sGC stimulator (BAY 41-8543) for the treatment of heart failure with reduced ejection fraction (HFrEF) and cardio-renal syndrome

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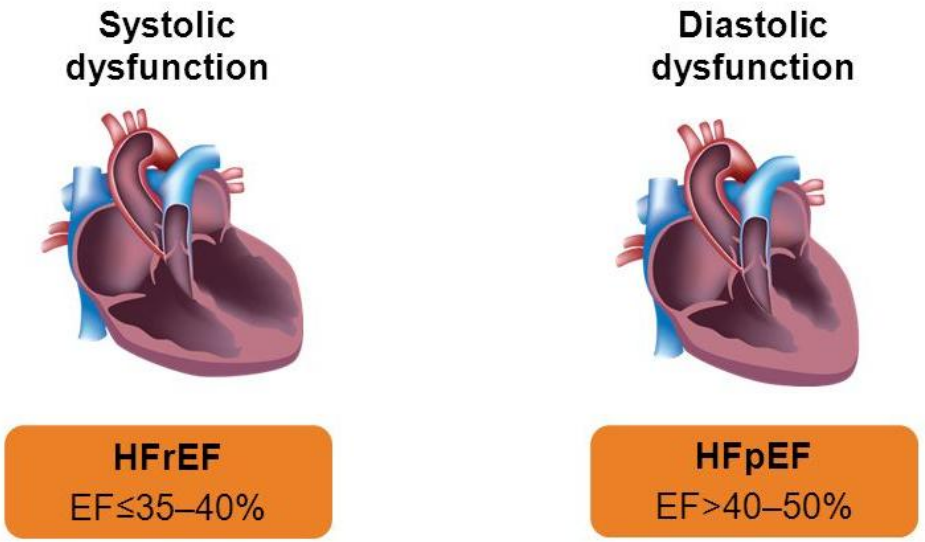
Czech Cardiovascular Research and Innovation Day 2022

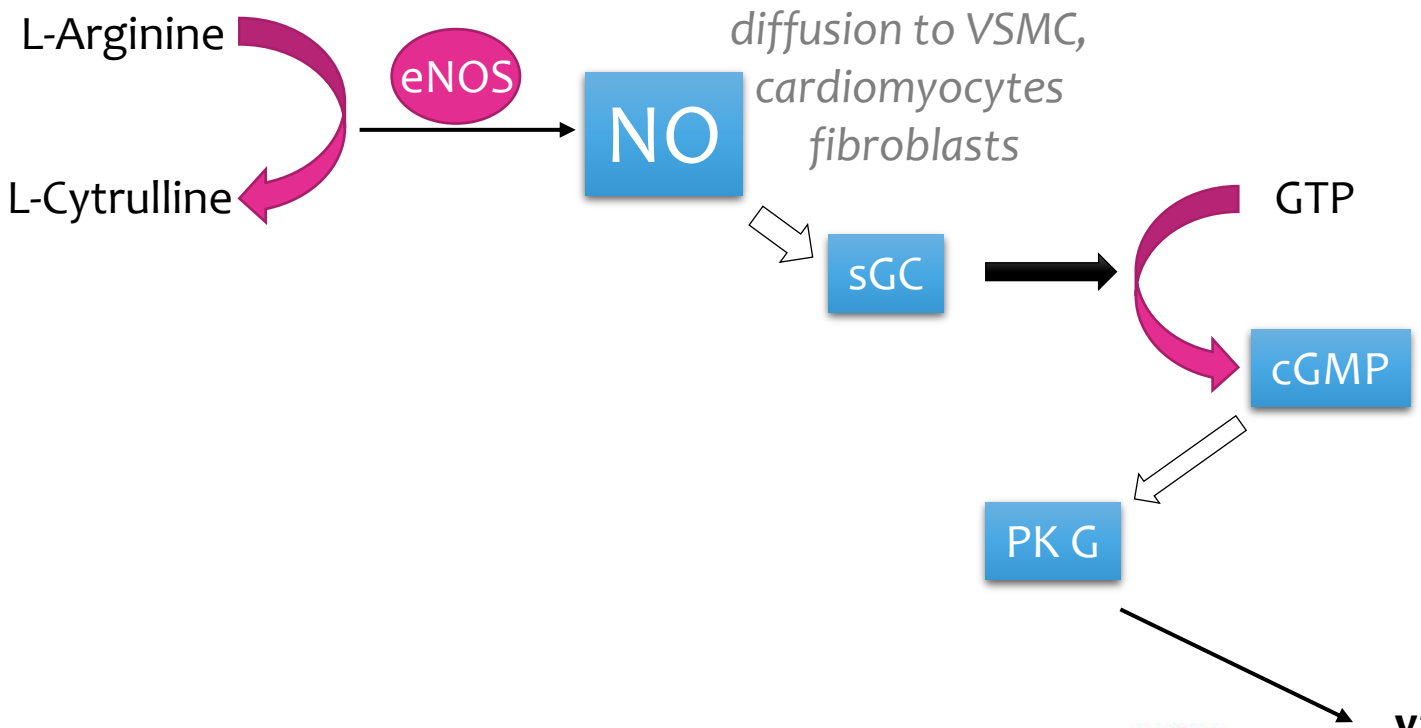
Heart Failure

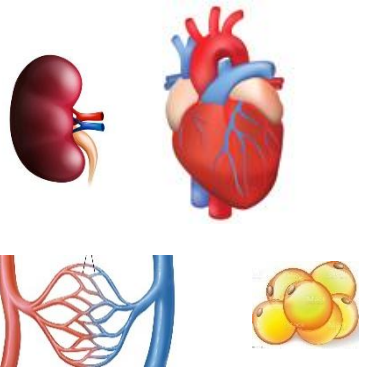
- ✓ the most prominent cause of hospitalization globally
- ✓ **3.6 million** newly diagnosed patients every year
- ✓ socioeconomic burden of **billions** of euros per year



New treatment strategies are urgently needed

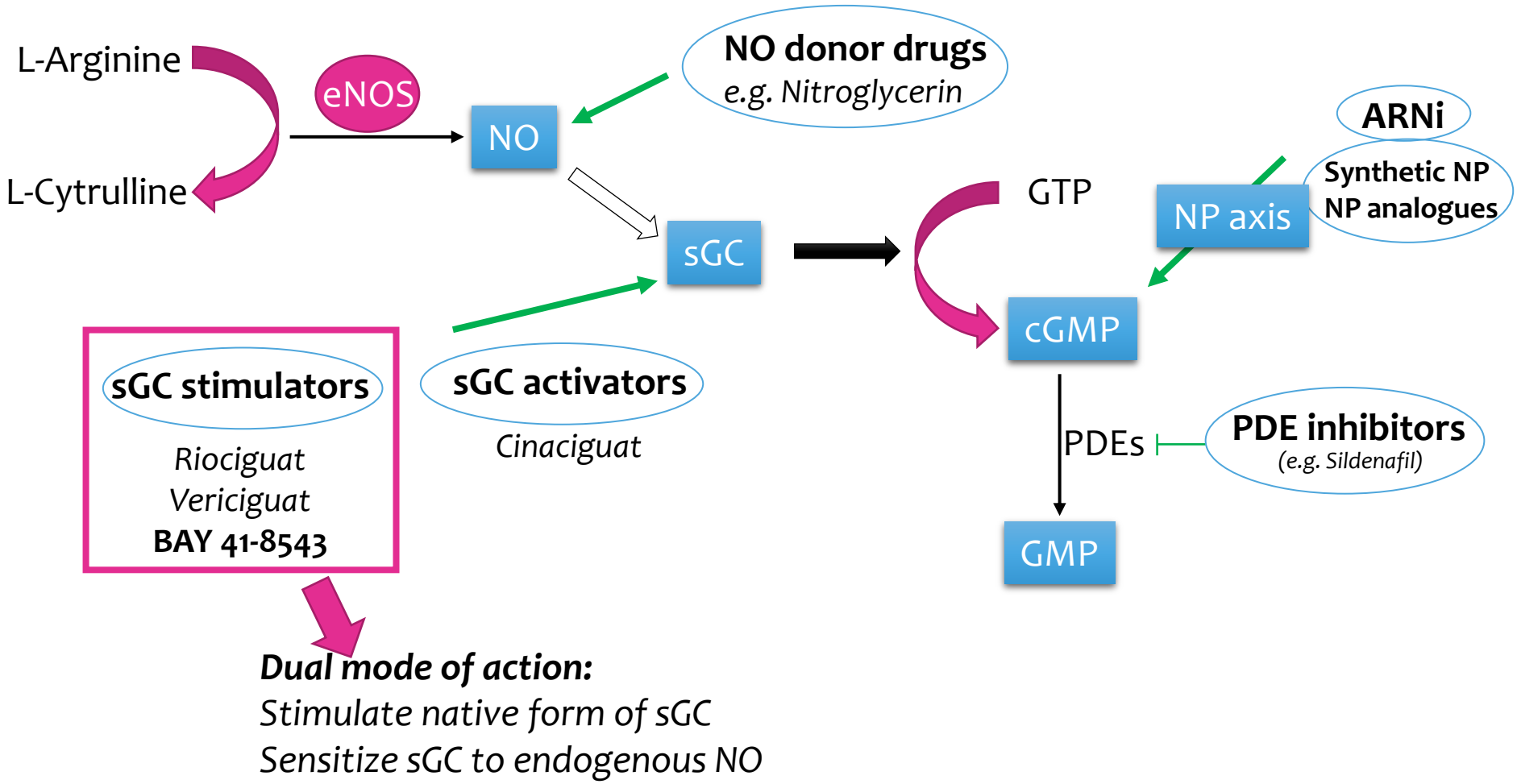
NO–sGC–cGMP pathway





vasodilation
myocardial relaxation
anti-inflammation
anti-proliferation
anti-hypertrophy
anti-obesity
anti-fibrosis
renal protection

