



What can we learn from diabetes and obesity trials to manage post-approval drop outs from ongoing long term MASLD trials?



Pr Bertrand CARIOU, MD, PhD

L'unité de recherche de l'institut du thorax
Inserm UMR 1087 / CNRS UMR 6291
Nantes, France



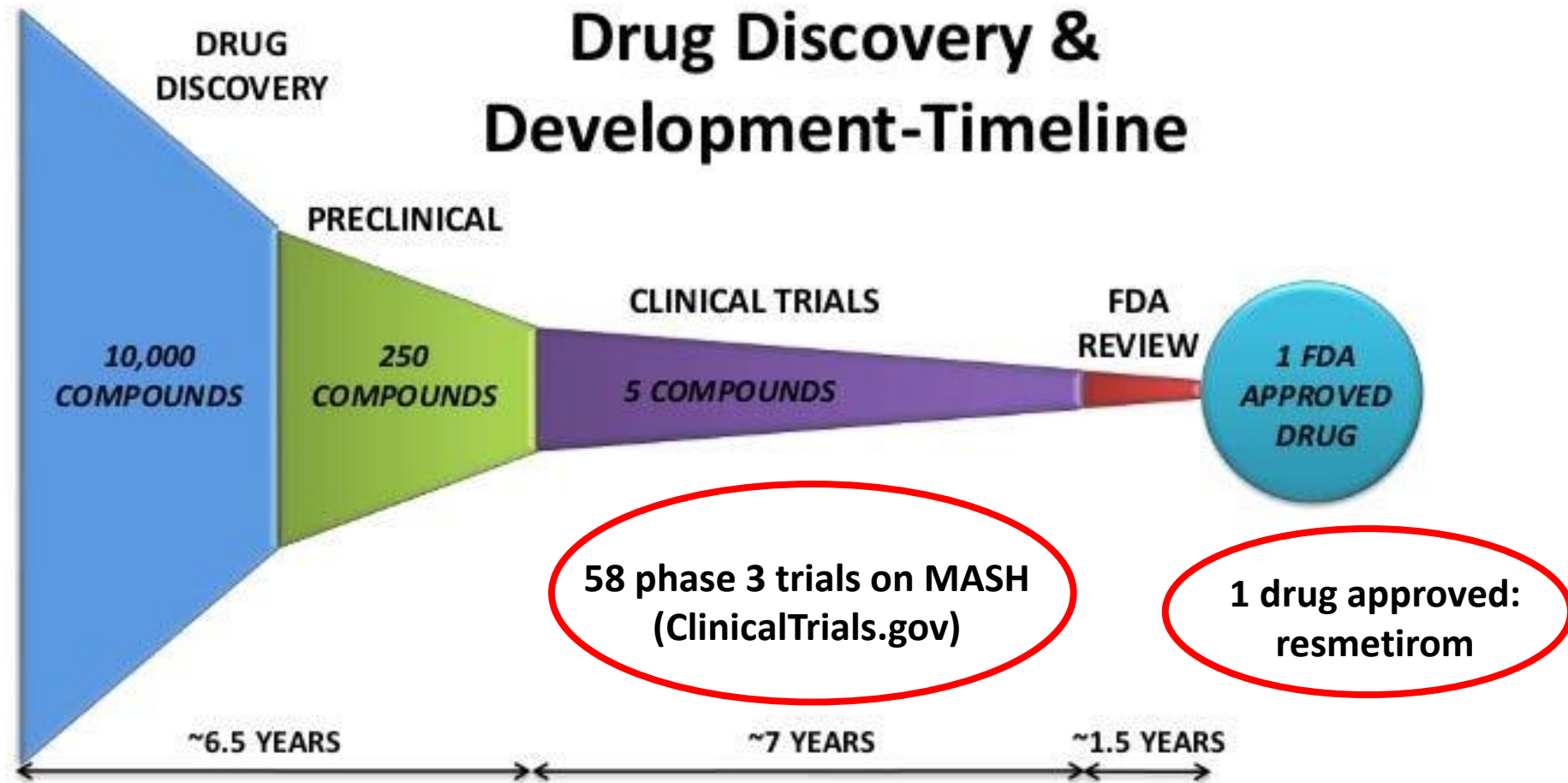
What does this such « disruptive » title mean ?



