7e MASTERCLASS AMYLOSES CARDIAQUES
ÉVÉNEMENT HYBRIDE
PRÉSENTIEL & DISTANCIEL
Mercredi 11 décembre 2024
Fondation Biermans-Lapôtre ■ PARIS
www.masterclass-amylose.com

Où en est-on des traitements spécifiques en cours dans les ATTR

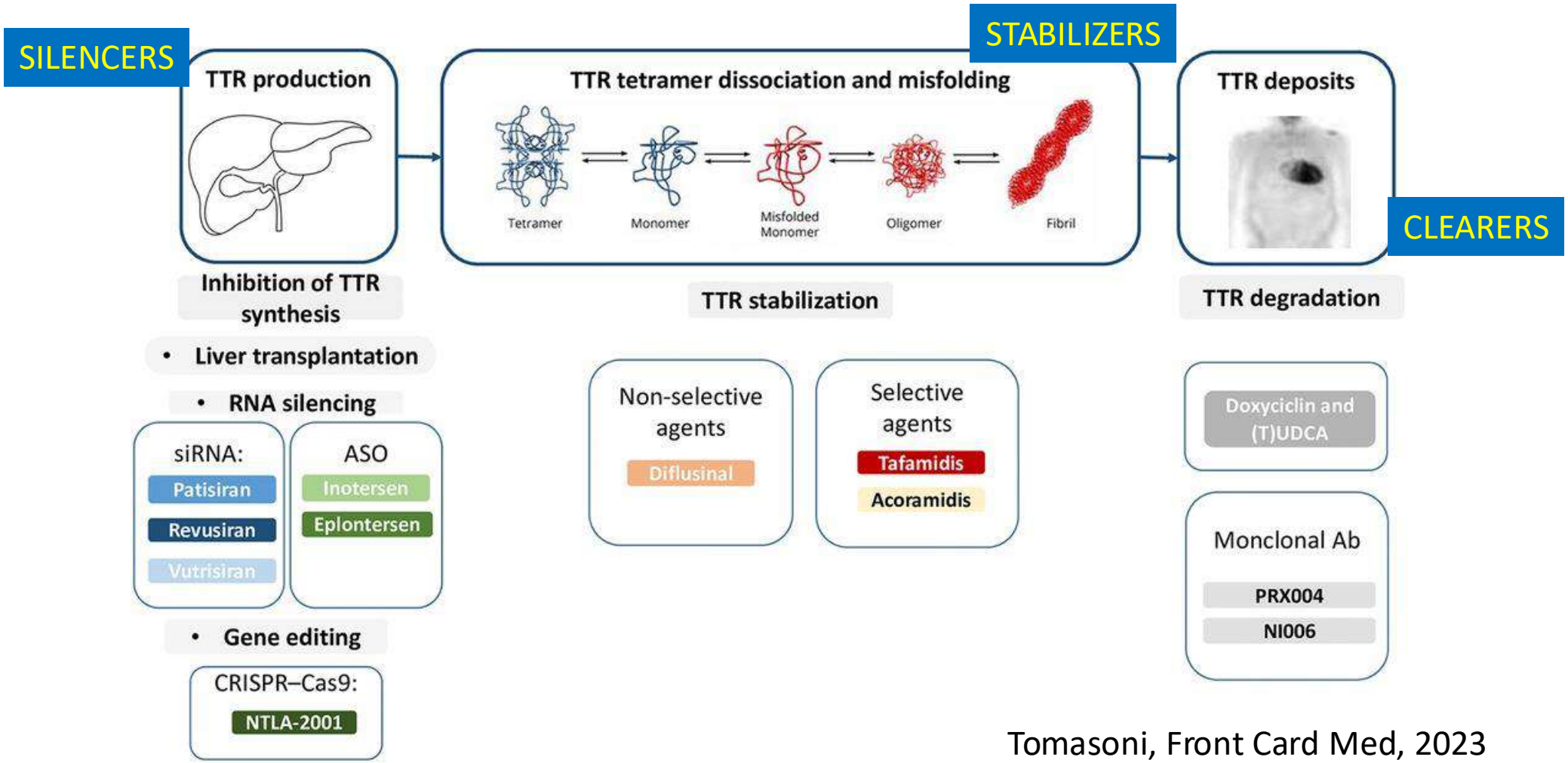
Comment adapter le traitement de nos patients à la vue d'HELIOS-B ?