NO–sGC–cGMP targeted therapy

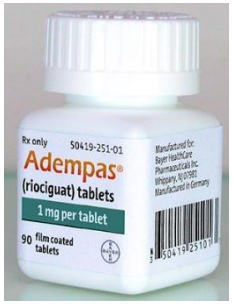


NP axis natriuretic peptide axis (BNP, ANP, CNP)

ARNi Dual-Acting Angiotensin Receptor – Neprilysin Inhibitor

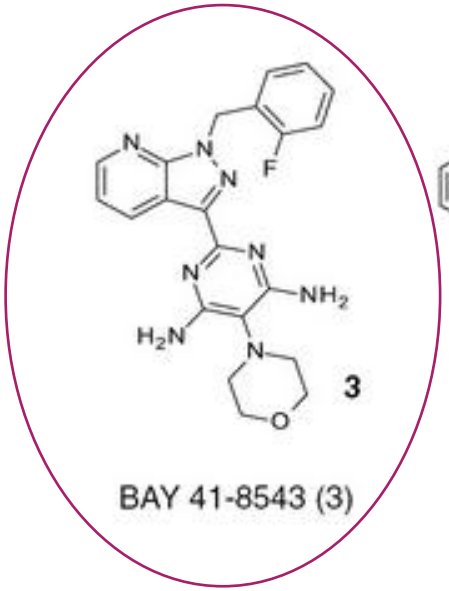
PDEs phosphodiesterases

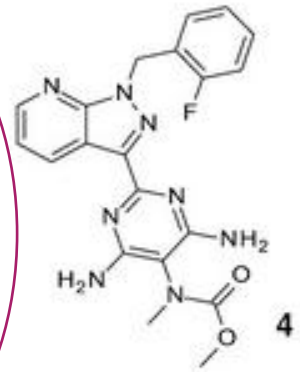
sGC stimulators – clinical use

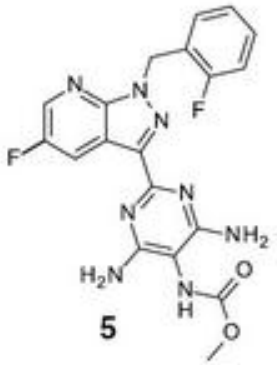


Riociguat (Adempas®) in clinical use for chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH)

Vericiguat (Verquvo®) accepted for the treatment of symptomatic chronic heart failure in adults with reduced ejection fraction (USA January 2021, UE July 2021)







Aim of the study

To evaluate the effects of chronic treatment

with sGC stimulator

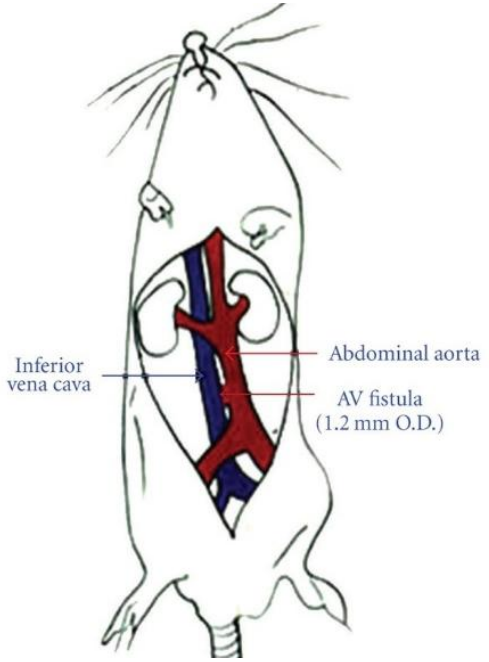
alone and combined with ACEi

on the progression of HFrEF in ACF TGR model

cGMP ↑ **RAAS ↓**

Experimental model of HFrEF

J Biomed Biotechnol 2011;2011:729497. doi: 10.1155/2011/729497. Epub 2011 Jan 11.



Ren-2 transgenic hypertensive rats (TGR) with Aorto-Caval Fistula (ACF)

- ✓ HFrEF due to the volume overload
- ✓ *systemic congestion and cardiac remodeling*
- ✓ *renal dysfunction (**„cardio-renal syndrome”**)*

Two detrimental factors promoting progression of HFrEF

hypertension and increased activity of RAAS

Experimental groups

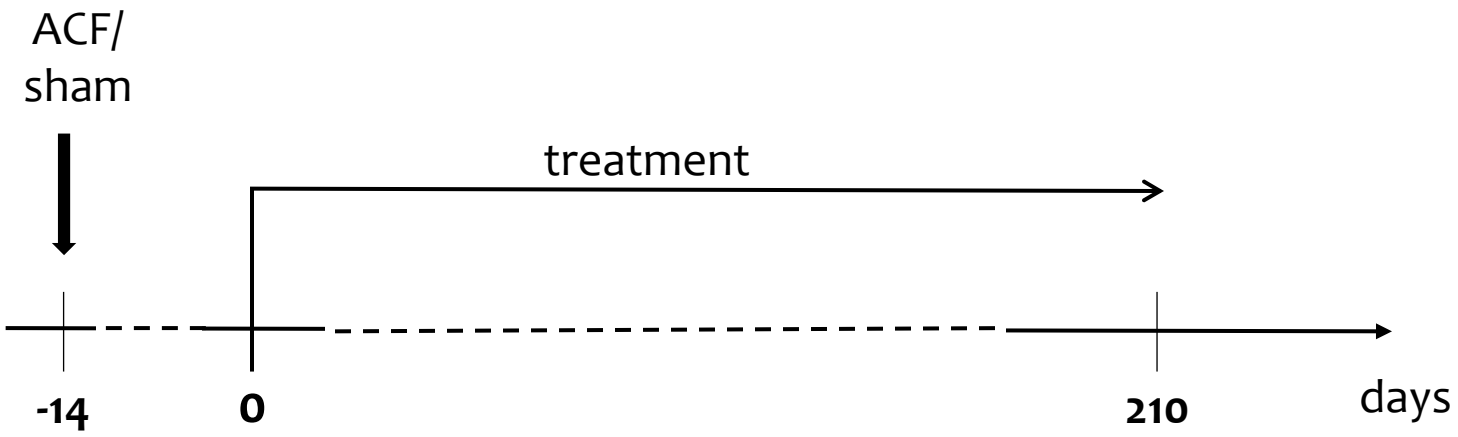
- ACF TGR (n=13)
- ACF TGR+ BAY41-8543 (n=8)
- ACF TGR + ACEi (n=9)
- ACF TGR + BAY41-8543 +ACEi (n=11)

sGC stimulator: 3 mg/kg/day in a diet
ACEi: trandolapril – GOPTEN®
2 mg/L in drinking water (0.25 mg/kg/day)

ACF – **A**orto-**C**aval **F**istula

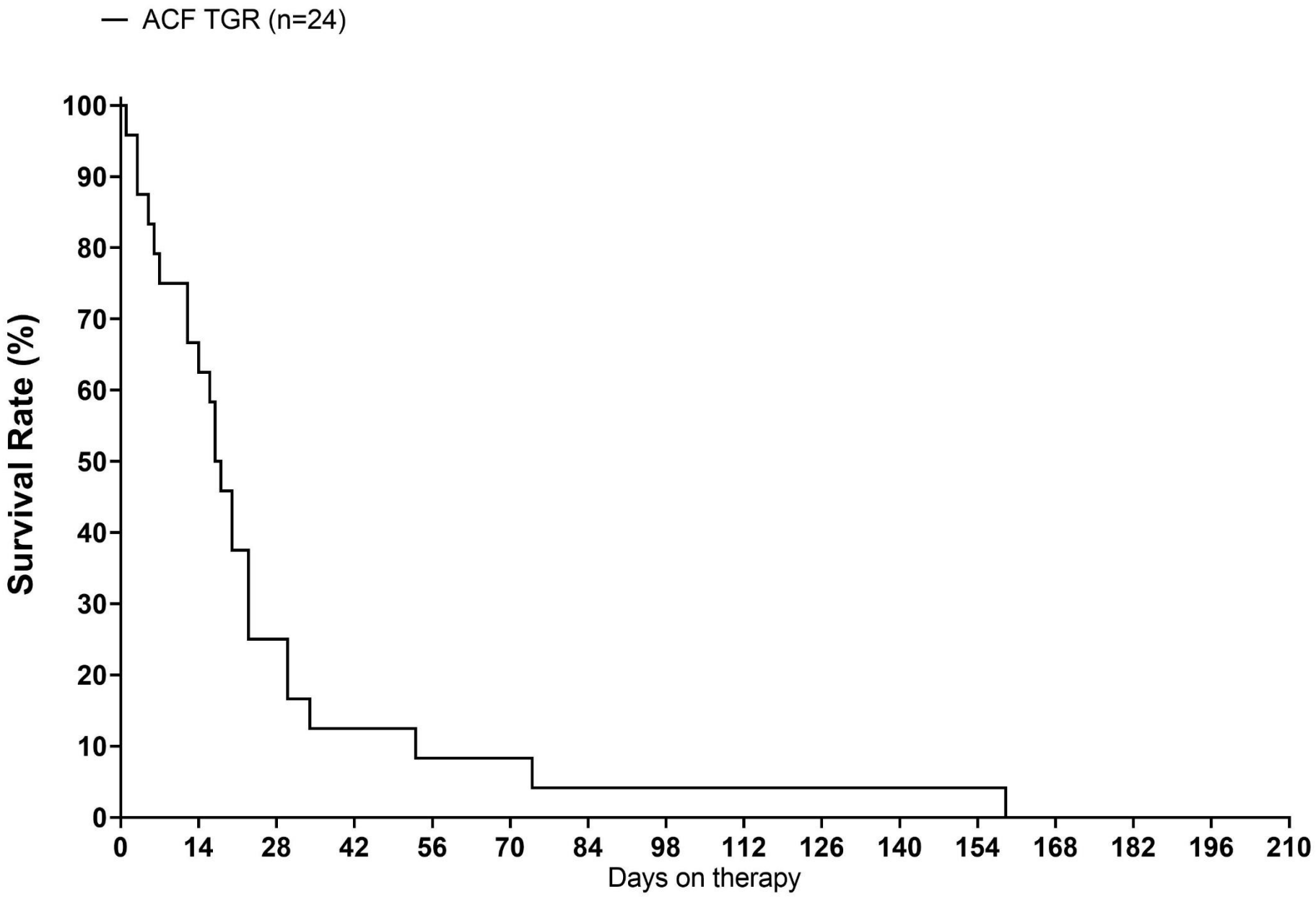
Experimental protocol (I)