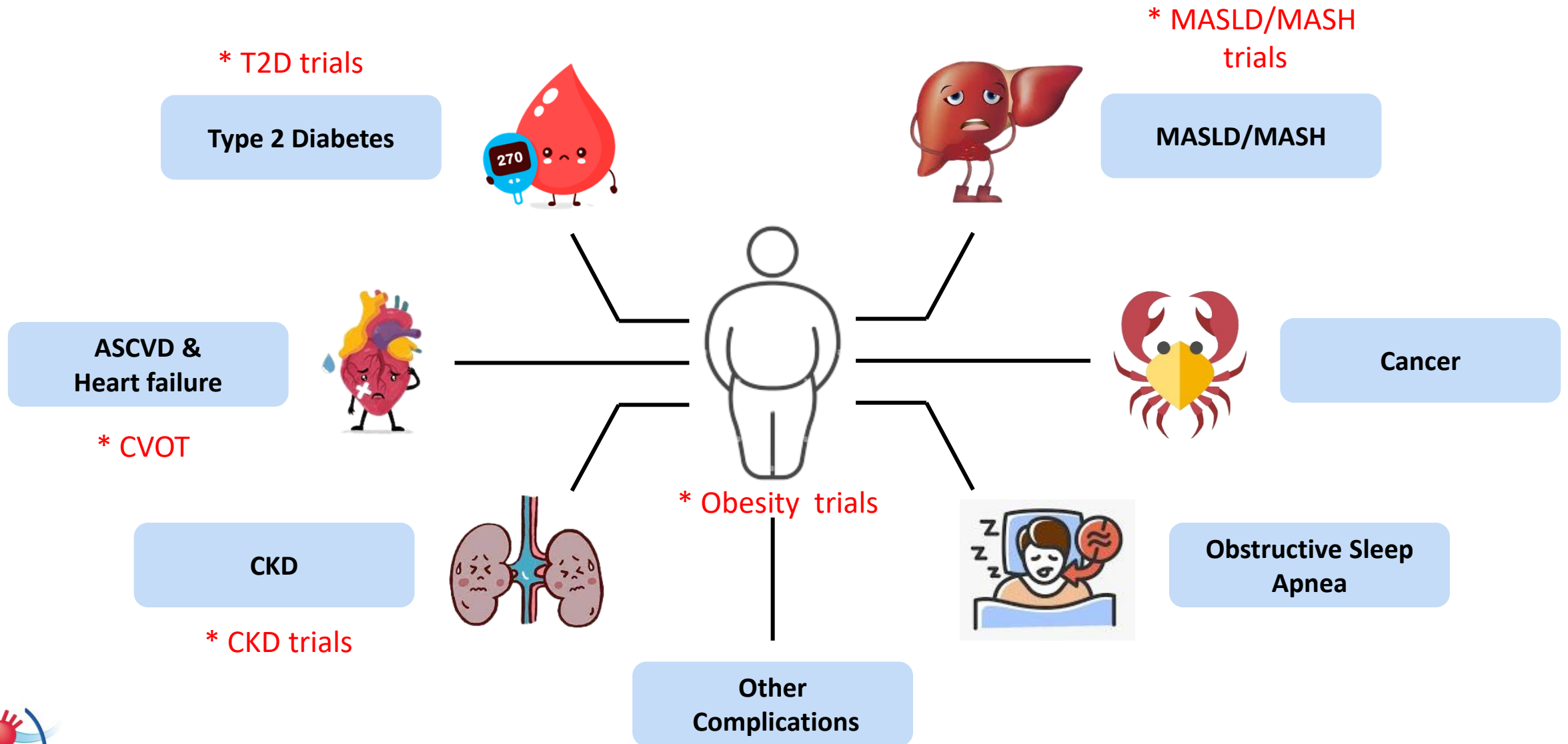
Disclosures

Pr Bertrand CARIOU								
<i>Company Name</i>	<i>Honoraria/ Expenses</i>	<i>Consulting/ Advisory Board</i>	<i>Funded Research</i>	<i>Royalties / Patent</i>	<i>Stock Options</i>	<i>Ownersh p/ Equity Position</i>	<i>Employee</i>	<i>Other (please specify)</i>
Abbott	x							
Amgen	x		x					
Astra-Zeneca	x							
Eli Lilly	x	x						
Novartis	x	x						
Novo Nordisk	x	x						
MSD		x						
Sanofi	x		x					
Ultragenyx	x	x						

The long journey of drug development



The typical MASH patient



The challenges for conducting long-term MASLD trials

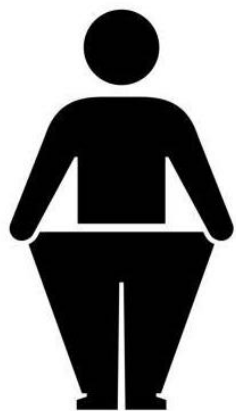
- **Competitive recruitment:** many drug candidates in MASH, but also in obesity, T2DM, CVD
- **Rapidly changing standard of care** for patients with cardiometabolic disease
- **Absence of approved surrogate marker** for the primary outcome → histological endpoint requires medium- to long-term follow-up
- **Absence of liver-related outcomes** to design some event-driven trials as in CVOTs
- The need to **manage metabolic comorbidities** throughout the trial
- Preventing **study drop-outs** to preserve the statistical power

The optimistic view: the retention of the patients is manageable

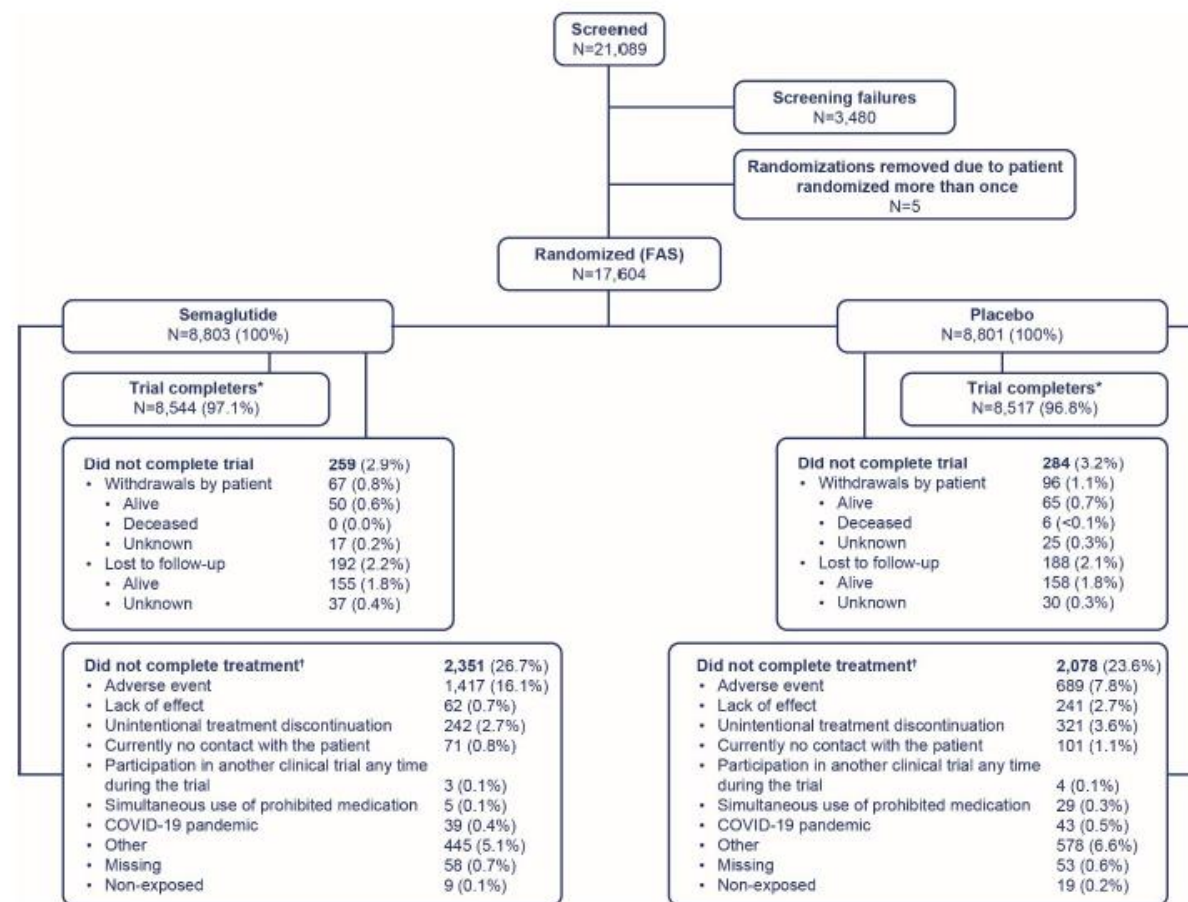
THE SELECT trial: the challenge of a CVOT with an anti-obesity drug



10% GI
AE leading
to trial product
discontinuation



8.5%
BW loss



**Drop-out & lost
to follow-up rates:**
2.9% Semaglutide
3.2% Placebo

A few practical tips to improve patient retention in clinical trials

- the **investigator** must be convinced that his patient can benefit from the best standard of care
- the patient must understand the purpose of the study and have the **right expectations**
 - SELECT was a CVOT not an obesity trial: the focus is on the heart not on body weight loss
 - For MASH trial, put the focus on the prevention of liver complications
- **anticipate** with the patient the possibility of being on a placebo
- stress the benefits of **regular medical monitoring** in the study and its potential health benefits: dietary monitoring, positive reinforcement, early detection of complications,...
- **for industrial promoters**: simplify administrative procedures (signing of multiple versions of consent, time taken for visits, number of questionnaires, reimbursement of travel expenses...) for better acceptance of the protocol by the patient

A proposal from the liver forum for the management of comorbidities in non-alcoholic steatohepatitis therapeutic trials

Raluca Pais^{1,2}, Bertrand Cariou³, Mazen Nouredin⁴, Sven Francque^{5,6}, Jörn M. Schattenberg⁷, Manal F. Abdelmalek⁸, Gadi Lalazar⁹, Sharat Varma¹⁰, Julie Dietrich¹¹, Veronica Miller¹², Arun Sanyal¹³, Vlad Ratziu^{1,14*}, on behalf of the Liver Forum NAFLD-Associated Comorbidities Working Group

Table 3. Abbreviated recommendations for the management of major metabolic comorbidities after inclusion in NASH therapeutic trials.