Dr Fabrice BAUER

CHU Bicêtre - Paris-Saclay

UMR – 999 – Innovation thérapeutique en hypertension pulmonaire

Treatment targets in ATTR cardiac amyloidosis



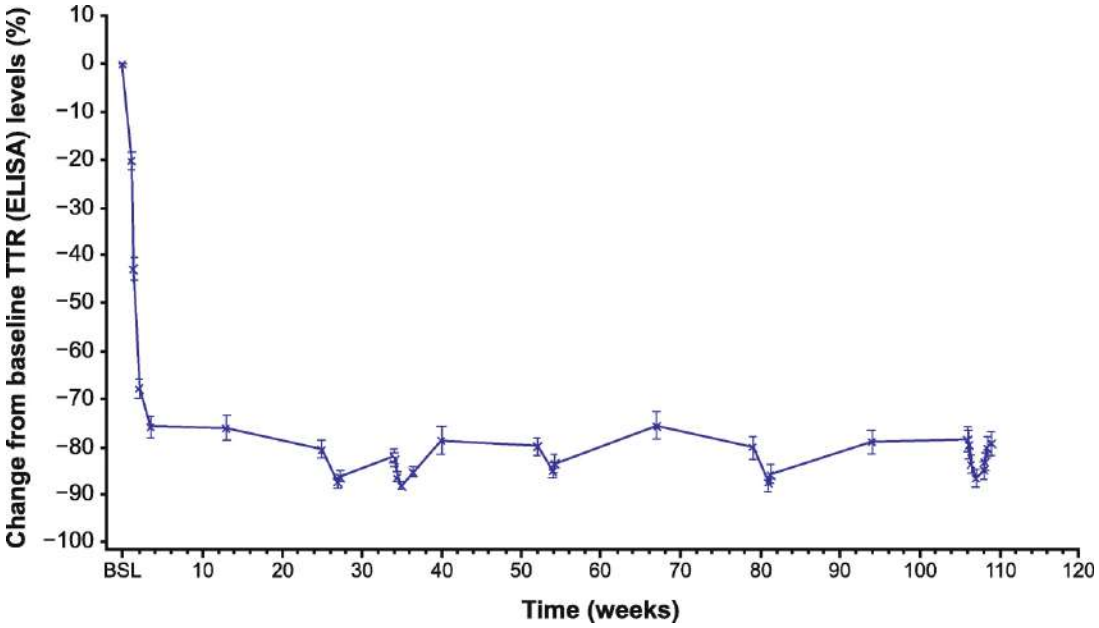
Tomasoni, Front Card Med, 2023

Silencers are early(est) targets in ATTR metabolism

Targets

- RNA silencing
  - SIRAN
    - PATISIRAN
    - VUTRISIRAN
  - TERSEN
    - INOTERSEN
    - EPLONTERSEN
- Gene editing
  - Crisper-CAS9

Transthyretin concentration with PATISIRAN



HELIOS B - trial

Study population

- Wild-type or hereditary ATTR with confirmed cardiomyopathy and symptomatic heart failure (HF)
- Patients on no background therapy (60%) or tafamidis at baseline (40%)

Who and what?