Survival rate

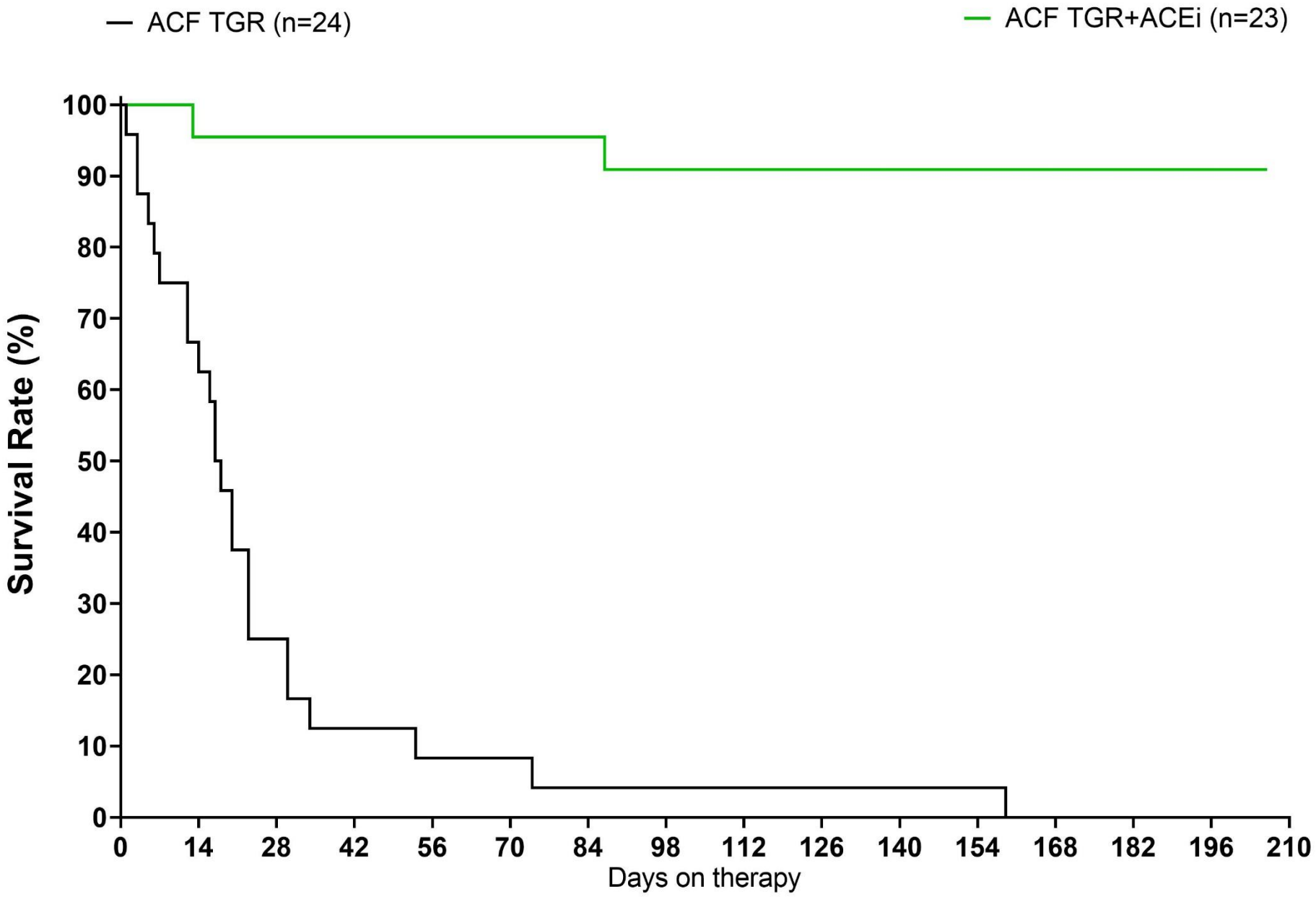


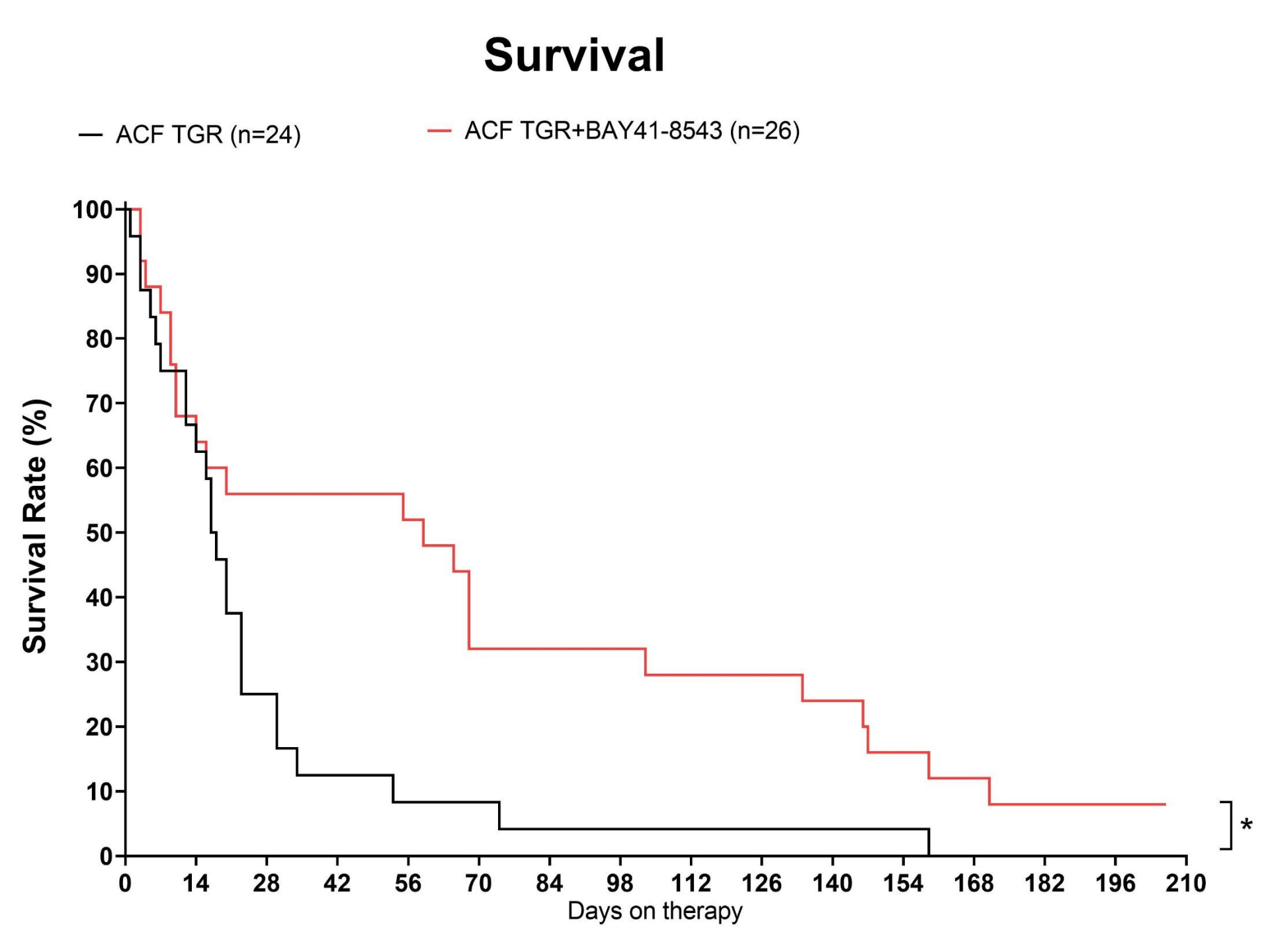
ACF – **A**orto-**C**aval **F**istula

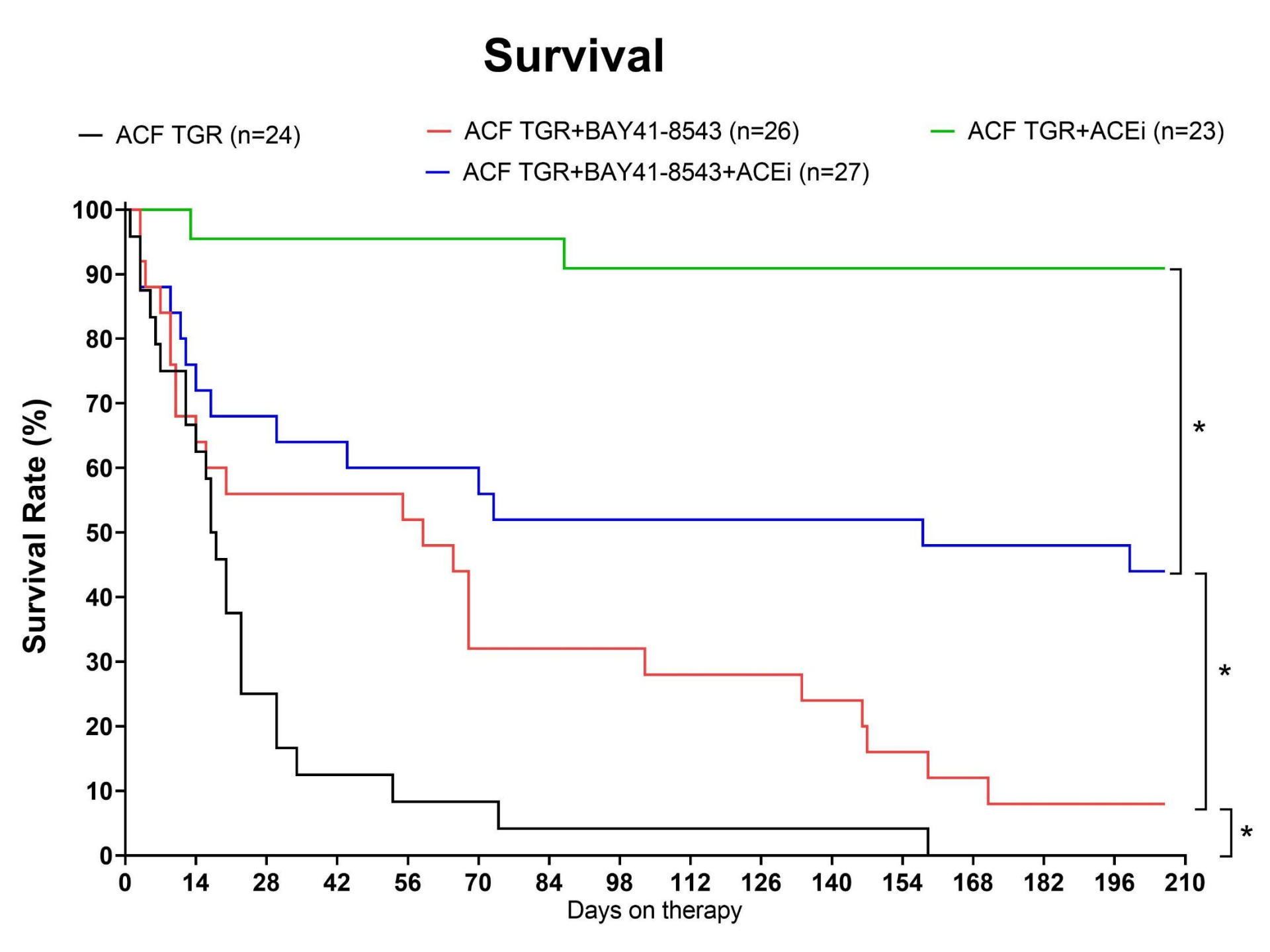
Survival


ACF TGR (n=24)
Survival Rate (%)
100
90
80
70
60
50
40
30
20
10
0
0
14
28
42
56
70
84
98
112
126
140
154
168
182
196
210
Days on therapy

Survival

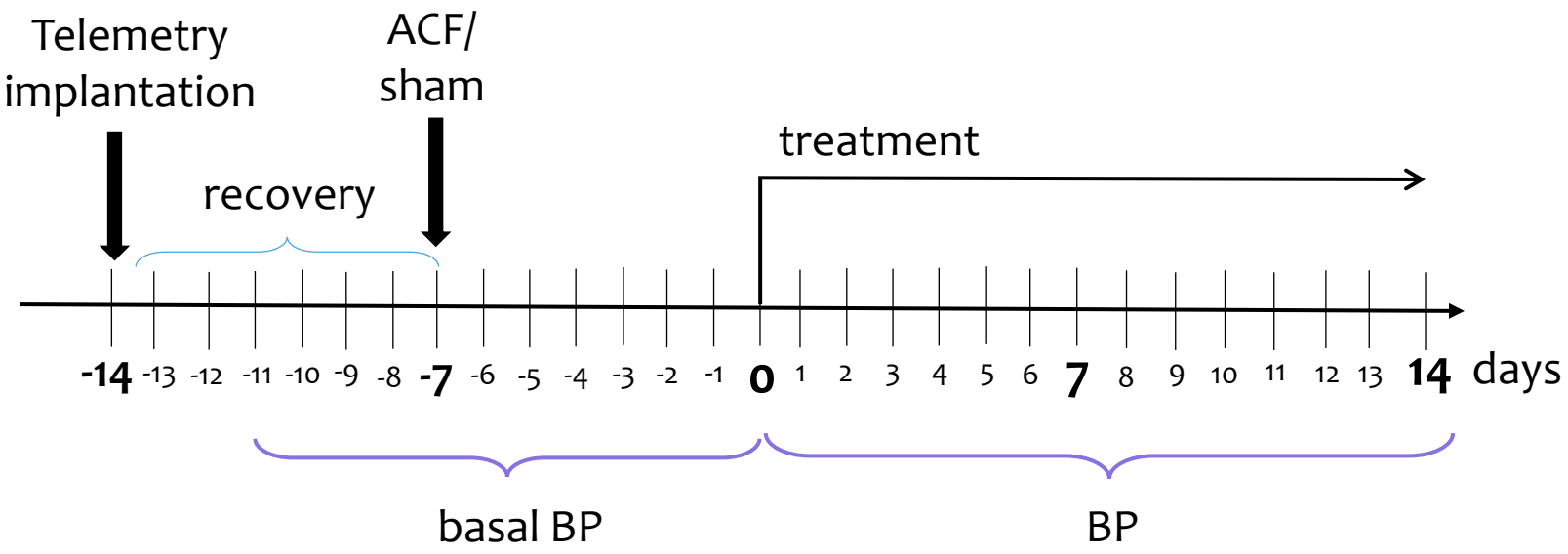

ACF TGR (n=24)
ACF TGR+ACEi (n=23)
Survival Rate (%)
100
90
80
70
60
50
40
30
20
10
0
0
14
28
42
56
70
84
98
112
126
140
154
168
182
196
210
Days on therapy


Survival
ACF TGR (n=24)
ACF TGR+BAY41-8543 (n=26)
Survival Rate (%)
100
90
80
70
60
50
40
30
20
10
0
0
14
28
42
56
70
84
98
112
126
140
154
168
182
196
210
Days on therapy
*


Survival
ACF TGR (n=24)
ACF TGR+BAY41-8543 (n=26)
ACF TGR+ACEi (n=23)
ACF TGR+BAY41-8543+ACEi (n=27)
Survival Rate (%)
100
90
80
70
60
50
40
30
20
10
0
0
14
28
42
56
70
84
98
112
126
140
154
168
182
196
210
Days on therapy
*
*
*

