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XXXIII.

VÝROČNÍ SJEZD
ČESKÉ KARDIOLOGICKÉ
SPOLEČNOSTI

THE SARAH TRIAL

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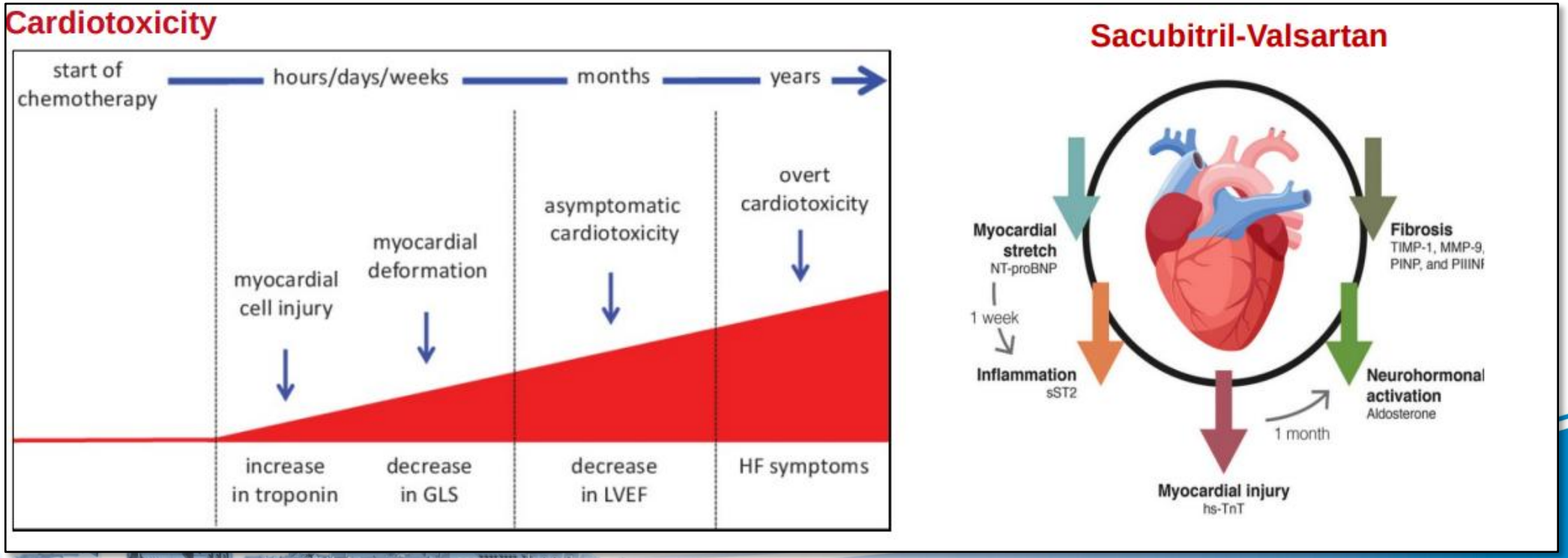
Studie SARAH

EFFECTS OF SACUBITRIL-VALSARTAN ON PREVENTION OF CARDIOTOXICITY IN HIGH-RISK PATIENTS UNDERGOING ANTHRACYCLINE CHEMOTHERAPY: A DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL: THE SARAH TRIAL

- prezentace studie 11/2024 (kongres AHA)

Background:

- riziko kardiotoxicity závislé na dávce (10 – 65%) , limituje terapii či zvyšuje morbiditu



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Základní cíl:

- sakubitril/valsartan je schopen efektivně prevenovat rozvoj kardiotoxicity u vysoce rizikových pacientů podstupujících terapii antracykliny

Design studie:

- monocentrická, randomizovaná, dvojitě zaslepená placebem kontrolovaná
- 3-8/2024 (Erasto Gaertner Hospital, Curitiba, Brazílie)
- 100 pacientů, follow-up 24 týdnů

Podmínky pro zařazení do studie:

- p. starší 18 let s rakovinou podstupující chemoterapii ANT, u kterých došlo po podání ANT ke zvýšení hladiny vysoce citlivého troponinu I (hs-TnI) nad 99. percentil.