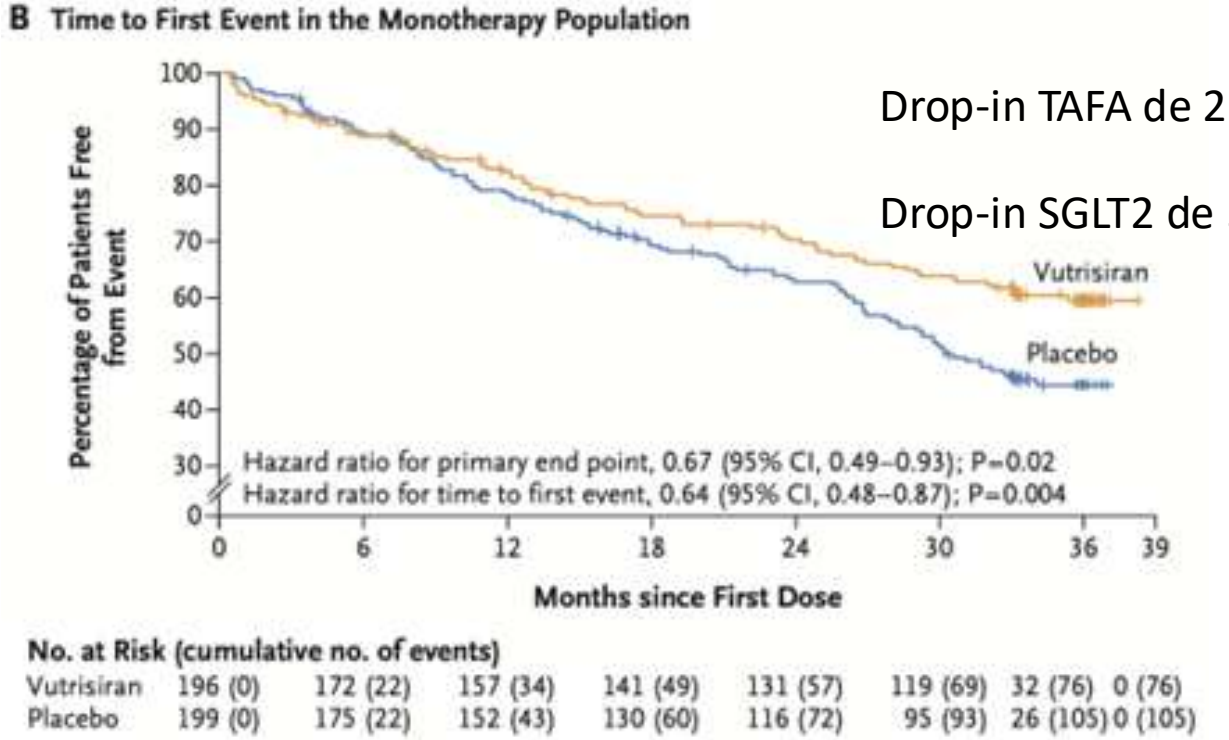
655 Patients

randomised 1:1

Vutrisiran SC 25 mg every 3 months

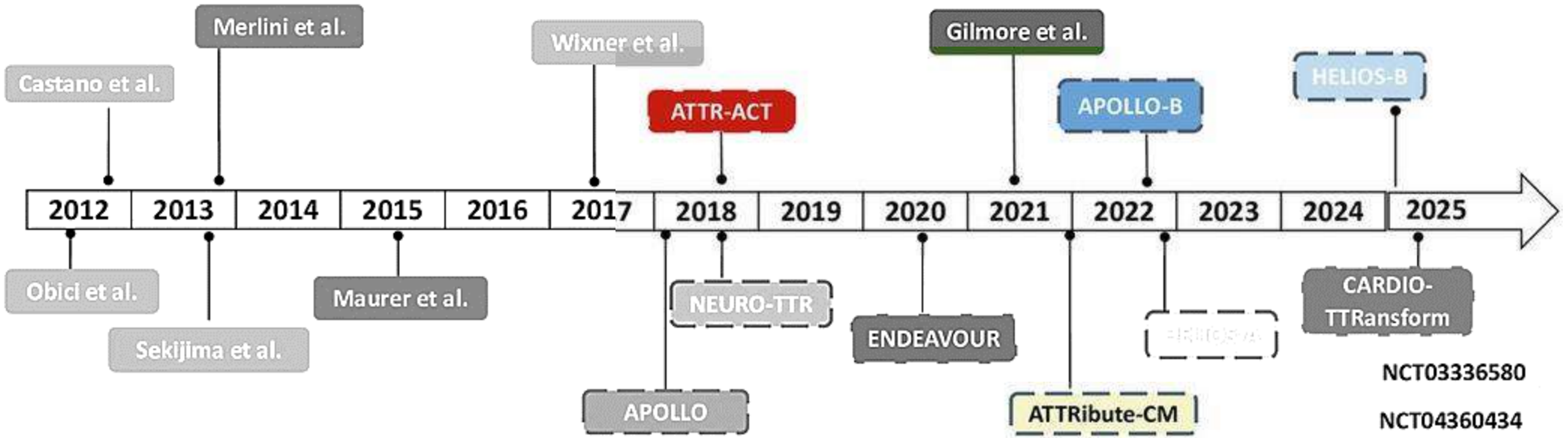
Placebo

Follow-up Up to 36 months



Drop-in TAFA de 22%

Drop-in SGLT2 de 35%

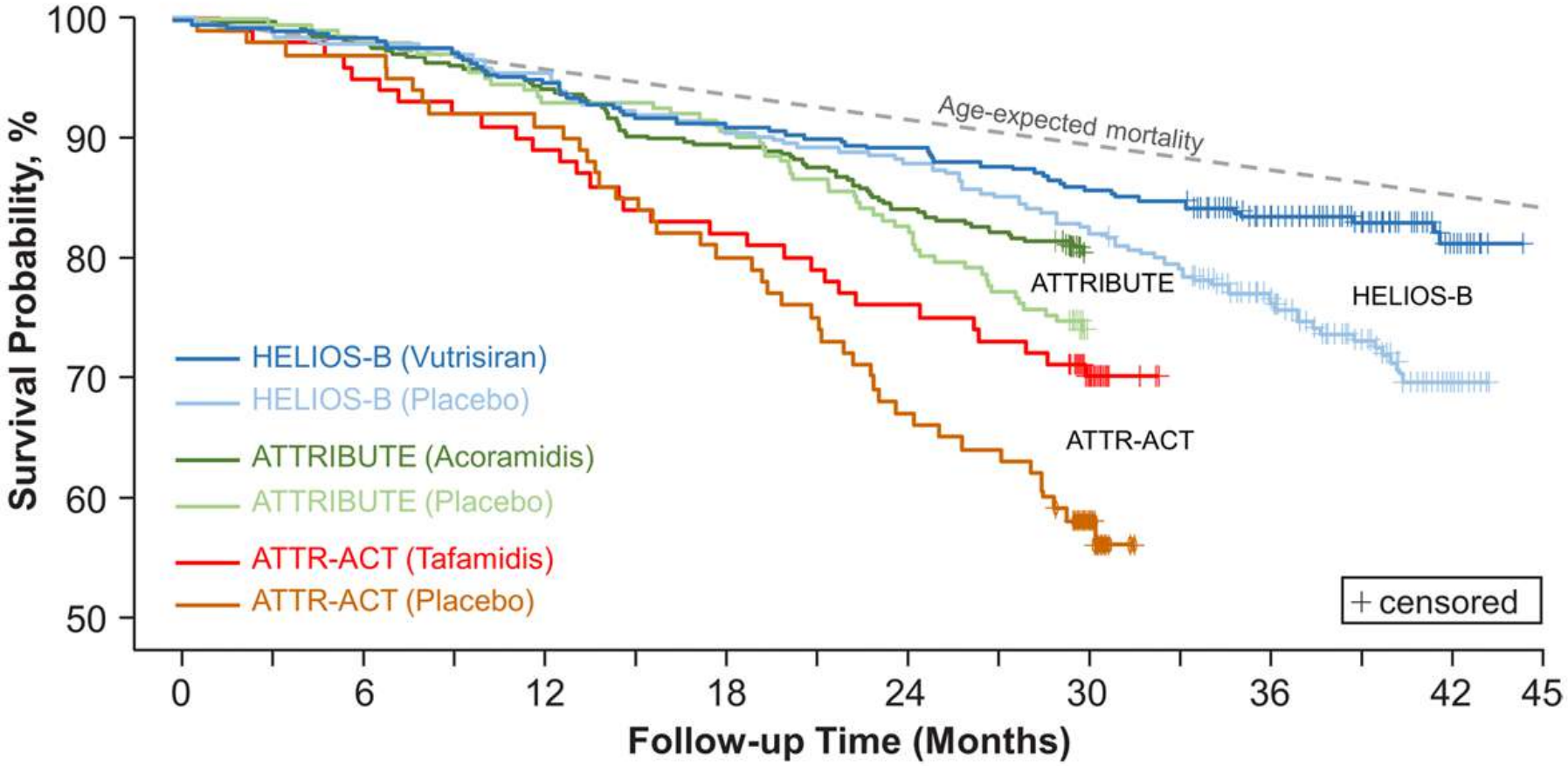


Tomasoni, Front Card Med, 2023

Comparison to other approved therapy

- ATTR-ACT → TAFAMIDIS
- ATTRIBUTE-CM → ACORAMIDIS
- HELIOS-B → VUTRISIRAN

Not only the primary end-point to look @



Girard, Heart Failure Review, 2024

Question addresses with VUTRISIRAN

Beijin, Summer olympics 2008

VUTRISIRAN FIRST

U Bolt

VUTRISIRAN COMBO « SIMULTANEOUSLY »

Nickel Ashmead

VUTRISIRAN COMBO « SEQUENTIALLY »

Shelly Ann Fraser

Question addresses with VUTRISIRAN

Beijin, Summer olympics 2008

VUTRISIRAN FIRST

We do not know !!

VUTRISIRAN COMBO
« SIMULTANEOUSLY »

We do not know !!