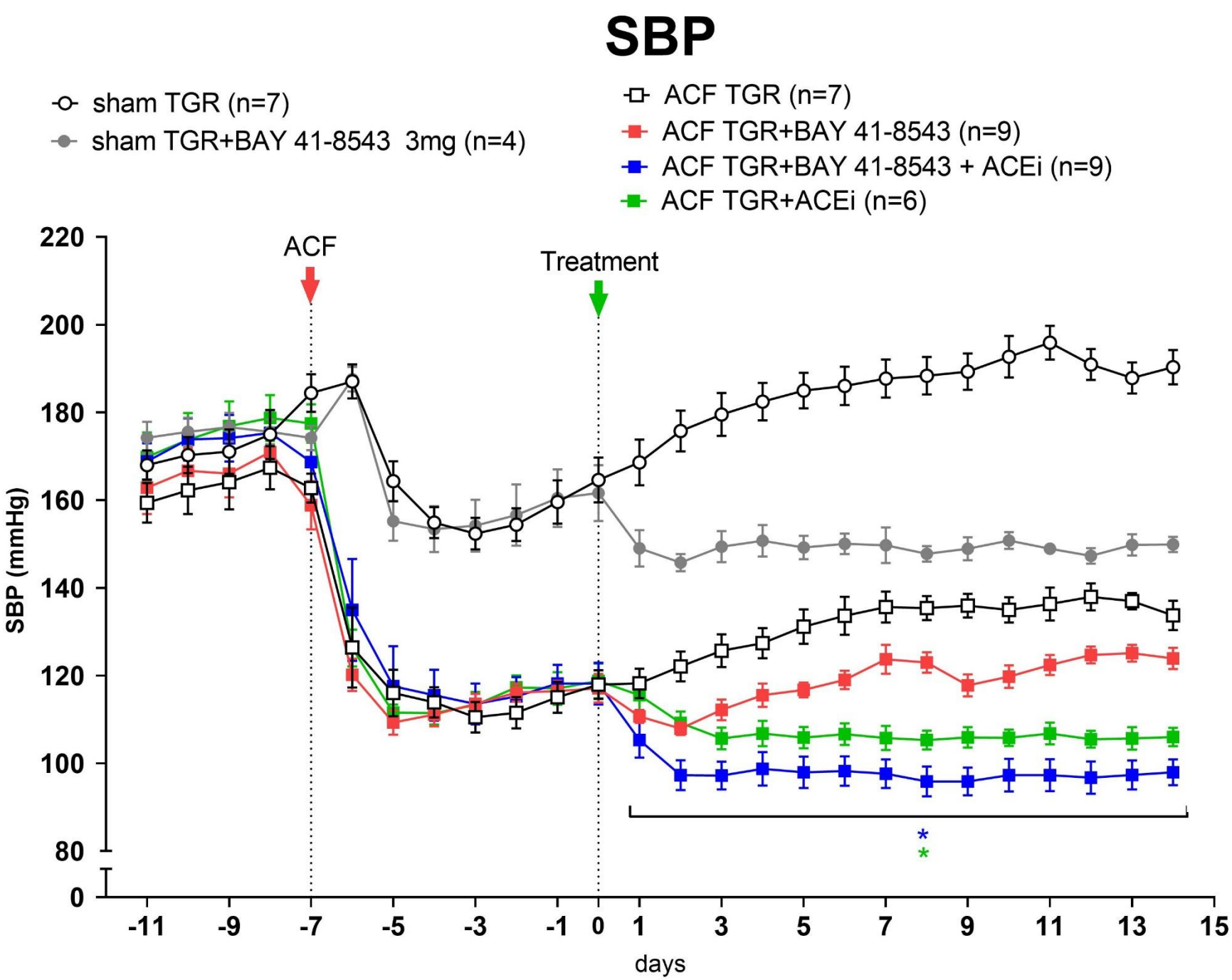
Experimental protocol (II)

Blood pressure measurment



Hypotension might be detrimental for patients with heart failure

ACF – **A**orto-**C**aval **F**istula


SBP
sham TGR (n=7)
sham TGR+BAY 41-8543 3mg (n=4)
ACF TGR (n=7)
ACF TGR+BAY 41-8543 (n=9)
ACF TGR+BAY 41-8543 + ACEi (n=9)
ACF TGR+ACEi (n=6)
ACF
Treatment
SBP (mmHg)
220
200
180
160
140
120
100
80
0
-11
-9
-7
-5
-3
-1
0
1
3
5
7
9
11
13
15
days
*
*

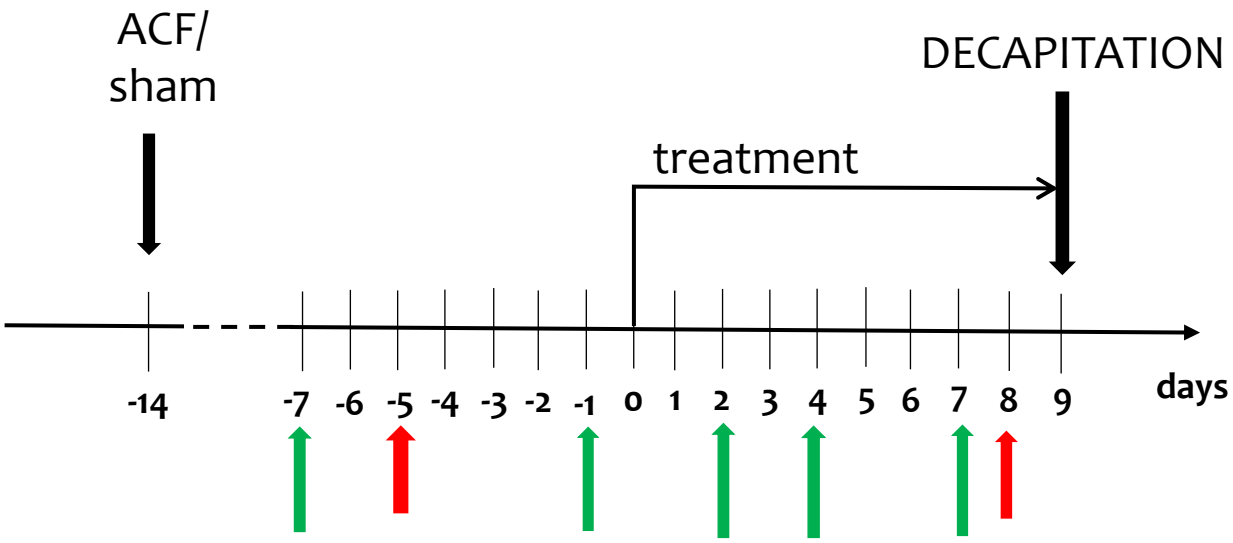
Experimental protocol (III)

Blood and urine collection

Metabolic cages (days -7,-4,-1, 2, 4, 7)

Blood collection (days -5, 8)

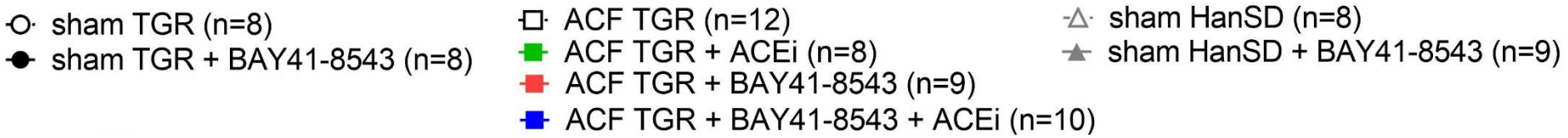
cGMP
ANG II
NOx
renal and cardiovascular biomarkers



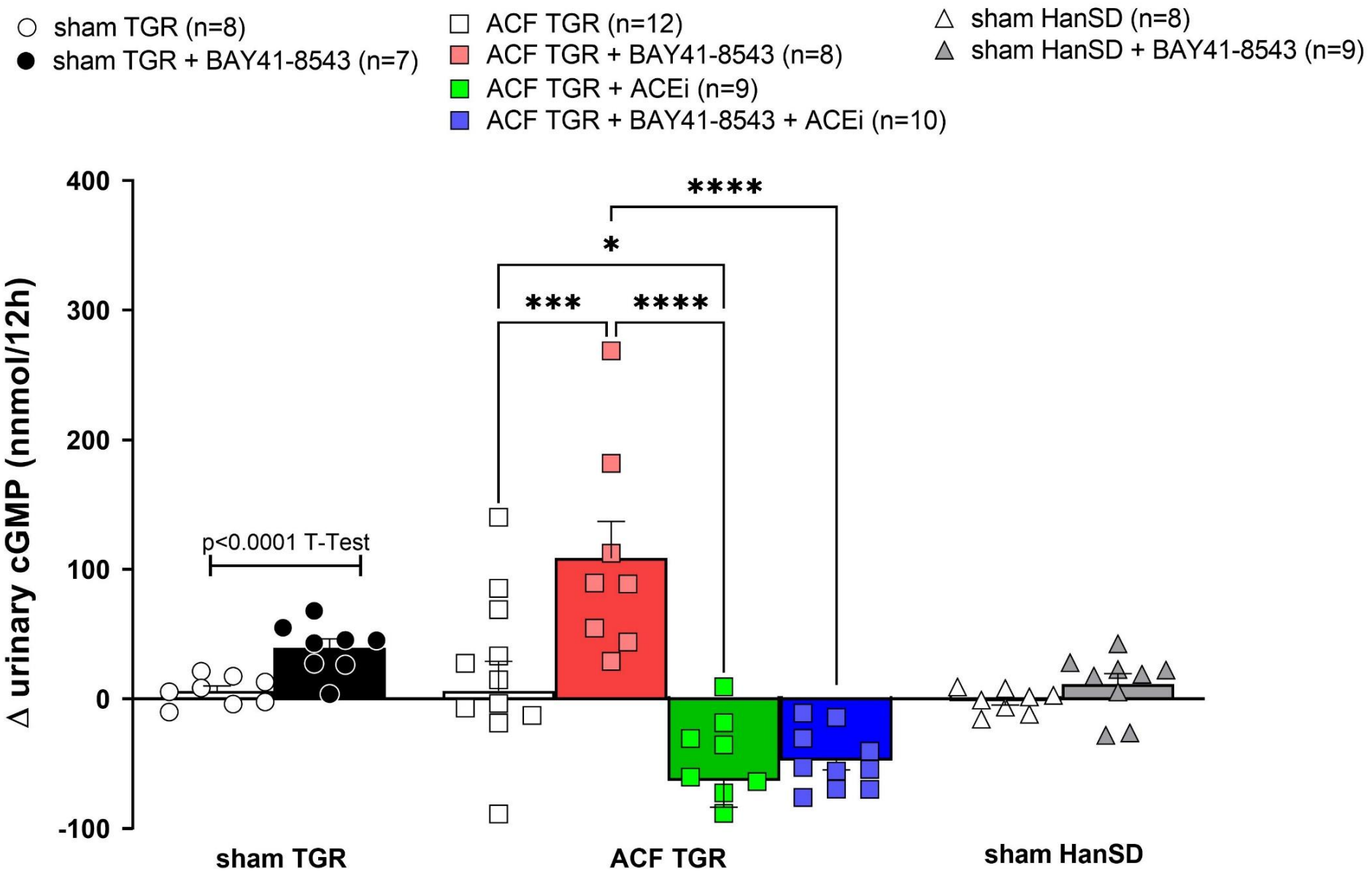
Organ weights
Tissue collection

ACF – **A**orto-**C**aval **F**istula

Urinary excretion of cGMP



Change in the urinary excretion rate of cGMP



ACF – Aorto-Caval Fistula

Summary

BAY 41-8543:

- ✓ **improved survival rate of ACF TGR in comparison to untreated rats with HFrEF**
- ✓ caused only transient decrease in BP
- ✓ increased excretion rate of cGMP

Conclusions and future plans

- ✓ sGC stimulators might represent a valuable tool for the treatment of HFrEF due to volume overload and cardio-renal syndrome, **but further studies are necessary**

NEXT:

- ✓ to clarify some of the „puzzling results" (diminished survival of combined treatment of BAY41-8543 and ACEi)

- ✓ To test sGC stimulators in other models
  - Chemotherapy-induced HF
  - Combined HFrEF with CKD

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Prof. Dr.rer.nat. Peter Sandner, PhD

Mgr. Zuzana Husková, Ph.D.

Thank you for your attention

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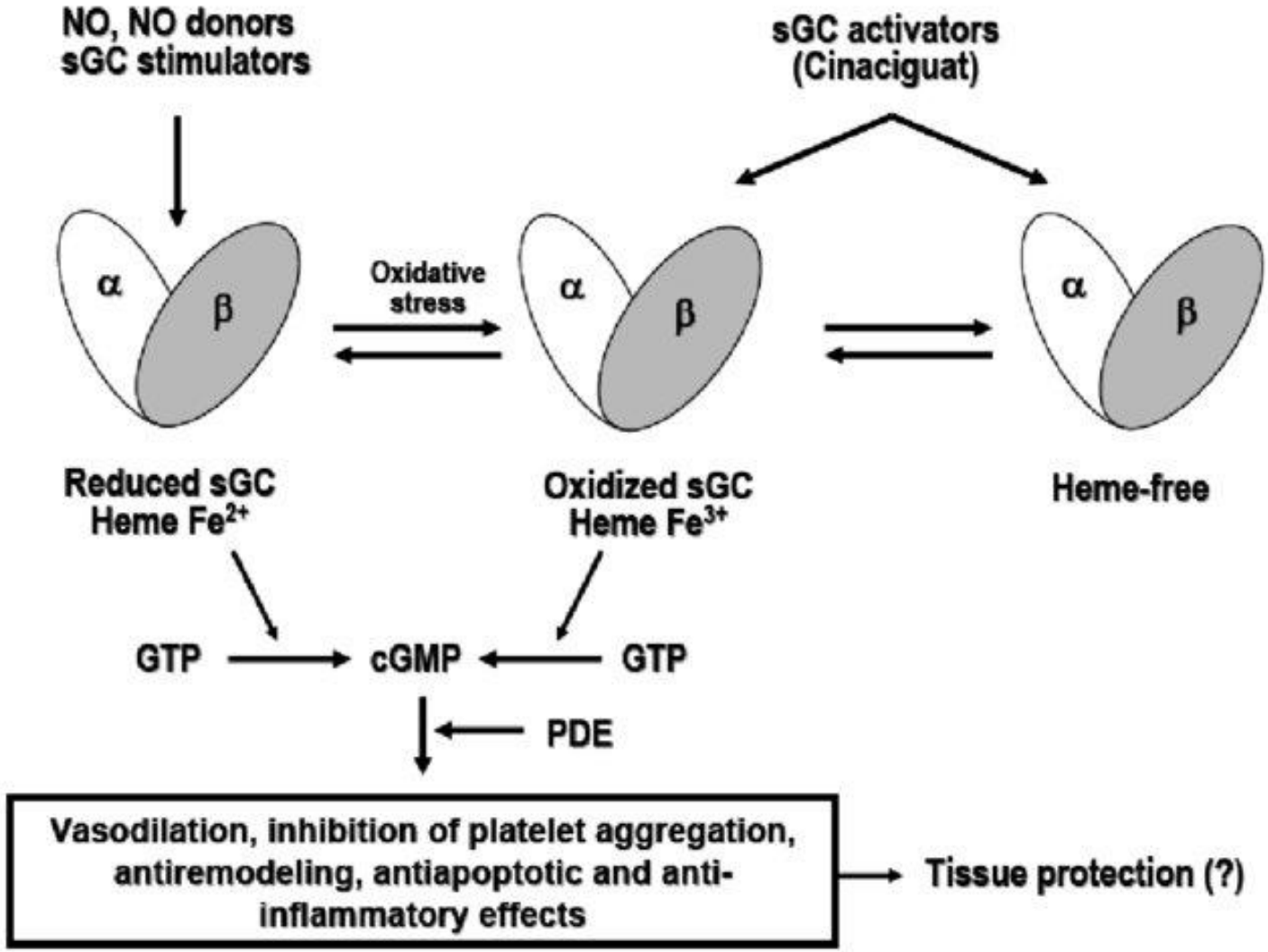
Mgr. Matúš Miklovič

MVDr. Zuzana Honetschlägerová, Ph.D.

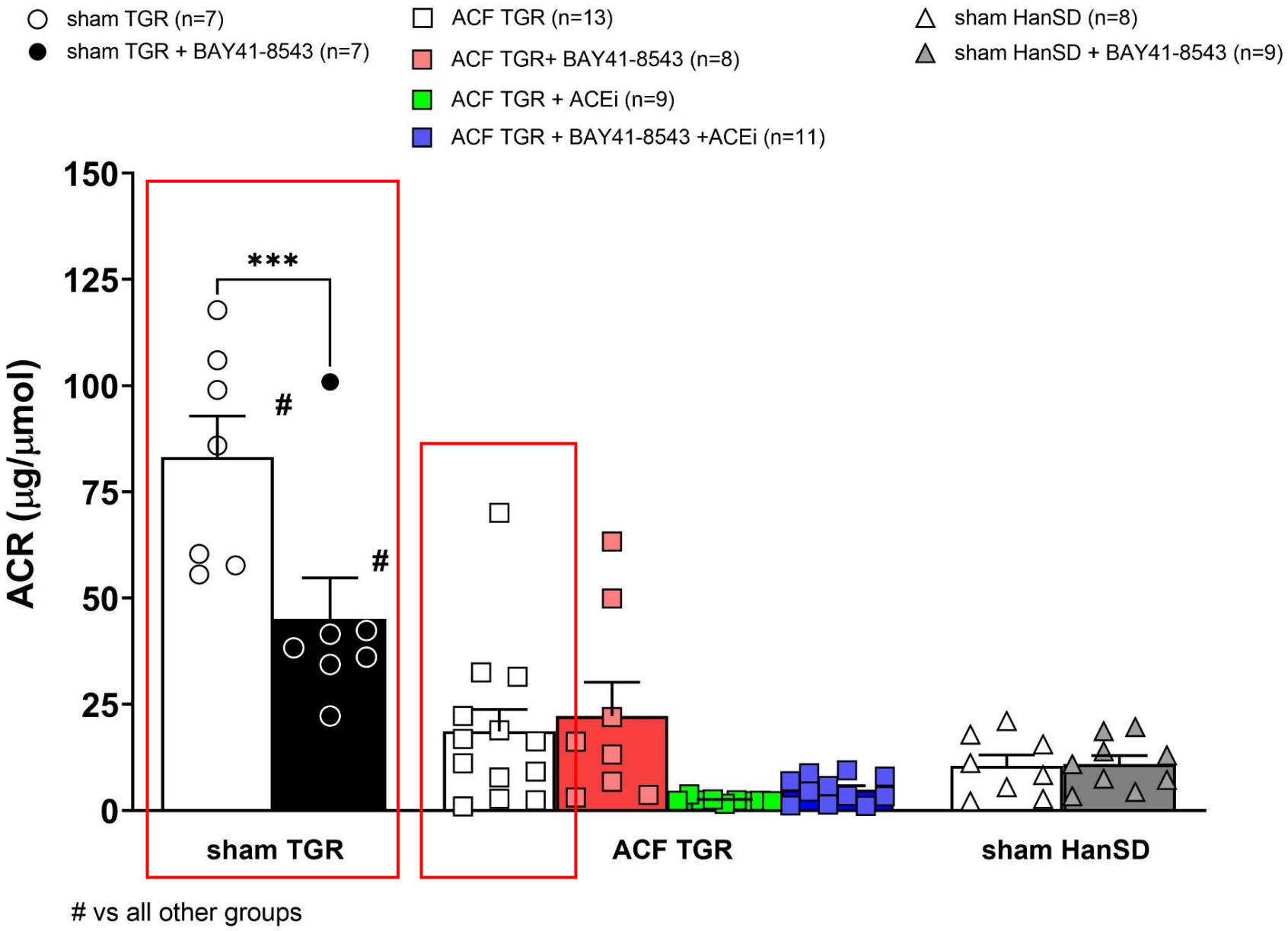
Mgr. Soňa Kikerlová

Ing. Zdeňka Vaňourková, Ph.D.