Type 2 diabetes	High blood pressure	Dyslipidaemia	Weight
<ul style="list-style-type: none"> For short-term trials (<6 months), favour non-pharmacological measures and nutritional counselling. If possible defer therapeutic intervention until after trial completion. For longer trials (≥1 years), consider adapting treatment if HbA1c ≥7.0% or if there is a >1.5% increase in HbA1c from baseline. Consider dose escalation of existing treatment or introducing a new drug according to guidelines. Favour drugs that do not impact on liver histology (e.g. metformin, sulfonylureas, or DPP4i and if possible avoid GLP1 RAs. 	<ul style="list-style-type: none"> Treat to target blood pressure in accordance with local or international guidelines, concomitant comorbid conditions and cardiovascular risk. 	<ul style="list-style-type: none"> For short-term trials (<6 months), lipid-lowering therapy could be deferred in case of LDL-C increase in those patients that are not already taking statins. In patients already taking statins, for every 15-20% increase in LDL-C, the dose of statin should be up-titrated regardless of the duration of the trial. If necessary, new drugs (ezetimibe or PCSK9 inhibitors) can be added. In case of mild hypertriglyceridemia (2 to 9.9 mmol/L) occurring during the trial, statin therapy should be continued, and the prevention of cardiovascular events should be prioritised. In case of severe hypertriglyceridaemia (≥10 mmol/L) statins should be discontinued and the priority should be given to prevention of acute pancreatitis (start fibrates, omega 3, etc). 	<ul style="list-style-type: none"> Monitor changes in weight and compliance with diet and lifestyle recommendations. Aside from exceptional circumstances, avoid initiating treatment for weight loss with weight loss agents.

DPP4i, dipeptidylpeptidase-4 inhibitors; GLP1 RAs, glucagon-like protein 1 receptor agonists; HbA1c, glycated haemoglobin; LDL-C, low-density lipoprotein-cholesterol; PCSK9, pro-protein convertase subtilisin/kexin type 9.

The realistic view: how manage MASLD trials at the era of gut hormone multi-agonists ?

Multi-receptor drugs: one bullet for multiple targets

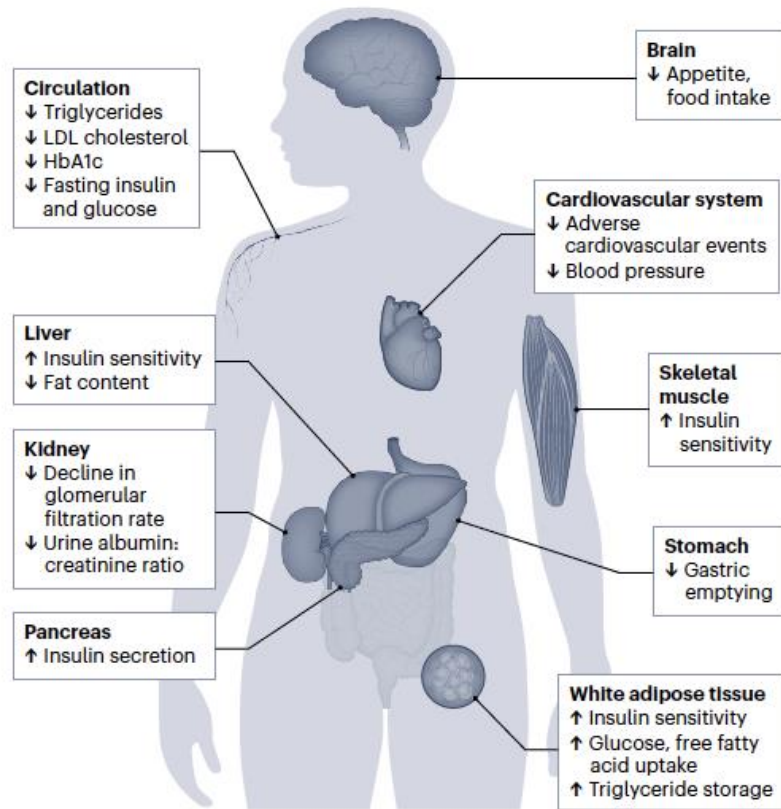
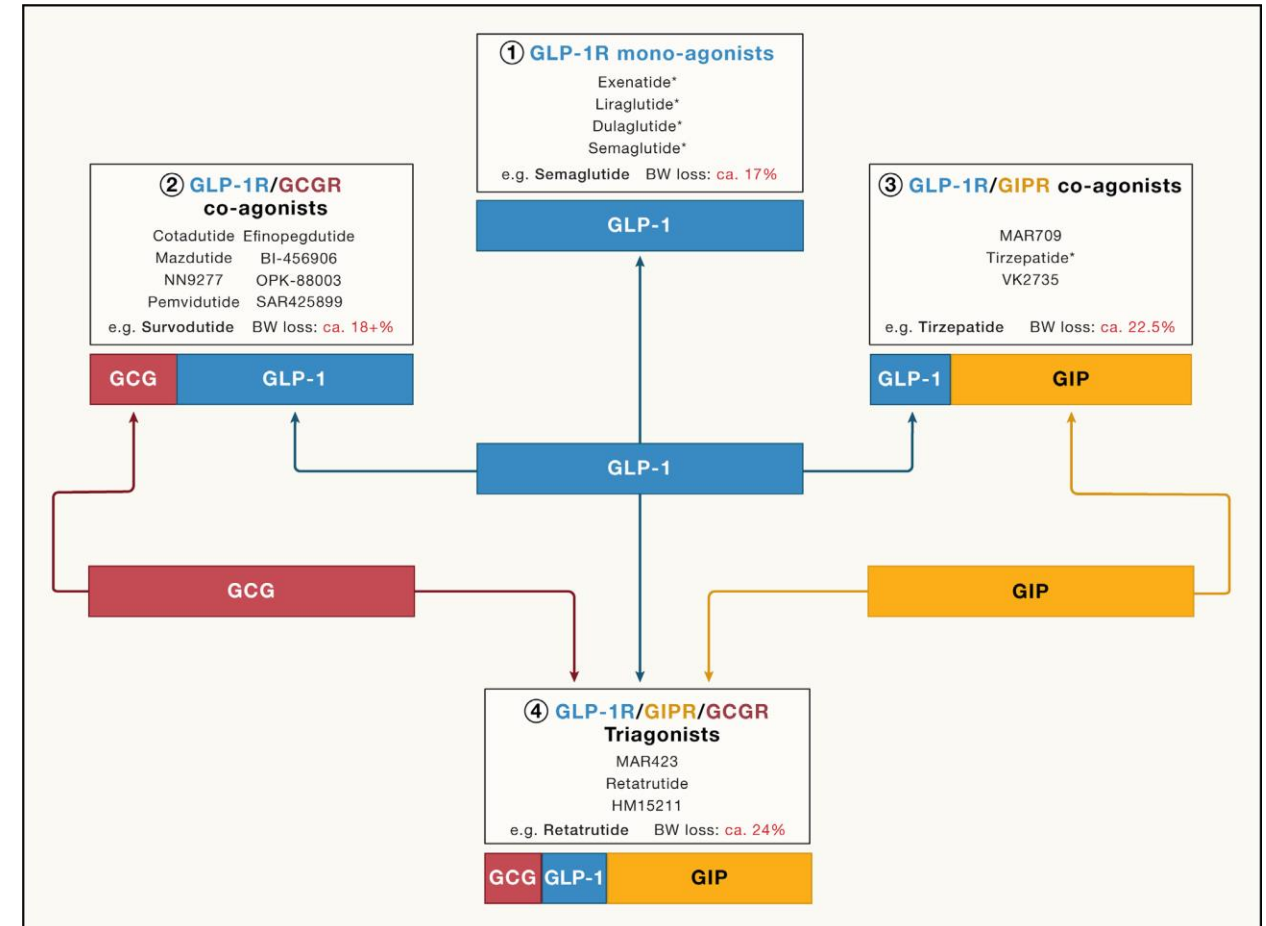
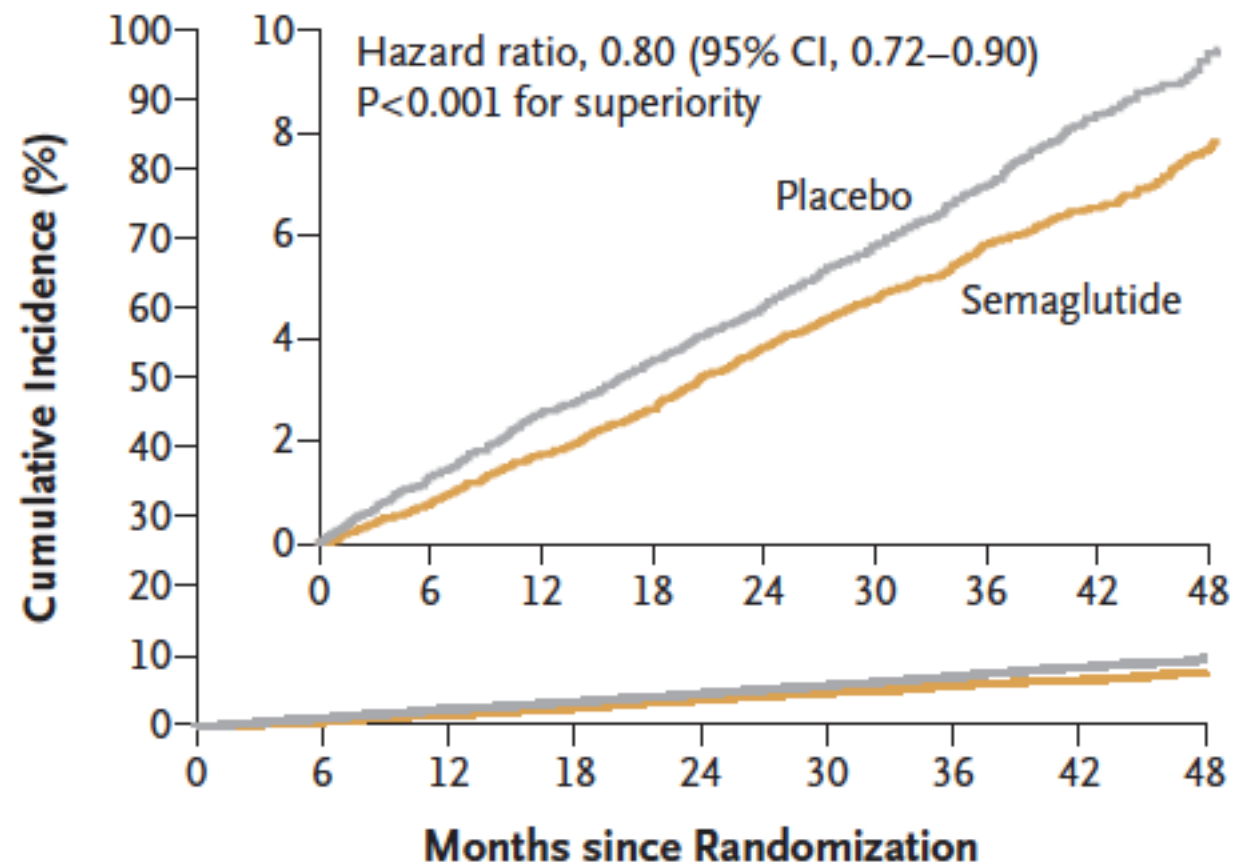