Vyřazení ze studie:

- nemožnost stanovit LVEF
- předchozí chemo-/radioterapie, terapie RAASi a betablokátory
- preexistující onemocnění myokardu (KMP, ICHS, srdeční vada)
- kontraindikace sakubitrilu (angioedém, stenóza a.renalis, GFR<30 ml/min/m², K >5,0 mmol/l, těhotné ženy, sTK <100 mmHg

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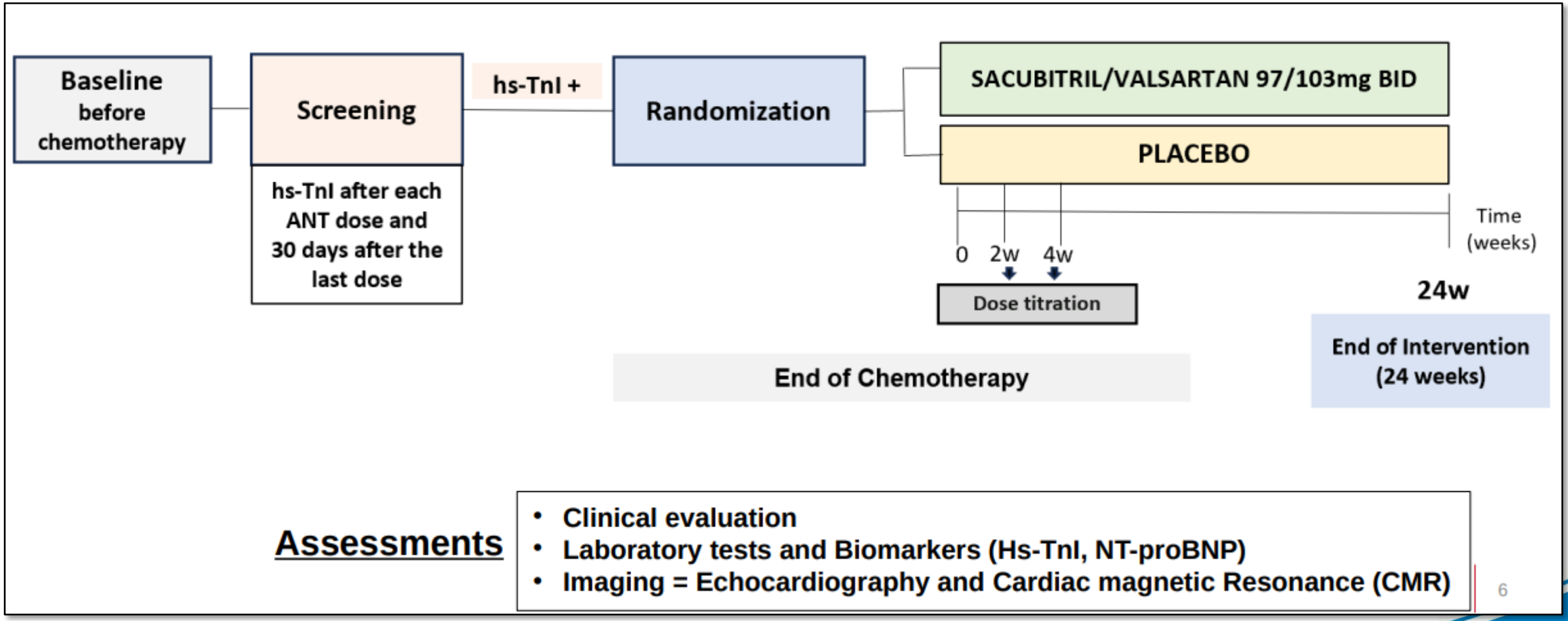
Design studie:



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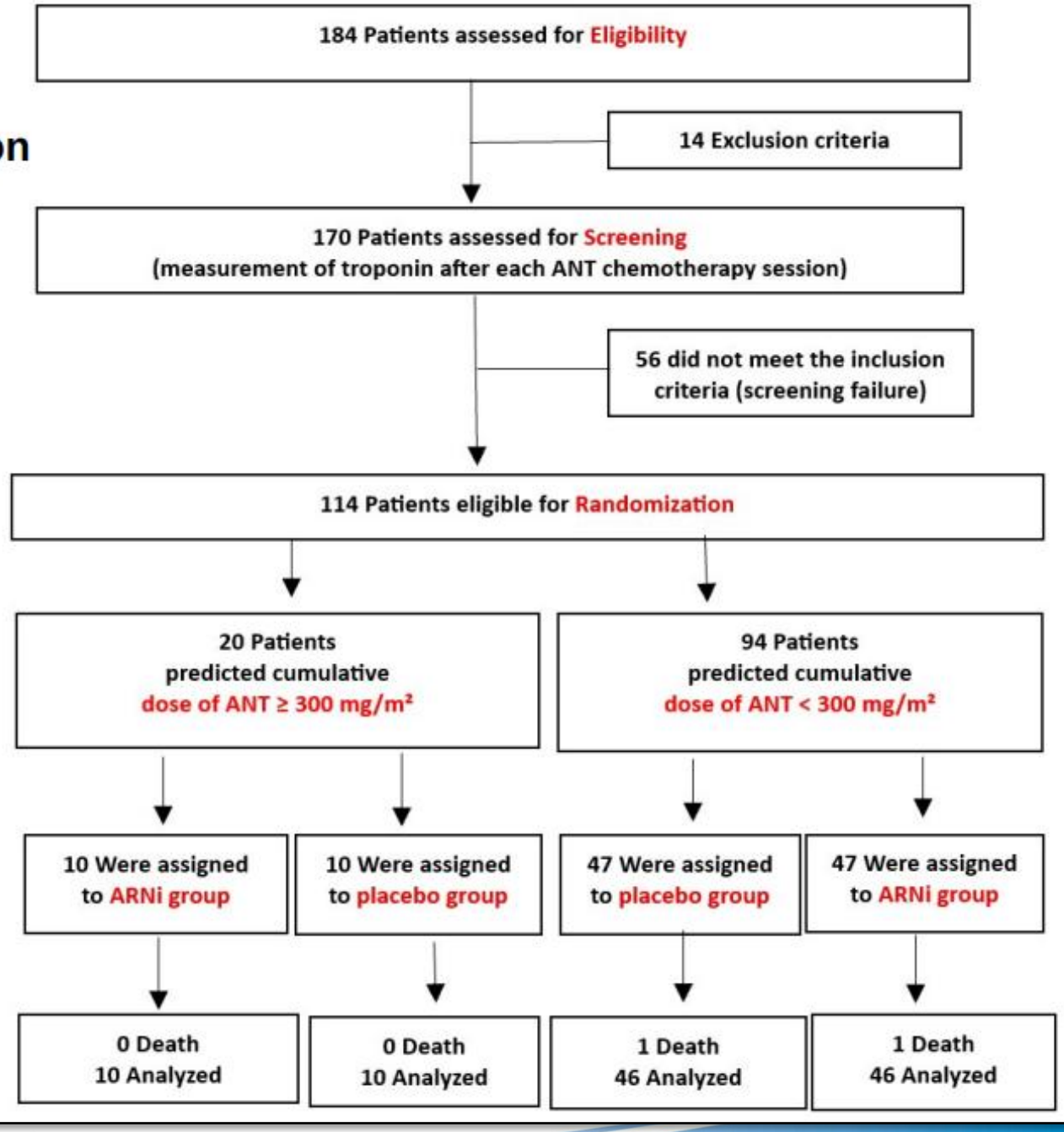
SARAH TRIAL

