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DEPT. OF CARDIOLOGY
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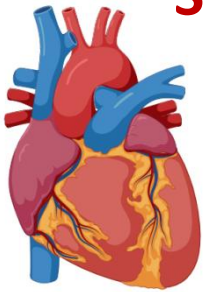
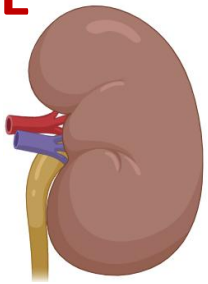
CHARLES UNIVERSITY



SELECTIVE ENDOTHELIN TYPE A RECEPTOR BLOCKADE ATTENUATES HEART AND RENAL FAILURE IN RODENT MODELS



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CCRID, 2023

KARDIOLOGICKÁ KLINIKA
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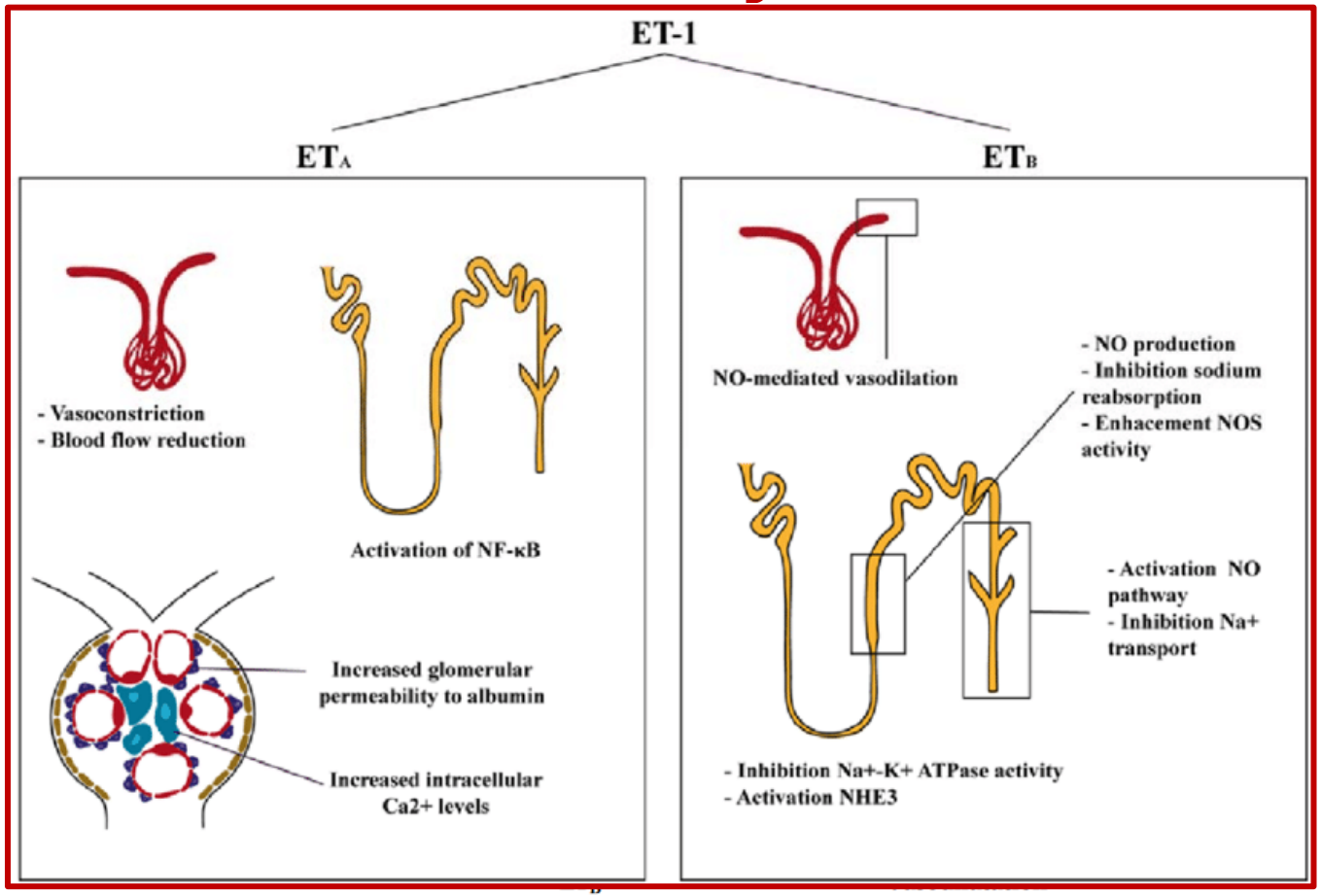
Endothelin system