Fig. 2 | Main actions and target tissues for gut hormone co-agonists. Results obtained from phase 1, 2 and 3 trials with dual agonists and triagonists.



The paradigm shift in obesity treatment

A Primary Cardiovascular Composite End Point

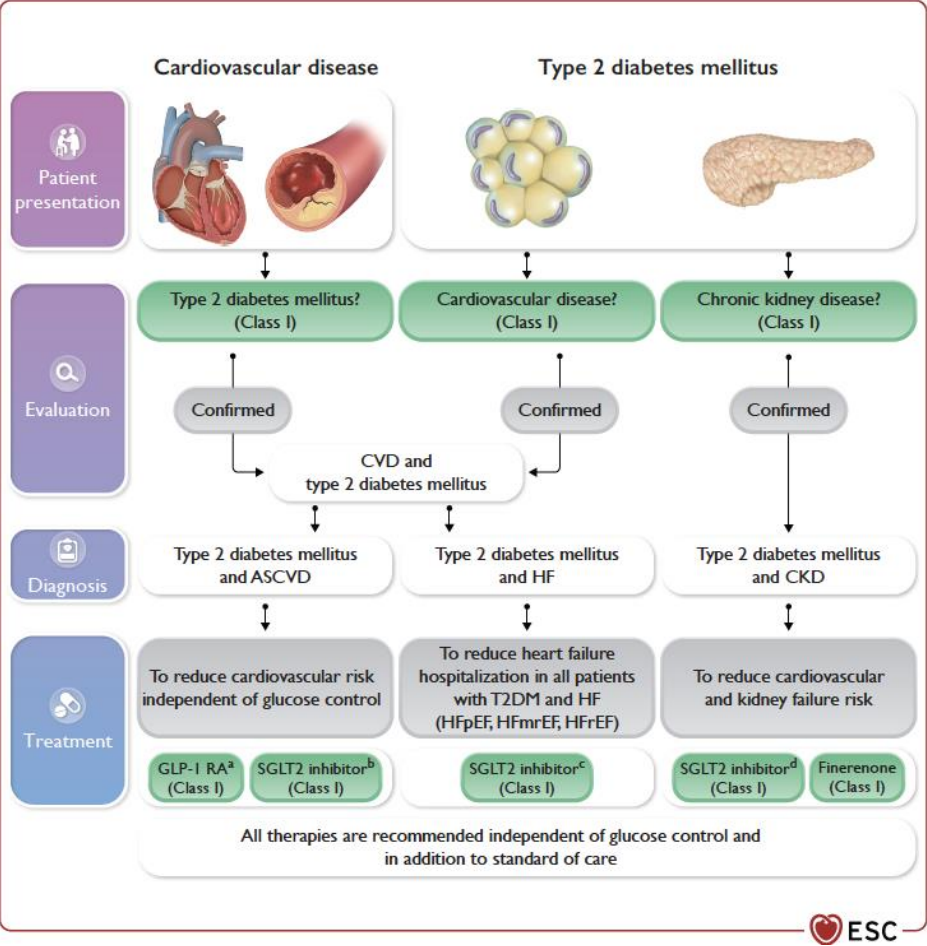


No. at Risk

Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734

The standard of care for metabolic patients is moving quickly

ESC Guidelines 2023: management for CVD in patients with diabetes



Recommendation Table 19 — Recommendations for sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome (see also Evidence Table 19)

Recommendations	Class ^a	Level ^b
CCS patients with type 2 diabetes		
SGLT2 inhibitors with proven CV benefit ^c are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication. ^{86,688,695,697,700}	I	A
GLP-1 receptor agonists with proven CV benefit ^d are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication. ^{710,711}	I	A
CCS patients without type 2 diabetes		
The GLP-1 receptor agonist semaglutide should be considered in overweight (BMI >27 kg/m ²) or obese CCS patients without diabetes to reduce CV mortality, MI, or stroke. ⁴⁶⁵	IIa	B

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How to manage gut hormone multi-agonists as background therapy in MASH trials in 2024 ?