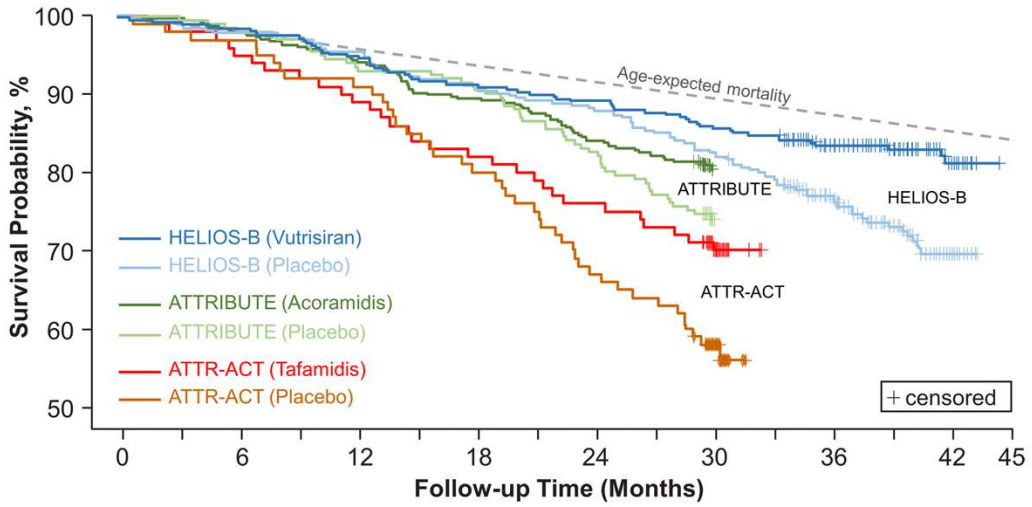
VUTRISIRAN COMBO
« SEQUENTIALLY »

Possibly

VUTRISIRAN FIRST ?!

	ATTR-ACT [10, 14, 17] Tafamidis (n = 264)	ATTRIBUTE-CM [7] Acoramidis (n = 421)	HELIOS-B [15] Vutrisiran (n = 326)
Age, years	75 (range 46–88)	77.4 ± 6.5	77.0 (range 45–85)
Sex			
Males	91.3%	91.2%	91.7%
Females	8.7%	8.8%	8.3%
Race			
White	79.9%	87.4%	85.0%
Black	14.0%	4.8%	7.1%
Genotype			
Wild type	76.1%	90.3%	88.7%
Variant	23.9%	9.7%	11.3%
NYHA class			
I	9.1%	12.1%	15.0%
II	61.4%	69.6%	76.7%
III	29.5%	18.3%	8.3%
NT-proBNP, pg/mL	2995.9 (752–4862)	2326 (1332–4019)	2021 (1138–3312)
NAC stage			
1	45.1%	57.2%	63.8%
2	36.0%	31.8%	30.7%
3	18.9%	10.9%	5.5%

"Silencers vs. stabilizers trials would certainly have addressed this question, but they will definitely not be conducted."



Girard, Heart Failure Review, 2024

Another difficulties in comparing these studies

- Timing, inclusion criteria, baseline characteristics different
- Cross-trail comparison impossible
  - Different endpoints
  - Different statistical methodolgy
    - HELIOS-B: event-driven
    - ATTR-ACT: win ratio
    - ATTRIBUTE-CM: win ratio
  - Duration
    - HELIOS-B: 36 mois
    - ATTR-ACT: 30 mois
    - ATTRIBUTE-CM: 30 mois

VUTRISIRAN COMBO SIMULTANEOUSLY ?!