Webb et al. *Trends in Pharmacological Sciences.* 2007 Martínez-Díaz et al. *Int J Mol Sci.* 2023

Endothelin system

ET receptor antagonists (blockers)

- non-selective (ET_A/ET_B) - bosentan (20:1)*, macitentan (50:1)*
- selective (ET_A) - ambrisentan (200:1)*, **atrasentan (1 200:1)**, zibotentan (10 000:1)
- others

* PAH guidelines

X side effects - peripheral oedema, fluid retention

(more in non-selective blockade inc. ET_B – Na^+ retention, reducing renal blood flow, …)

Kidney disease (CKD)

- SONAR trial (2019) – atrasentan in DM nephropathy – reduced doubling of creatinin levels and ESKD
- ZENITH-CKD (2023) – zibotentan + dapagliflozin in CKD +/- DM – reduced albuminuria
- PROTECT (2023) – sparsentan (dual ET+ARB) vs. irbesartan in IgA nephropathy – reduced proteinuria and eGFR decline

Heart failure (CHF)

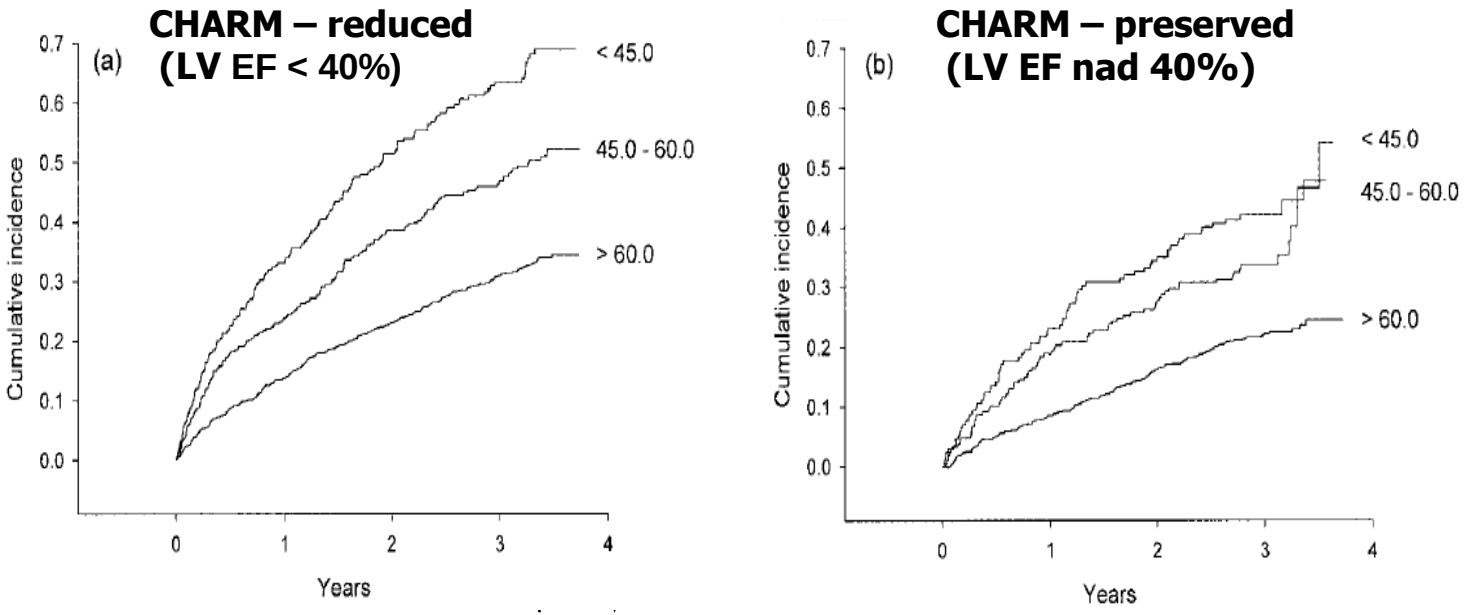
- Big-ET and ET-1 plasmatic levels predict negative outcome
- clinical trials with ET block. unconvincing (non-selective, less-selective)
  - more fluid retention