Patient Enrollment and Randomization



Intention-to-treat analysis

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Baseline charakteristika

	ARNi (n = 57)	Placebo (n = 57)
Age, yrs	51.6 ± 11.6	51.7 ± 11.6
Women, n (%)	53 (93.0)	50 (87.7)
Oncological disease		
Breast cancer, n (%)	47 (82.5)	45 (79)
Leukemia, n (%)	0 (0)	1 (1.8)
Lymphoma, n (%)	9 (15.7)	10 (17.4)
Sarcoma, n (%)	1 (1.8)	1 (1.8)
Any Comorbidities, n (%)	37 (64.9)	36 (63.2)
Hypertension, n (%)	18 (31.6)	18 (31.6)
Diabetes mellitus, n (%)	6 (10.5)	5 (8.8)
Hypercholesterolemia, n (%)	10 (17.5)	3 (5.3)
Smokers, n (%)	1 (1.8)	2 (3.5)
Body mass index, kg/m^2	27.4 ± 5.3	29.0 ± 5.0
Systolic blood pressure, mmHg	120 (100 to 195)	130 (100 to 160)
Diastolic blood pressure, mmHg	78.5 (60 to 127)	80 (60 to 100)
Serum creatinine, mg/dL	0.8 (0.4 to 1.3)	0.7 (0.5 to 1.5)
Serum potassium, mmol/L	4.5 ± 0.4	4.4 ± 0.4
Tolerated dose ARNi/placebo, mg/day	345	344
Cumulative ANT dose mg/m2	240 (144 to 357)	239 (174 to 473)
Radiotherapy, n (%)	41 (71.9)	41 (71.9)
Serum hs-TnI baseline, ng/L	1.5 (1.5 to 8.1)	1.5 (1.4 to 8.2)
GLS baseline (%)	-20.2 (-28.9 to -15.9)	-20.1 (-29 to -15.5)
Echo LVEF baseline, (%)	64.4 ± 4.9	63.7 ± 3.9
Serum hs-TnI randomization, ng/L	24.9 (3.2 to 398.3)	19.1 (4 to 148.1)
Serum NT-ProBNP randomization, pg/mL	10 (2 to 238)	12 (2 to 277)
GLS randomization (%)	-18.8 ±2.8	-19.1 ± 3.2
Echo LVEF randomization, (%)	63.3 ± 3.9	62.3 ± 4.3
CMR LVEF randomization, (%)	58.8 ± 8.7	60.3 ± 5.8

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PRIMARY ENDPOINT

SARAH Trial met the Primary Endpoint

Primary Endpoint	ARNi (n=56)	Placebo (n=56)	OR (95% CI)	P value
GLS decrease >15%, n (%)	4 **(7.1%)**	14 **(25%)**	**0.23** (0.07 to 0.75)	**0.015**

Relative Risk Reduction = 77%

NNT = 5.59

The differences between groups occurred independently of risk factors such as:
mean indexed cumulative dose of ANT, HER2 positivity, presence of hypertension and age

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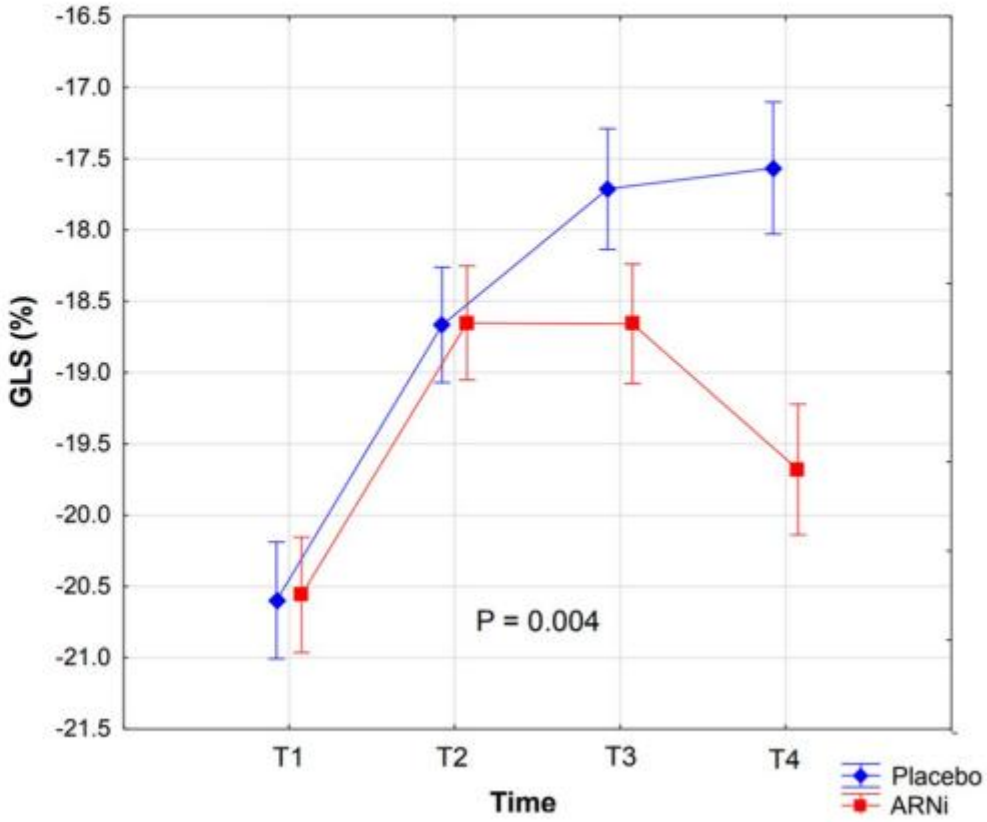
SECONDARY ENDPOINT