The current situation: there is still no GLP-1 RA or multi-agonists approved for MASH

You have to consider the additional clinical benefits of GLP-1 RAs

- If the MASH candidate drug is a GLP-1 RA => SGLT2i can be selected as a priority in patients with T2D for ASCVD prevention
- In patients with obesity and/or diabetes with established ASCVD => it seems difficult to exclude GLP-1 RAs
- If the MASH candidate drug is not a GLP-1 RA => it is important to stratify on GLP-1 RA use

How to manage gut hormone multi-agonists as background therapy in MASH trials in 2024 ?

The oncoming situation: a GLP-1 RA or multi-agonist will be approved for MASH

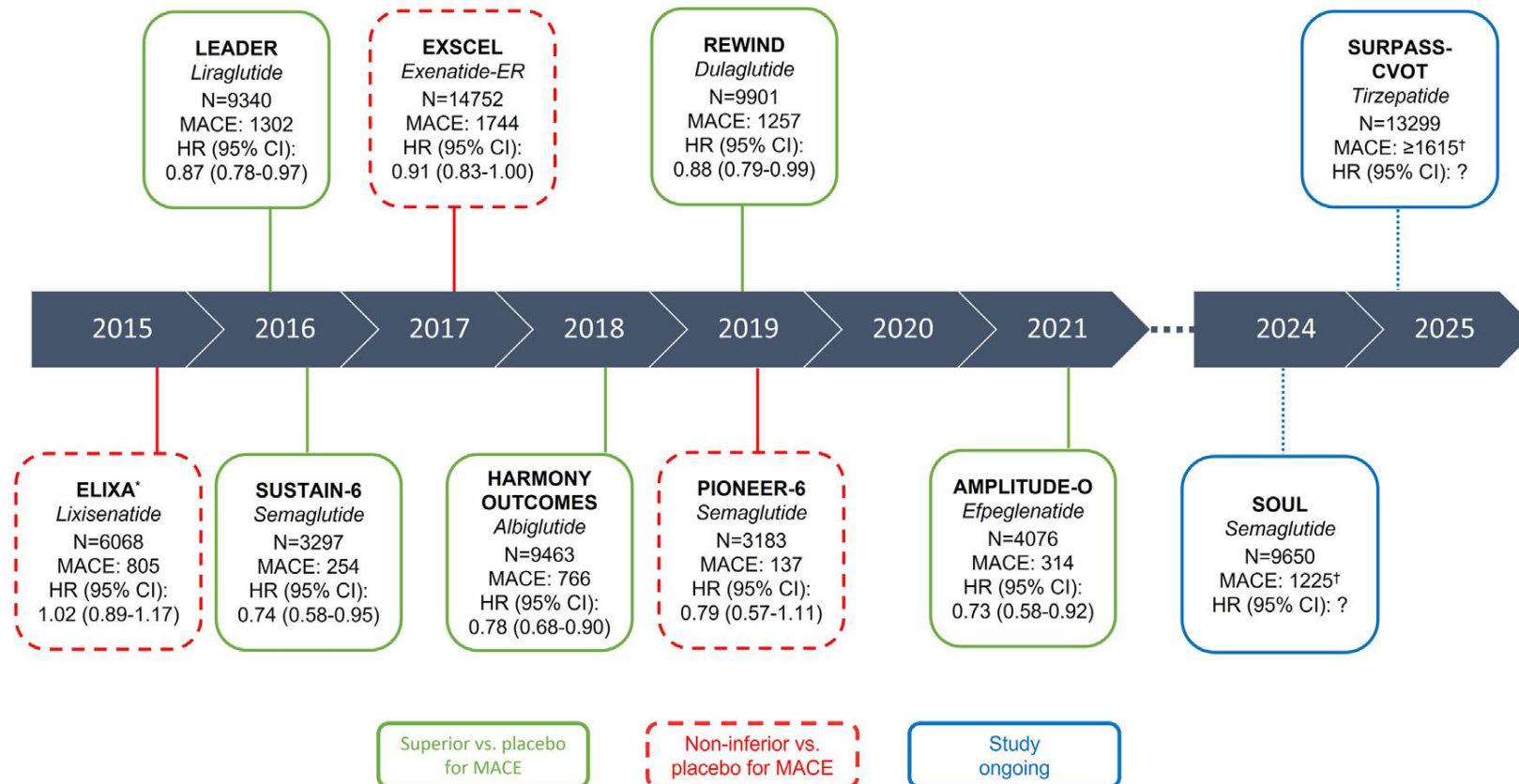


The first approved drug would be part of the new standard of care in patients with MASLD/MASH

How to manage gut hormone multi-agonists as background therapy in MASH trials in 2024 ?

The oncoming situation: a GLP-1 RA or multi-agonist will be approved for MASH

- Use an active comparator to ensure optimized standard care

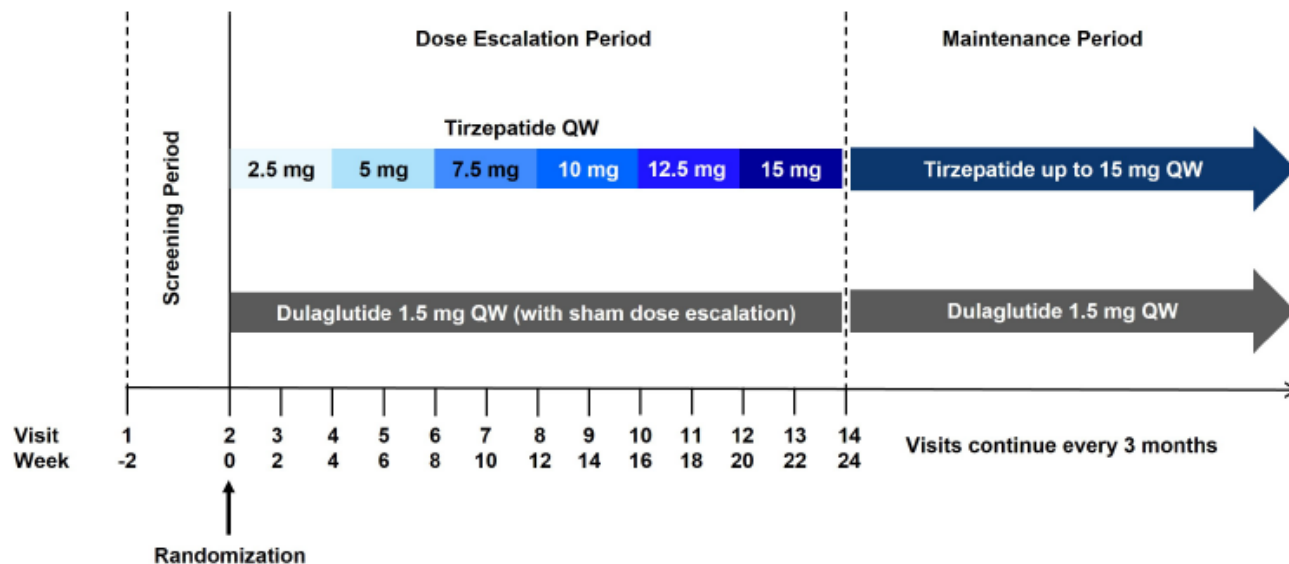


How to manage gut hormone multi-agonists as background therapy in MASH trials in 2024 ?

