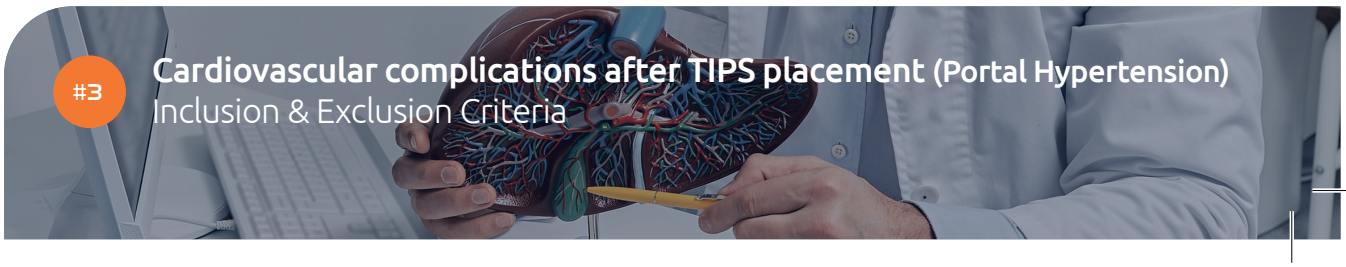


INCLUSION CRITERIA

- Age ≥18 years
- Indication validated of the TIPS (Bavéno VII), except not-controlled acute haemorrhagic.
- Recurrent variceal bleeding after failure of the usual pharmacological and endoscopic methods
- Refractory or recurrent ascites or difficult to treat
- Refractory Hydrothorax
- Subjects with diagnosis of liver cirrhosis (based on clinical, laboratory, endoscopic, and ultrasonographic features or on histology).

EXCLUSION CRITERIA

- Portosinusoidal vascular disease
- Complete portal vein thrombosis
- Subjects with surgical porto-caval shunts.
- Subjects with evidence of current locally advanced or metastatic malignancy
- Subjects with acute or chronic heart failure (New York Heart Association [NYHA]).
- Subjects with chronic obstructive pulmonary disease GOLD grade III/IV
- Subjects with chronic kidney disease requiring renal replacement therapy
- Subjects with a known infection with human immunodeficiency virus (HIV) or have clinical signs and symptoms consistent with current HIV infection
- Subjects with previous liver transplantation



#4

CLINICAL CASE N° 4:

Prediction of cardiac complications due to HCC treatments*

*Including surgical interventions, ablation, TACE and immunotherapies

CLINICAL QUESTIONS & EXPECTATIONS

Is this intermediate stage HCC patient at high risk of cardiac complications if treated with transplantation, TACE or systemic treatment (immune checkpoint inhibitors (ICI) or tyrosine kinase inhibitors (TKI))?

Is this (very) early-stage HCC patient at high risk of cardiac complications after a liver resection or transplantation?

Is this advanced stage HCC patient at high risk of cardiac complications if treated with systemic therapies?

Can a virtual twin predict and optimize TIPS intervention from a hemodynamic point of view for a diversity of cirrhosis patients?

Can one infer from longitudinal data of portal hypertension patients treated with TIPS with and without HF the possible mechanisms of HF by a combination of AI & mechanistic models?

MODELING QUESTIONS & EXPECTATIONS

PRIMARY OBJECTIVE

Assessment of the feasibility of the predictive role of a computational model on the incidence of cardiovascular events related to therapeutic responses in HCC patients

SECONDARY OBJECTIVES

- Assessment of intervention that could **prevent the onset of HCC**

PRIMARY OUTCOME MEASURE

Incidence rate of cardiac-related events; including myocardial complications, heart failure and heart attack
| *Time Frame: 2 years*

SECONDARY OUTCOME MEASURES

- Delay of HCC event in relation to the diagnosis of NASH | *Time frame: 2 years*

#4

Prediction of cardiac complications due to HCC treatments
Objectives & Outcomes

INCLUSION CRITERIA

- Age ≥18 years
- Diagnostic of HCC (any aetiology)
- Imaging follow-up of liver diseases
- Non-cirrhotic or no more than Child-Pugh A cirrhosis.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Patients without history of prior HCC
- Patients with a history of hypertension should be well controlled (< 140/90 mmHg) on a regimen of antihypertensive therapy

EXCLUSION CRITERIA

- Uncontrolled inter-current illness or psychiatric illness or social situations that would limit compliance with study requirements.
- Subjects with history of another primary cancer
- Fully recovered from any prior surgery and/or radiation and none within 2 weeks of initiating treatment.
- Subjects with active hepatitis B or C on anti-viremic compounds may remain on such treatment, except for interferon.

ARTEMIS

The Power of Virtual Twins to Fight MAFLD

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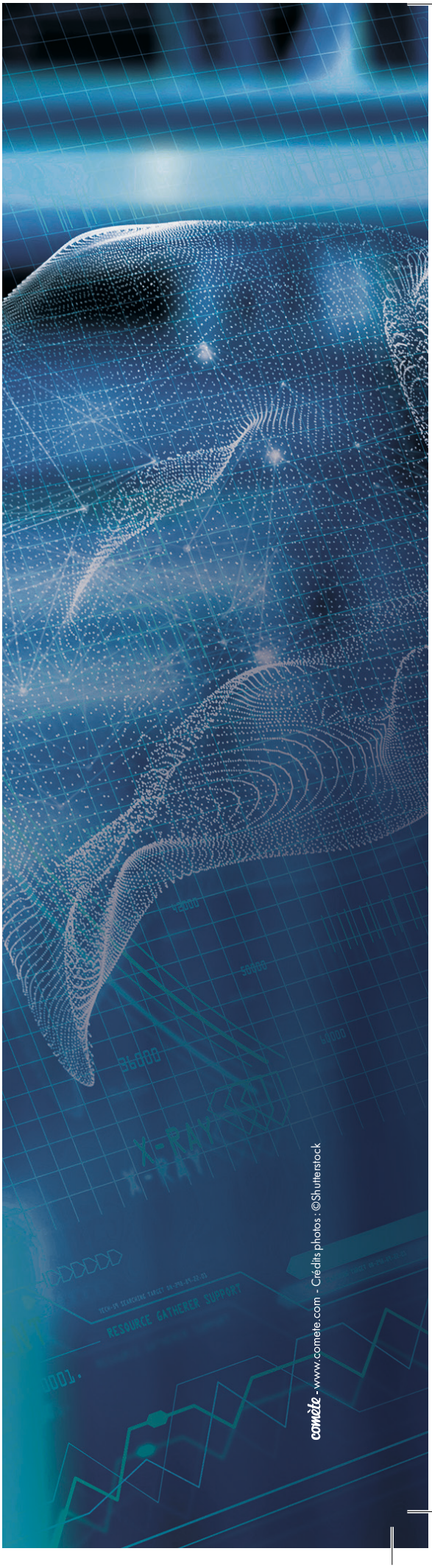
on the ARTEMIs' official website

COMING SOON



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