GLS variation after 24 Weeks

Secondary Endpoints	ARNi (n=56)	Placebo (n=56)	P value
GLS (%)			
End of treatment	-19.5 ± 3.1	-17.6 ± 3.6	0.004
Absolute change	-0.5 (-12.7 to 10.3)	1.5 (-12.2 to 12.7)	<0.001
Percentual change	**Improvement 2.5 %**	**Decline 7.6 %**	**<0.001**



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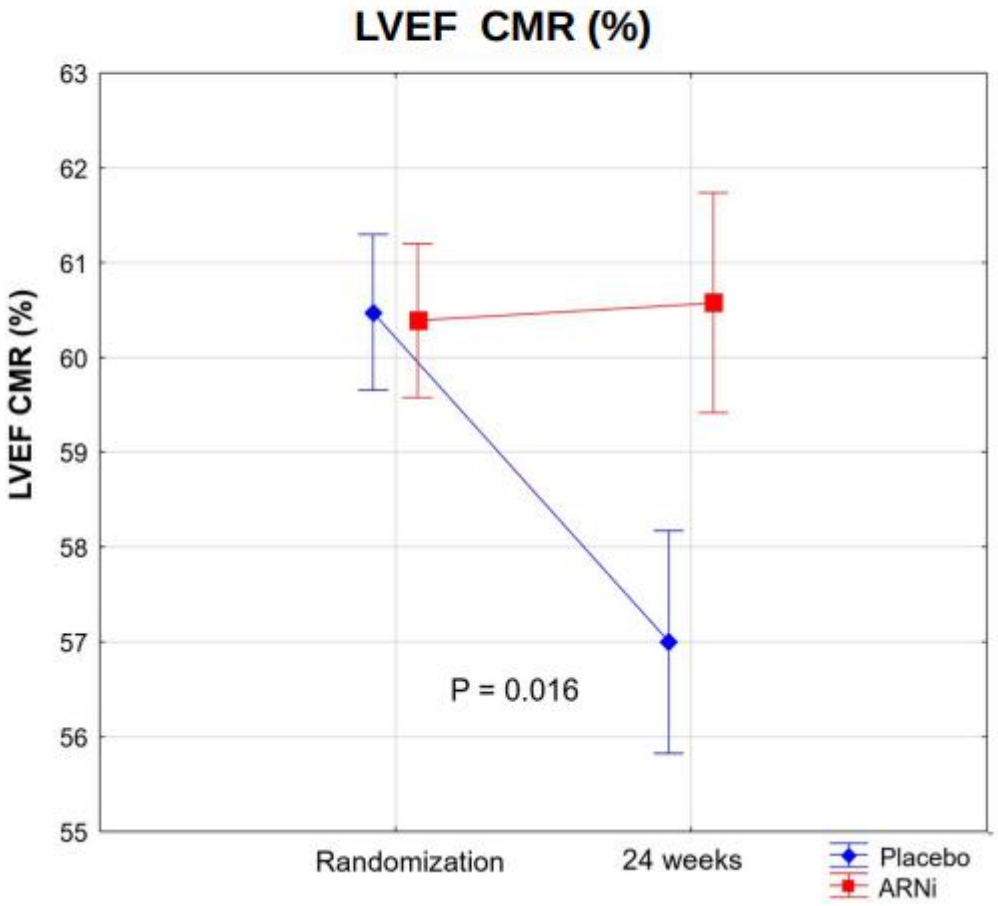
SECONDARY ENDPOINTS