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Supplementary figure 1. SURPASS-CVOT study design



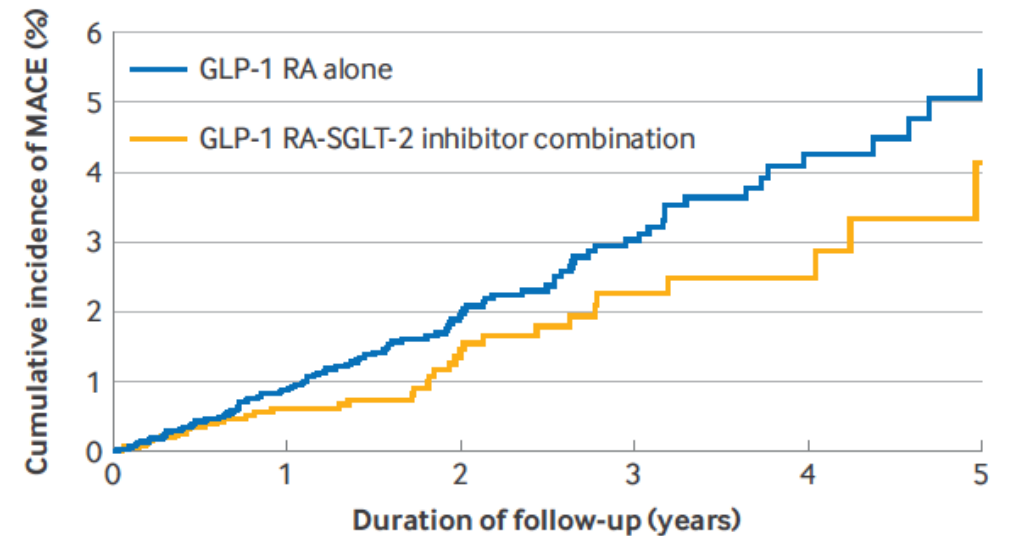
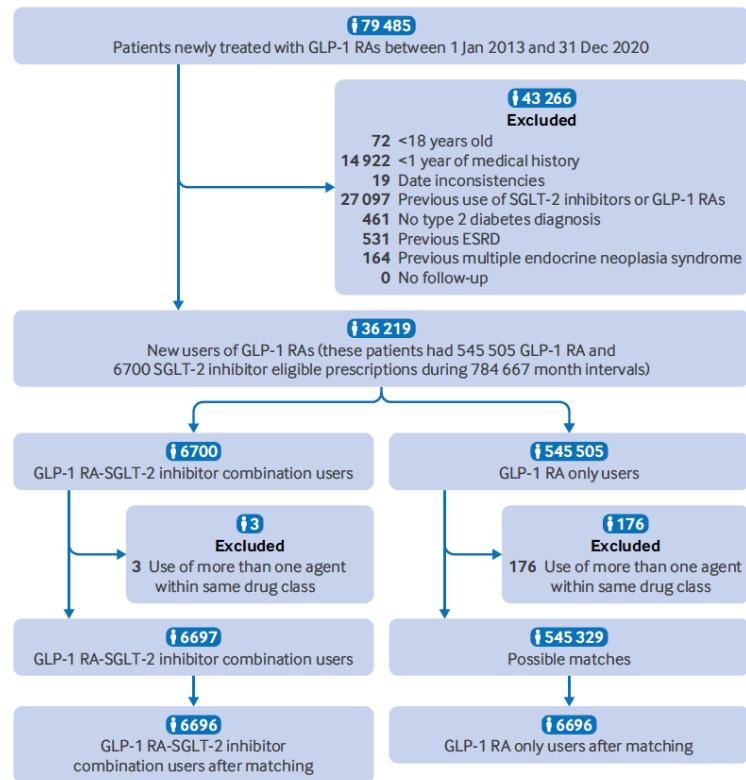
The primary analysis is noninferiority for time to first MACE of tirzepatide vs dulaglutide by demonstrating an upper confidence limit <1.05 , which will also confirm superiority vs a putative placebo, and also to determine whether tirzepatide produces a greater CV benefit than dulaglutide (superiority analysis).

Results expected in 2025

Population-based studies as alternative to RCT

Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study

Nikita Simms-Williams,¹ Nir Treves,² Hui Yin,¹ Sally Lu,³ Oriana Yu,^{3,4} Richeek Pradhan,⁵ Christel Renoux,^{3,6,7} Samy Suissa,^{3,6} Laurent Azoulay^{3,6,8}



No at risk

GLP-1 RA alone

6696 3798 1996 1072 532 242

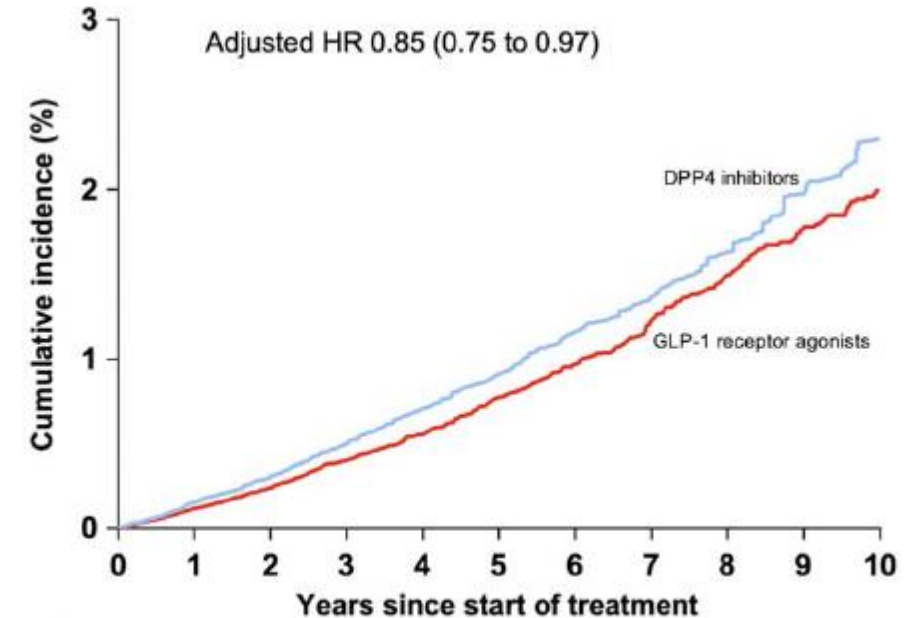
GLP-1 RA-SGLT-2 inhibitor combination

6696 1986 1000 519 259 114

Association of glucagon-like peptide-1 receptor agonists with serious liver events among patients with type 2 diabetes: A Scandinavian cohort study