Dhaun et al. *Nat Rev Cardiol*. 2019 Humbert et al. *Eur Heart J*. 2022 Heeespink et al. *Lancet*. 2019 Rovin et al. *Lancet*. 2023
Barton et al. *Hypertension*. 2019 Enevoldsen et al. *J. Clin. Med.* 2020 Heeespink et al. *Lancet*. 2023

Combination of CHF and CKD

Project CHARM (candesartan x placebo) in CHF

All-cause and CV death, HF hospitalization



Effect of CKD on CHF prognosis

Mortality in HF trials **2,3x higher** with **eGFR** < 60ml/min and **1,7x higher** with **albuminuria.**

Hillege et al. *Circulation.* 2006 Damman et al. *European Heart Journal .* 2014

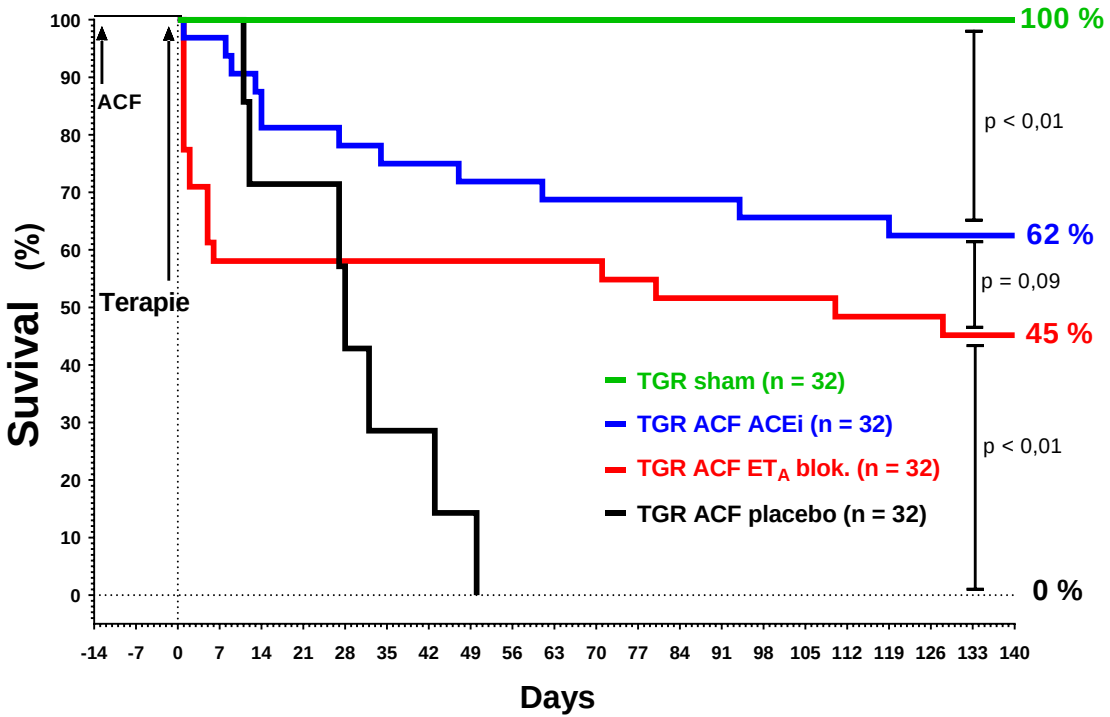
Combination of CHF and CKD

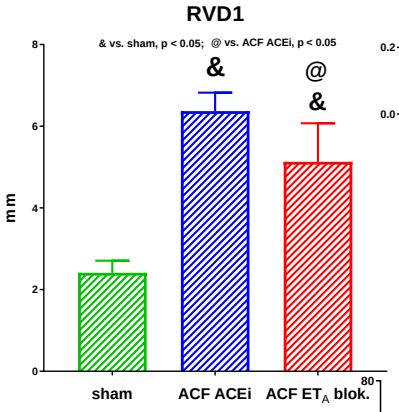
Trial	Exclusion	<60 ml/min/1.73m2	>60 ml/min/1.73 m2
DAPA -HF (96)	eGFR<30	0.72 [0.66-0.86]	0.76 [0.63-0.92]
DELIVER (18)	eGFR<25	0.81 [0.69-0.94]	0.84 [0.70-1.00]
EMPEROR-Preserved (17)	eGFR<20	0.78 [0.66-0.91]	0.81 [0.66-1.00]