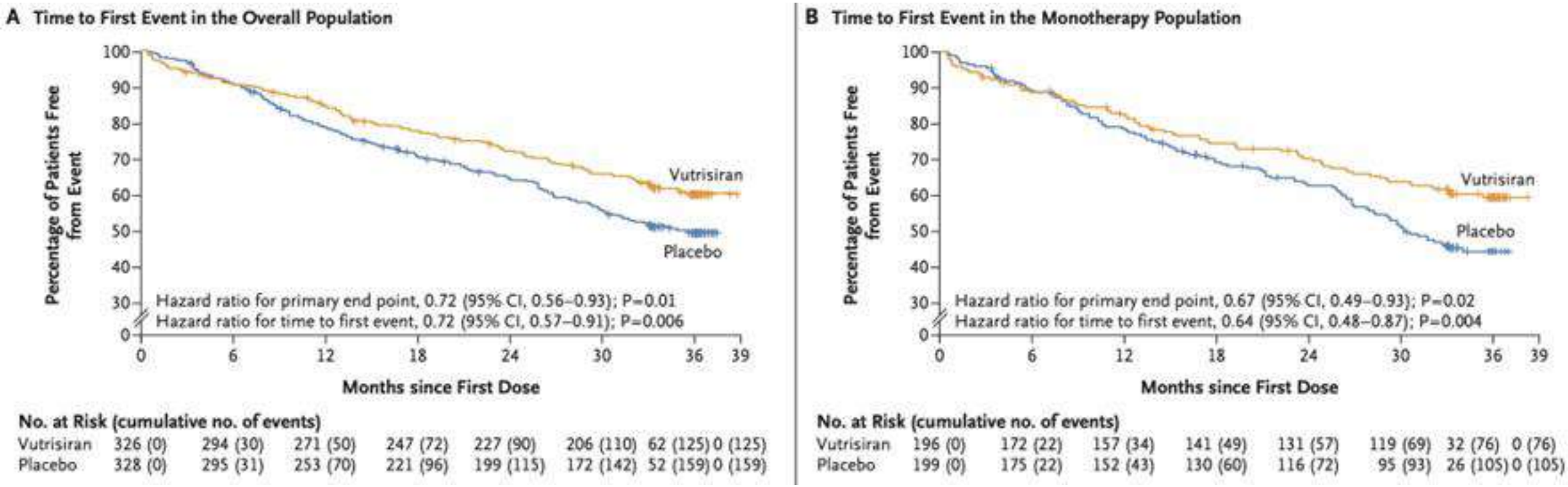
“single vs. dual combination therapy trials would certainly have addressed this question, and could be definitely be conducted."

In ATTR-ACT, ATTRIBUTE-CM and HELIOS-B, there is a signal that « less sick » patients had better outcomes.

VUTRISIRAN COMBO SEQUENTIALLY ?!
No trial but a signal

	ATTR-ACT [10, 14, 17] Tafamidis (n = 264)	ATTRIBUTE-CM [7] Acoramidis (n = 421)	HELIOS-B [15] Vutrisiran (n = 326)
Tafamidis use			
Baseline	N/A	0%	40%
Drop-in	N/A	14.5%	13.5%

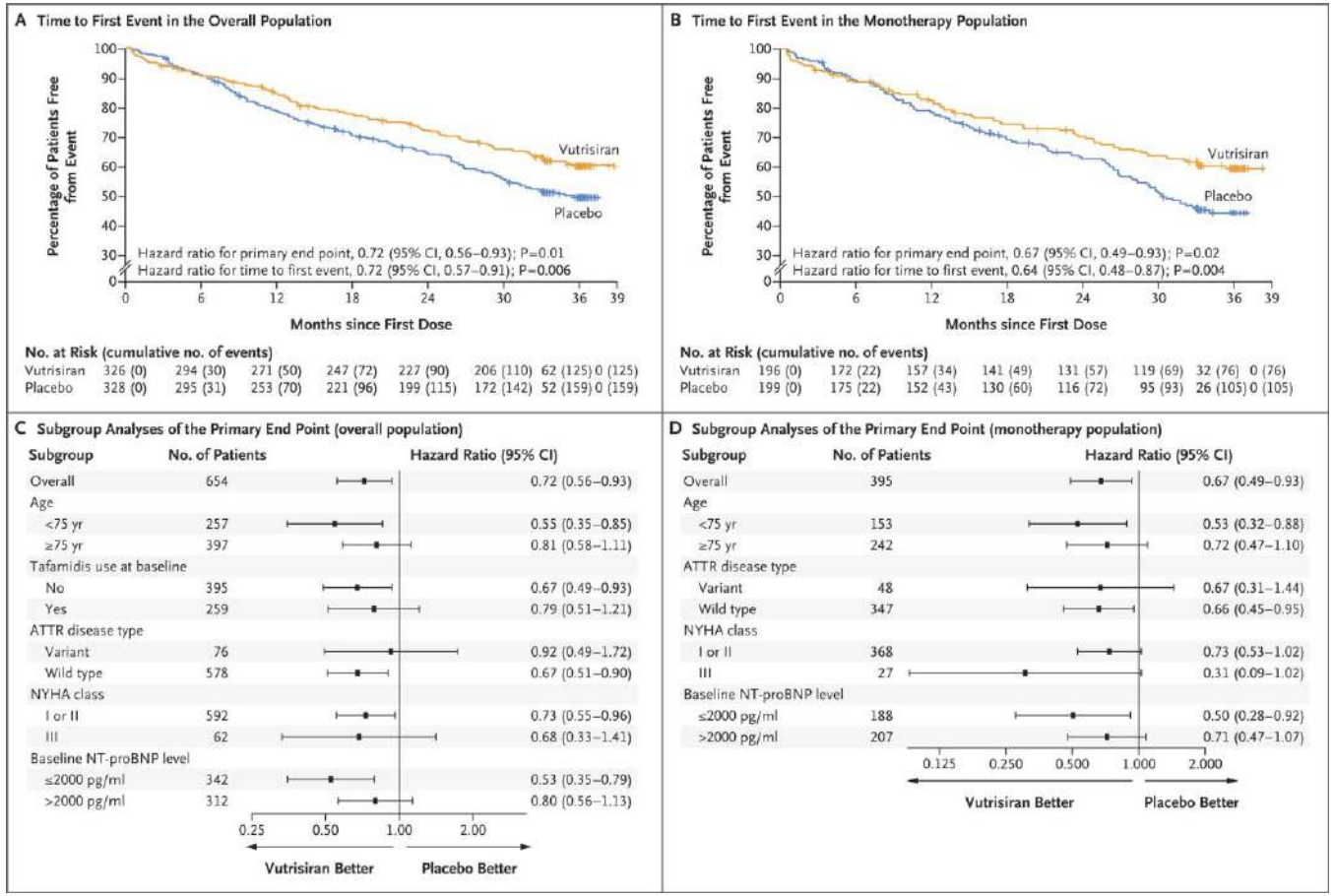
VUTRISIRAN COMBO SEQUENTIALLY ?!
Not a trial but a signal