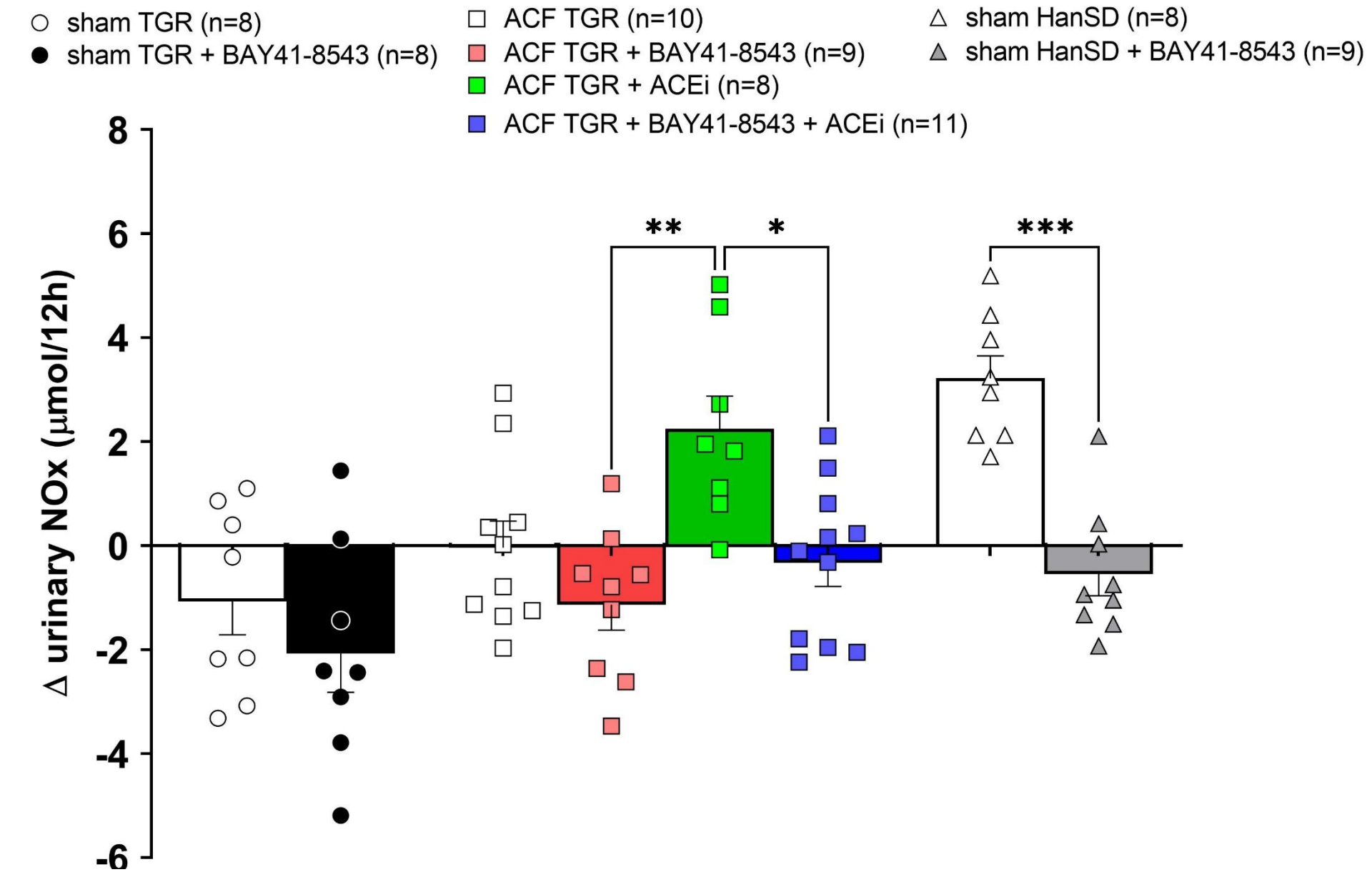
Tamargo et. al. Curr Med Chem. 2010;17(4):363-90.

Albumin to creatinine ratio in urine (ACR)