EMPEROR-Reduced (97)	eGFR<20	0.83 [0.69-1.00]	0.67 [0.55-0.83]
SOLOIST-HF (98)	eGFR<30	0.59 [0.44-0.79]	0.90 [0.58-1.37]
PIONEER-HF (67)	eGFR<30	0.73 [0.61-0.87]	0.70 [0.59-0.84]
PARAGON-HF(69)	eGFR<30	0.79 [0.66-0.95]	1.01 [0.80-1.27]
GALCTIC-HF (203)	eGFR<20	0.98 [0.89-1.07]	0.84 [0.75-0.94]
PARADIGM-HF (66)	eGFR<30	similar	similar
EMPHASIS (81)	eGFR<30	similar	similar

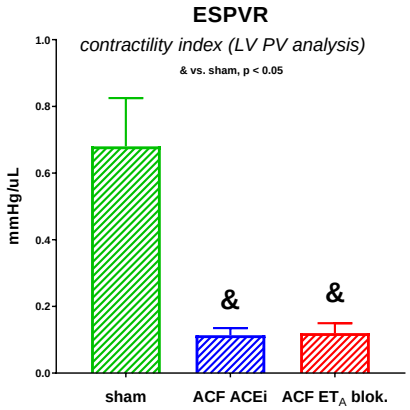
Despite the worst prognosis, CKD patients are usually excluded from HF trials.
- effect of standard theraphy?, dosage?

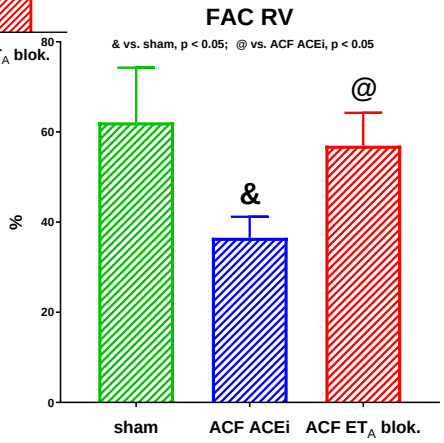
Uptodate.com

Previous work









1) ET_A blockade improves survival of animal CHF model (ACF TGR) similarly to ACEi monotheraphy.

2) ET_A blockade improves morphological and haemodynamical parameters in ACF TGR similarly to ACEi, even better in RV function and remodeling.