Arvid Engström¹ | Viktor Wintzell¹ | Mads Melbye^{2,3,4,5} | Henrik Svanström^{1,6} | Björn Eliasson⁷ | Soffia Gudbjörnsdóttir^{7,8} | Kristian Hveem^{4,9} | Christian Jonasson^{4,9} | Anders Hviid^{6,10} | Peter Ueda¹ | Björn Pasternak^{1,6}

- > **300 000** new users of GLP-1 RAs or DPP4i between 2007 & 2020, aged 35-84 y
- PRS matching
- Median follow-up: 3.0 to 3.6 years
- Primary liver composite outcomes: **cirrhosis + liver cancer**

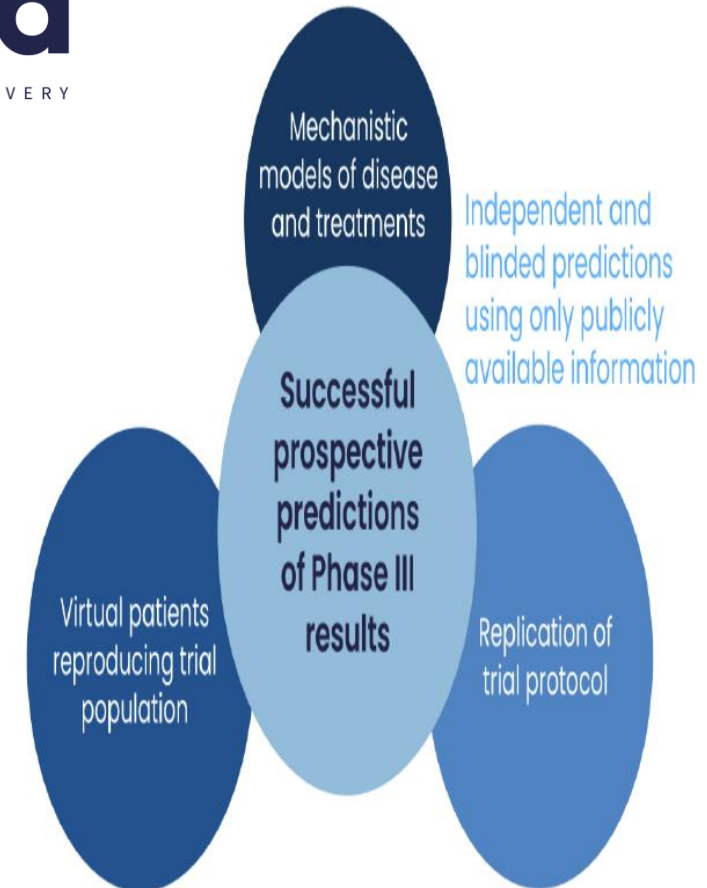
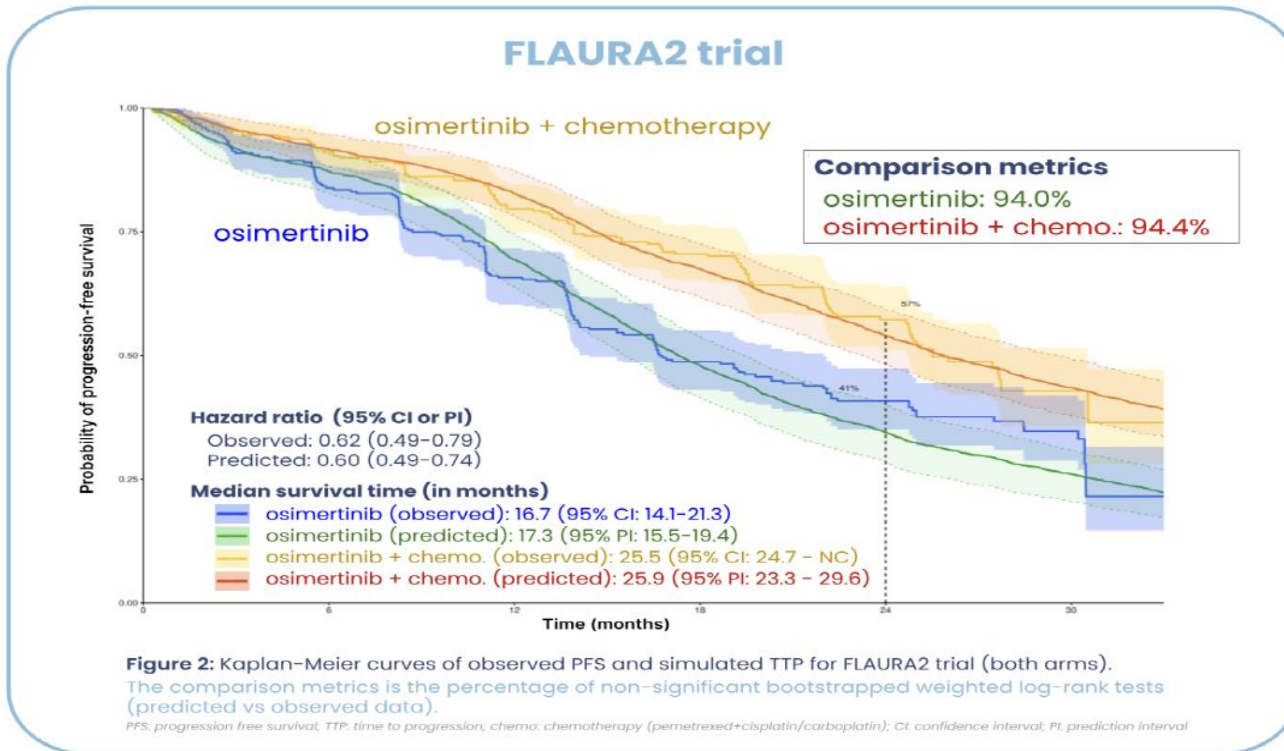


Number at risk										
GLP-1 receptor agonists	91479	71958	57609	45945	36919	29335	23152	18394	13800	9516
DPP4 inhibitors	244004	208838	171675	138869	108992	83908	63324	46880	32037	21138