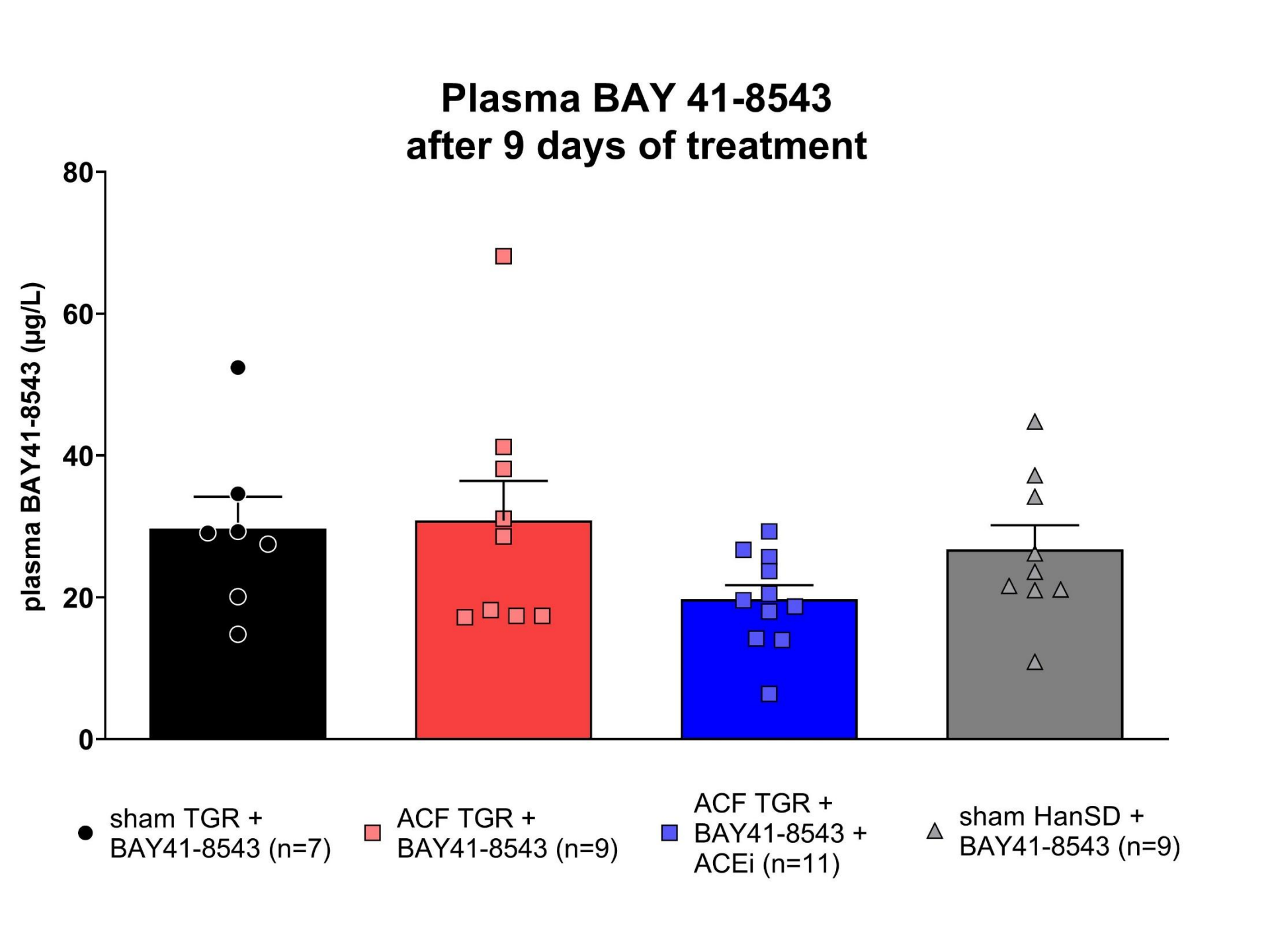


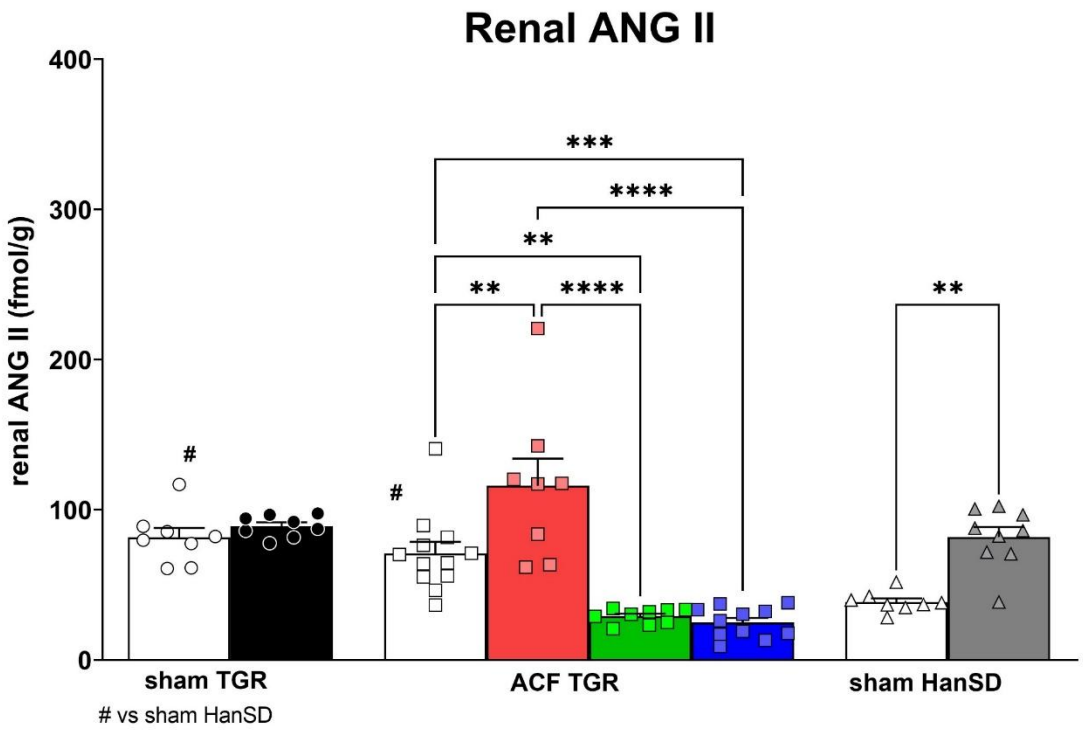
vs all other groups

Change in the urinary excretion rate of NOx



ACF – Aorto-Caval Fistula

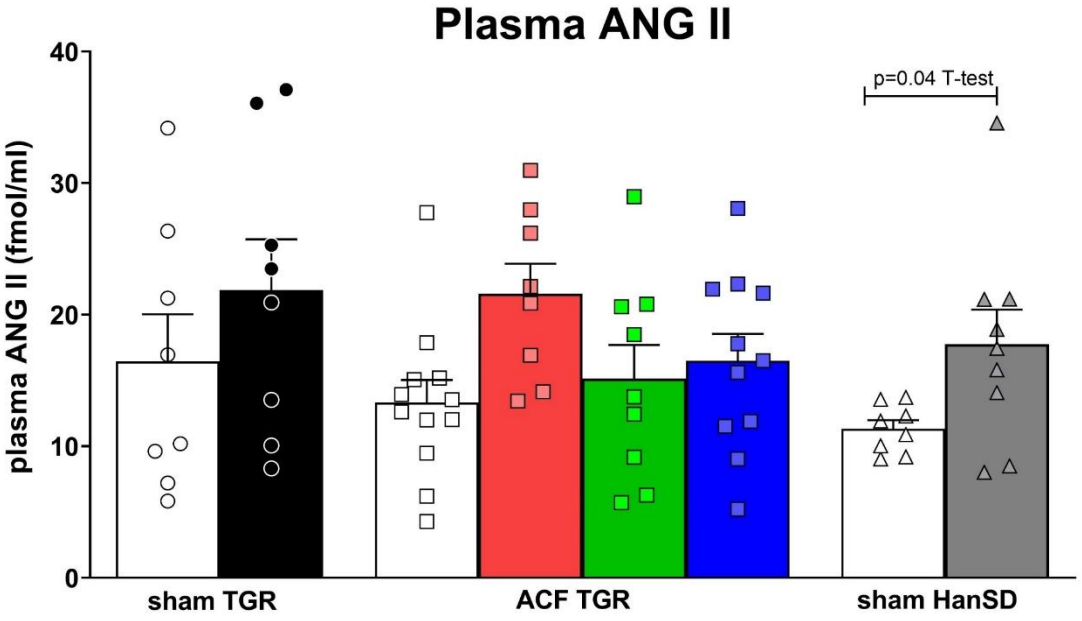

Plasma BAY 41-8543
after 9 days of treatment
plasma BAY41-8543 (µg/L)
80
60
40
20
0
sham TGR + BAY41-8543 (n=7)
ACF TGR + BAY41-8543 (n=9)
ACF TGR + BAY41-8543 + ACEi (n=11)
sham HanSD + BAY41-8543 (n=9)

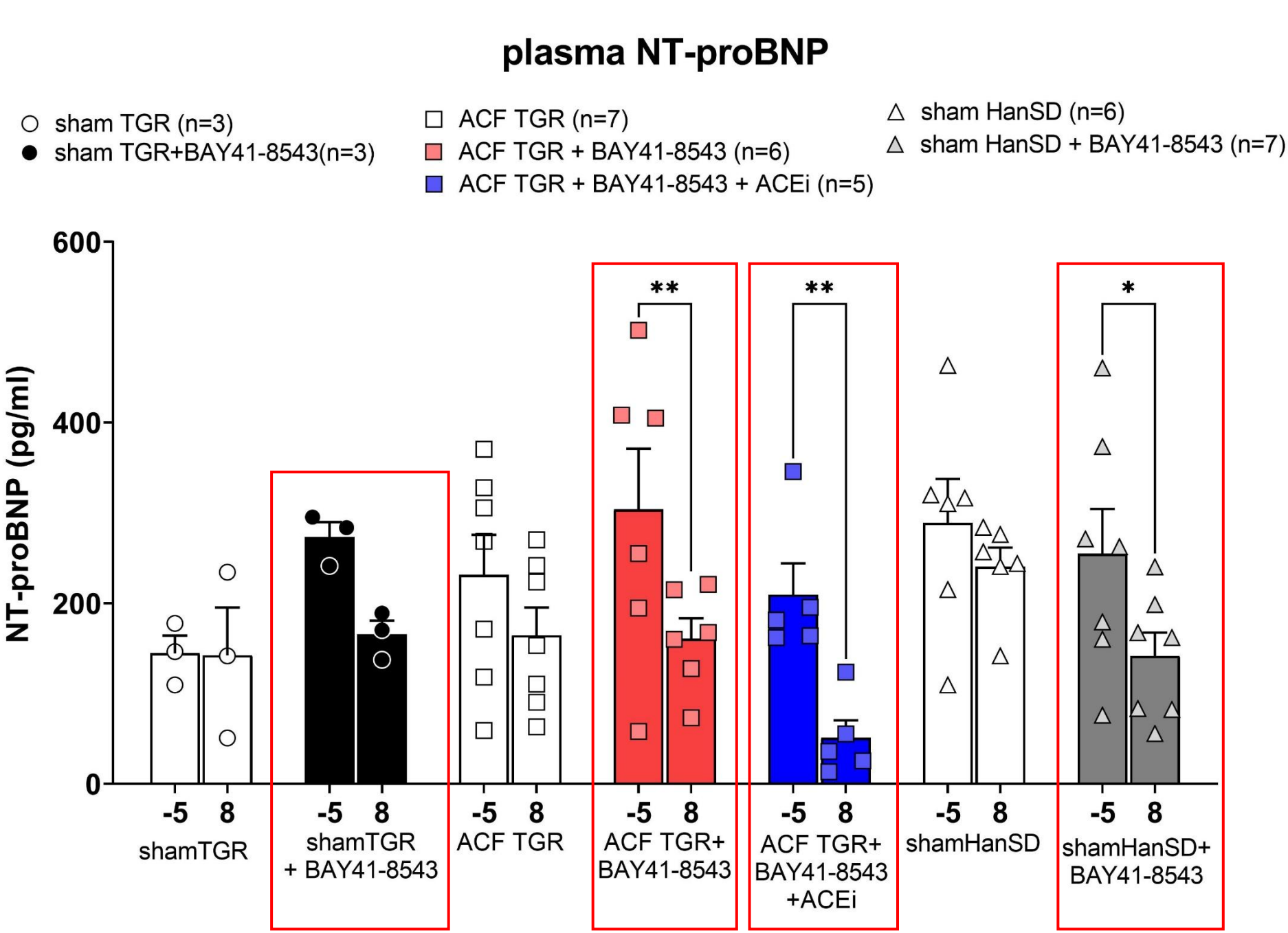


ACF TGR (n=12)
ACF TGR + BAY 41-8543 (n=9)
ACF TGR + ACEi (n=9)
ACF TGR + BAY 41-8543 + ACEi (n=11)

sham TGR (n=8)
sham TGR + BAY 41-8543 (n=8)

sham HanSD (n=8)
sham HanSD + BAY 41-8543 (n=9)




plasma NT-proBNP
sham TGR (n=3)
sham TGR+BAY41-8543(n=3)
ACF TGR (n=7)
ACF TGR + BAY41-8543 (n=6)
ACF TGR + BAY41-8543 + ACEi (n=5)
sham HanSD (n=6)
sham HanSD + BAY41-8543 (n=7)
NT-proBNP (pg/ml)
600
400
200
0
**
**
*
-5
8
shamTGR
shamTGR + BAY41-8543
ACF TGR
ACF TGR+ BAY41-8543
ACF TGR+ BAY41-8543 +ACEi
shamHanSD
shamHanSD+ BAY41-8543