Echo and CMR parameters after 24 Weeks

Secondary Endpoints	ARNi (n=56)	Placebo (n=56)	P value
LVEF decrease >10% with final value <53%			
• **ECHO**, n (%)	4 **(7.1%)**	4 **(7.1%)**	**1**
• **CMR**, n (%)	2 **(3.7%)**	6 **(11.3%)**	**0.161**
LVEF			
• **ECHO** (%)	**64** (42 to 79)	**62** (28.5 to 72)	**0.052**
• **CMR** (%)	**61** (27 to 73)	**58** (23 to 70)	**0.027**
LVEDV (ECHO) (mL)	**83.1** (42 to 160)	**92.4** (47.4 to 182)	**0.026**
LVESV (CMR) (mL)	**43** (19 to 166)	**48** (24 to 190)	**0.036**



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Left Ventricular Dysfunction Evaluated by Echo and CMR

	ARNi (n=56)	Placebo (n=56)	P value
LVEF <50% (CRM), n (%)	2 **(3.7%)**	9 **(17.0%)**	**0.029**
GLS > - 18%, n (%)	14 **(25.0%)**	27 **(48.2%)**	**0.018**
LVEF <50% (ECHO), n (%)	3 **(5.4%)**	6 **(10.7%)**	**0.489**

ARNi reduced the risk of ventricular dysfunction after 24 weeks

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Safety Endpoints and Variations in Hemodynamic and Laboratory Parameters

	ARNi (n=57)	Placebo (n=57)	P value
Adverse effects (all), n (%)	11 **(19.3%)**	9 **(15.8%)**	**0.806**
• **Hypotension**, n (%)	8 **(14%)**	1 **(1.8%)**	**0.032**
• **Nonspecific discomfort or weakness**, n (%)	3 **(5.3%)**	6 **(10.5%)**	**0.490**
• **Dizziness**, n (%)	0 **(0%)**	2 **(3.5%)**	**0.495**
Dose reduction, n (%)	8 **(14%)**	4 **(7%)**	**0.361**
Discontinuation, n (%)	2 **(3.5%)**	6 **(10.5%)**	**0.271**
Laboratory parameter			
Creatinine (mg/dl)	**0.70** (0.50 to 1.20)	**0.70** (0.50 to 1.40)	**0.759**
Potassium (mmol/L)	**4.31** ± 0.42	**4.16** ± 0.39	**0.047**
Troponin (ng/L)	**2.9** (1.5 to 27.1)	**2.5** (1.5 to 26)	**0.924**
NT-ProBNP (pg/ml)	**17** (2 to 499)	**17** (2 to 1475)	**0.872**
Hemodynamic parameters			
SBP (mmHg)	**124.7** ± 18.2	**130.4** ± 20.3	**0.121**
DBP (mmHg)	**80.1** ± 11.6	**82.7** ± 11.5	**0.242**
HR (bpm)	**78.7** ± 12.2	**79.3** ± 13.4	**0.814**

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Pozitiva studie

- design (randomizovaná, dvojitě zaslepená, placebem kontrolovaná) přispívá ke spolehlivým důkazům
- nový přístup k identifikaci pacientů s vysokým rizikem kardiotoxicity při nízkých dávkách antracyklinů
- včasná detekce ventrikulární dysfunkce
- nové monitorovací techniky včetně hs-TnI, GLS a CMR

Limitace studie

- monocentrická studie
- limitovaný soubor nemocných
- krátká doba sledování

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Terapie ARNi :

- **snížení projevů kardiotoxicity: hodnocené snížením GLS o více než >15 % u pacientů se zvýšenou hladinou hs-TnI po terapii ANT**
- **zlepšení remodelace LK: echokardiograficky (LVEDV, LVEF) i CMR (LVEF a LVESV) ve srovnání s placebem**
- **bezpečnost: terapie ARNi byla dobře snášena bez závažných nežádoucích účinků**

STUDIE SARAH je první studií, která prokazuje kardioprotektivní potenciál ARNi u vysoce rizikových pacientů léčených ATN

…děkuji za pozornost