40% of the patients were not treatment-naïve and were already receiving TAFAMIDIS

Fontana, JEJM, 2024

Do not expect from data what they did not tell you



Fontana, JEJM, 2024

HELIOS-B: not treatment-naïve patients

Inclusion Criteria:

- Age between 18 and 85 years.
- Diagnosis of genetic or wild-type transthyretin (TTR) cardiac amyloidosis (confirmed by histology or bone scintigraphy with cardiac uptake and no evidence of gammopathy).
- Septal thickness on echocardiography (TTE) greater than 12 mm.
- At least one hospitalization for heart failure or clinical signs of heart failure.
- NT-proBNP > 300 pg/mL and < 8500 pg/mL.
- Six-minute walking distance greater than 150 meters.
- Tafamidis treatment is possible at the time of inclusion.

Exclusion Criteria:

- NYHA class 4 or NYHA class 3 with NAC 3 amyloidosis.
- Severe polyneuropathy.
- Other causes of cardiomyopathy.
- Glomerular filtration rate (GFR) < 30 mL/min/m^2

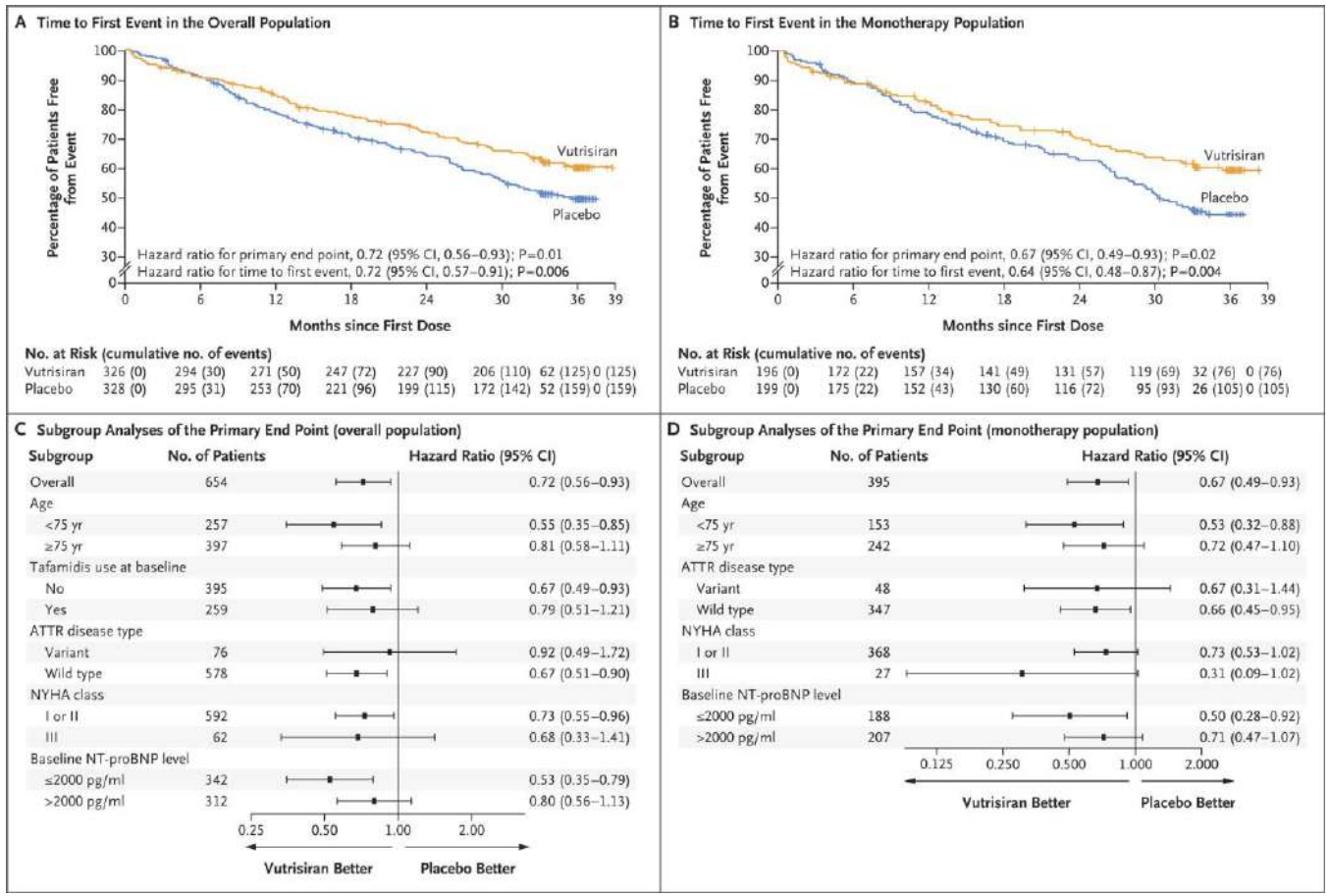
Eligibility for PATISIRAN nowadays: progression-based

EVALUATION DE LA PROGRESSION SOUS TAFAMIDIS 61mg selon le consensus de l'ESC ATTR-CM de 2021

1 paramètre minimum par domaine doit être coché

Clinique	Biologique	Imagerie
☐ **Nouvelle Hospitalisation pour IC en l'absence de facteurs déclenchants modifiables (inobservance, régime hyposodé, inobservance du traitement diurétique, fibrillation atriale paroxystique, infection)**	☐ Augmentation de NT-proBNP (30% ou 300pg/mL)	☐ Augmentation de l'épaisseur myocardique (2mm)