AI and *in silico* trials as alternative to RCT

***In silico* clinical trial simulations**
prospectively **predict outcomes** of
Phase III FLAURA2 clinical trial

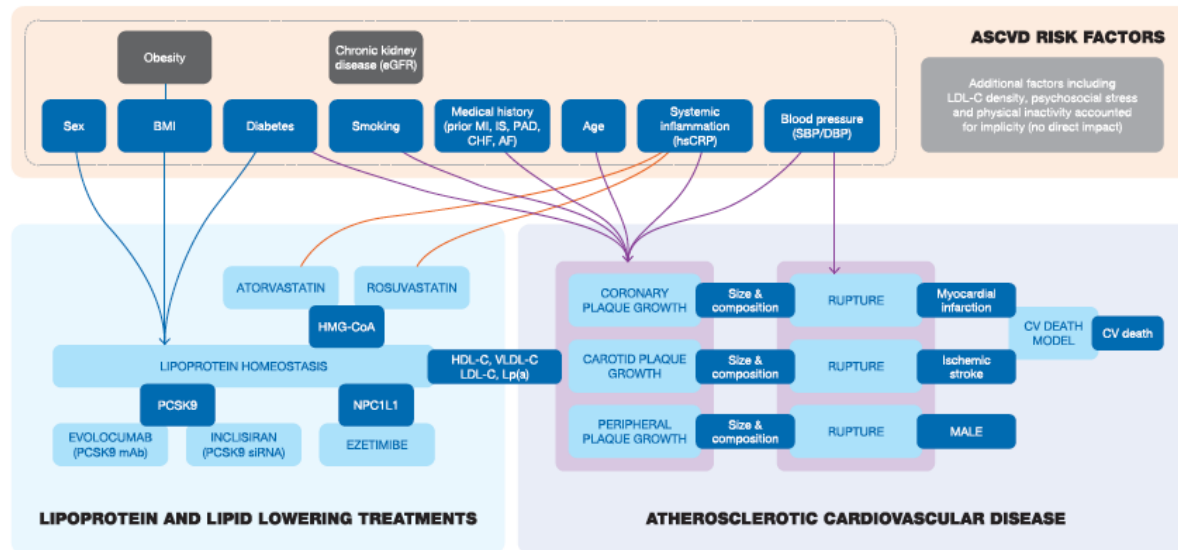
nova
DISCOVERY



EGF-R mutated lung adenocarcinoma

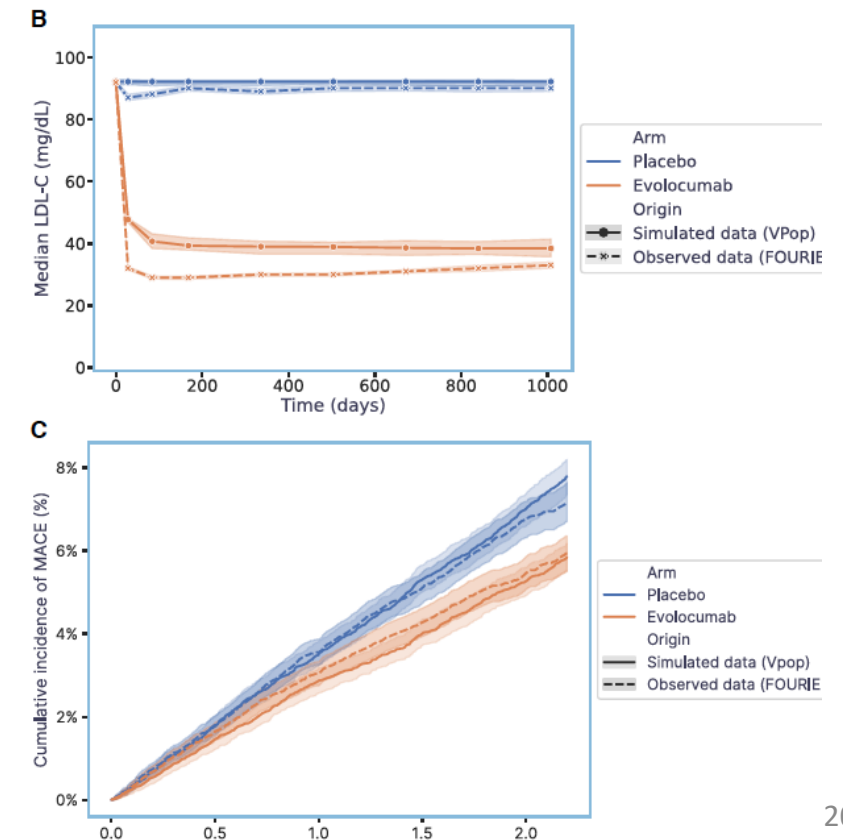
In-silico trial emulation to predict the cardiovascular protection of new lipid-lowering drugs: an illustration through the design of the SIRIUS programme

Denis Angoulvant^{1*}, Solène Granjeon-Noriot^{2†}, Pierre Amarenco³, Alexandre Bastien⁴, Emmanuelle Bechet², Franck Boccard⁵, Jean-Pierre Boissel², Bertrand Cariou⁶, Eulalie Courcelles², Alizée Diatchenko², Anne Filipovics⁴, Riad Kahoul², Guillaume Mahé⁷, Emmanuel Peyronnet², Lolita Portal⁴, Solène Porte², Yishu Wang², and Philippe Gabriel Steg⁸



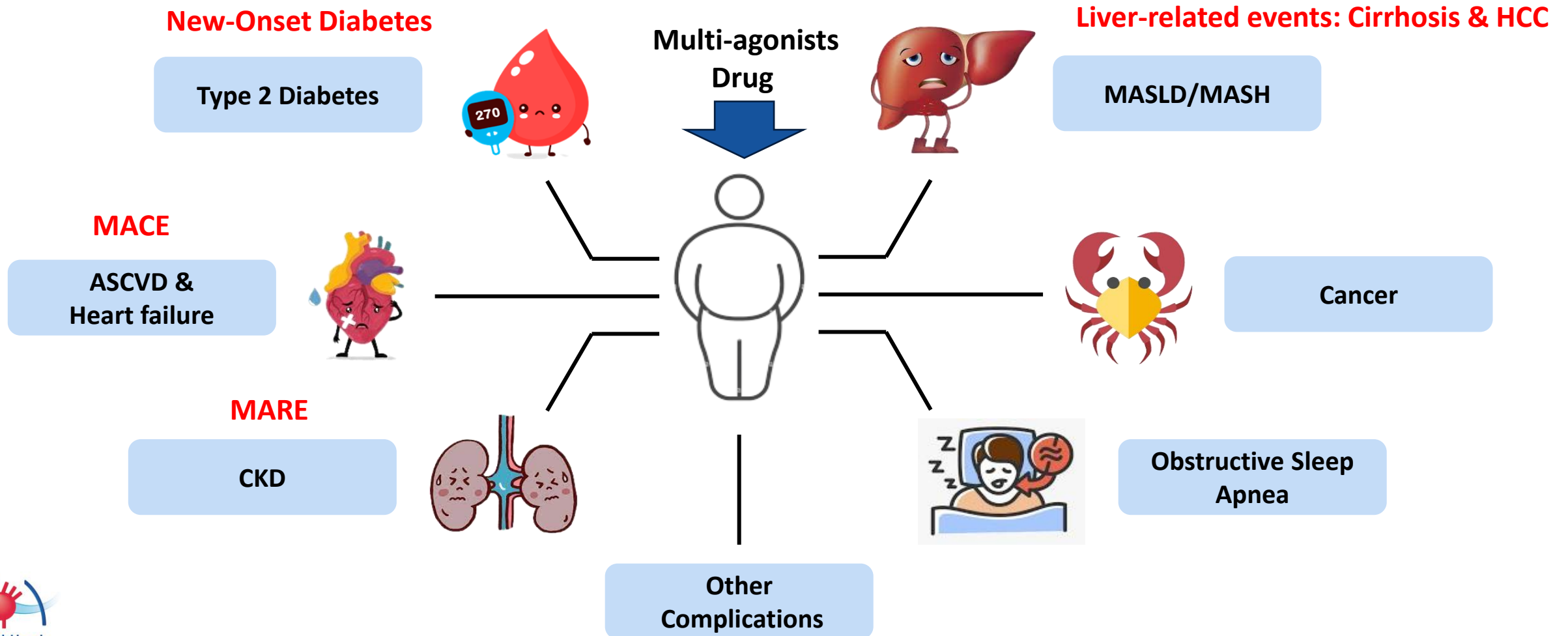
Knowledge-based mechanistic model

Calibration studies



Conclusion: a call for collecting MAME in RCT

MAME: **M**ajor **A**dverse **M**etabolic dysfunction-associated **E**vents



Thank you for your attention



GRAND OUEST NASH RESEARCH NETWORK