☐ **Augmentation de Classe NYHA**	☐ Augmentation de Troponine (30%)	☐ Augmentation du grade de fonction diastolique
☐ **Dégradation de Qualité de vie (déclin de 5-10 pts KCCQ ou 10% EQ-5D)**	☐ Augmentation du Score NAC	☐ Changement de la fonction systolique (≥5% déclin de la FEVG, ≥5mL de déclin du VES, ≥1% augmentation du SLG)
☐ **Déclin du TDM6 (30-40m)**		☐ Apparition ou aggravation de troubles conductifs
☐ **Majoration de la dose de diurétique de plus de 80 mg au cours des 12 mois précédents**		

Do not expect from data what they did not tell you, but somtimes make your mind up



Fontana, JEJM, 2024

In reality, In all 3 studies, there is a signal that "less sick" patients (i.e., based upon younger age, lower NTproBNP, lower NYHA class) had better outcomes. A cross-trial comparison highlights the fact that enrolling less sick patients at earlier stage disease in treatment trials from ATTR-ACT to ATTRIBUTE-CM and HELIOS-B has led all-cause mortality to approach the population expected 3-year rate

Conclusion:
How to adapt our patients' treatment in light of HELIOS-B?

- **Medical history is shaped by treatment timelines and evidence-based medicine.**
- **In CA, the paradigm should shift from titration based on disease worsening to a treat-to-target approach, aiming to address less severely ill patients.**
- **Therefore, VUTRISIRAN**
  1. ***does not currently appear as a first-line therapy***
  2. ***Should be initiated as soon as possible if risk stratification is not appropriate after FLT was started***
- ***A lot to do, a lot to learn … and still a lot to investigate before to conclude***