Kala et al. CKS Congress 2020

Hypothesis and Aims

Increased activity of endothelin system in CHF combined with CKD is maladaptive in long term and contributes to progression of both diseases

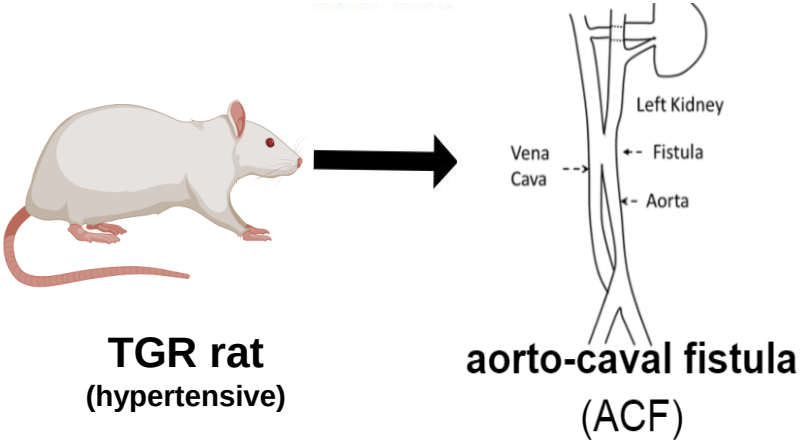
Combined chronic selective ET_A blockade (**atrasentan**) with ACE inhibitor (trandolapril):

→ **A** increse survival of TGR + ACF **(CHF)** by improvment of **cardiac** and **renal functions**

→ **B** increse survival of HanSD + 5/6 Nx + ACF **(CKD + CHF)** by improvement of **renal function** and **morphology**

A

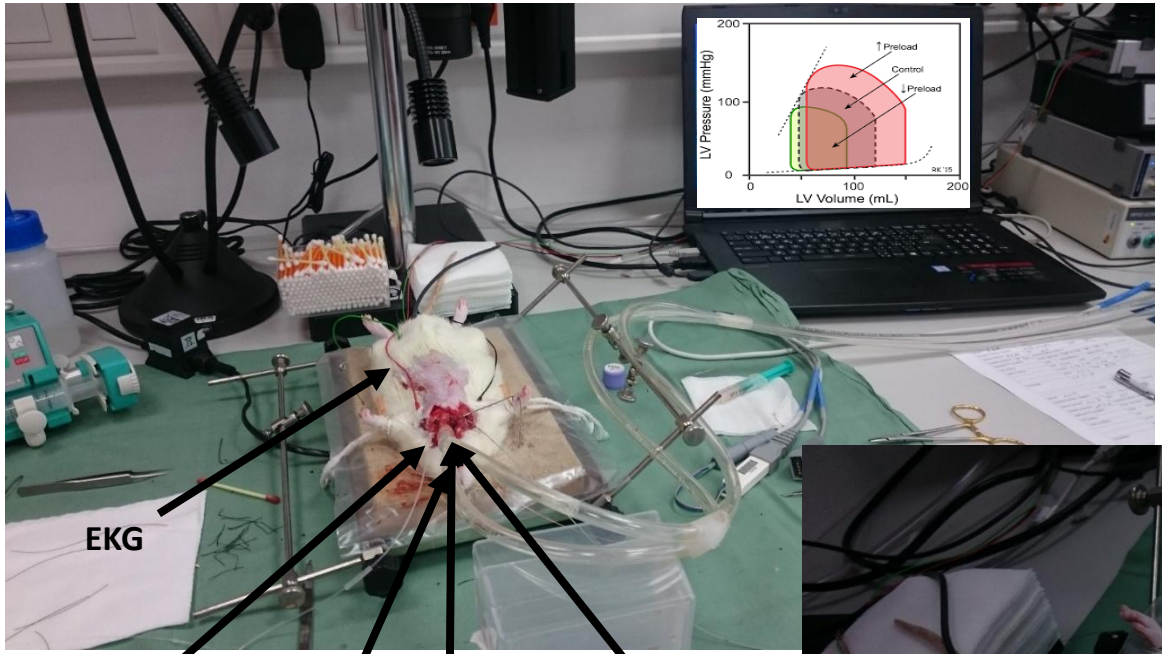
CHF model



TGR rat
(hypertensive)

aorto-caval fistula
(ACF)

P-V analysis in rat

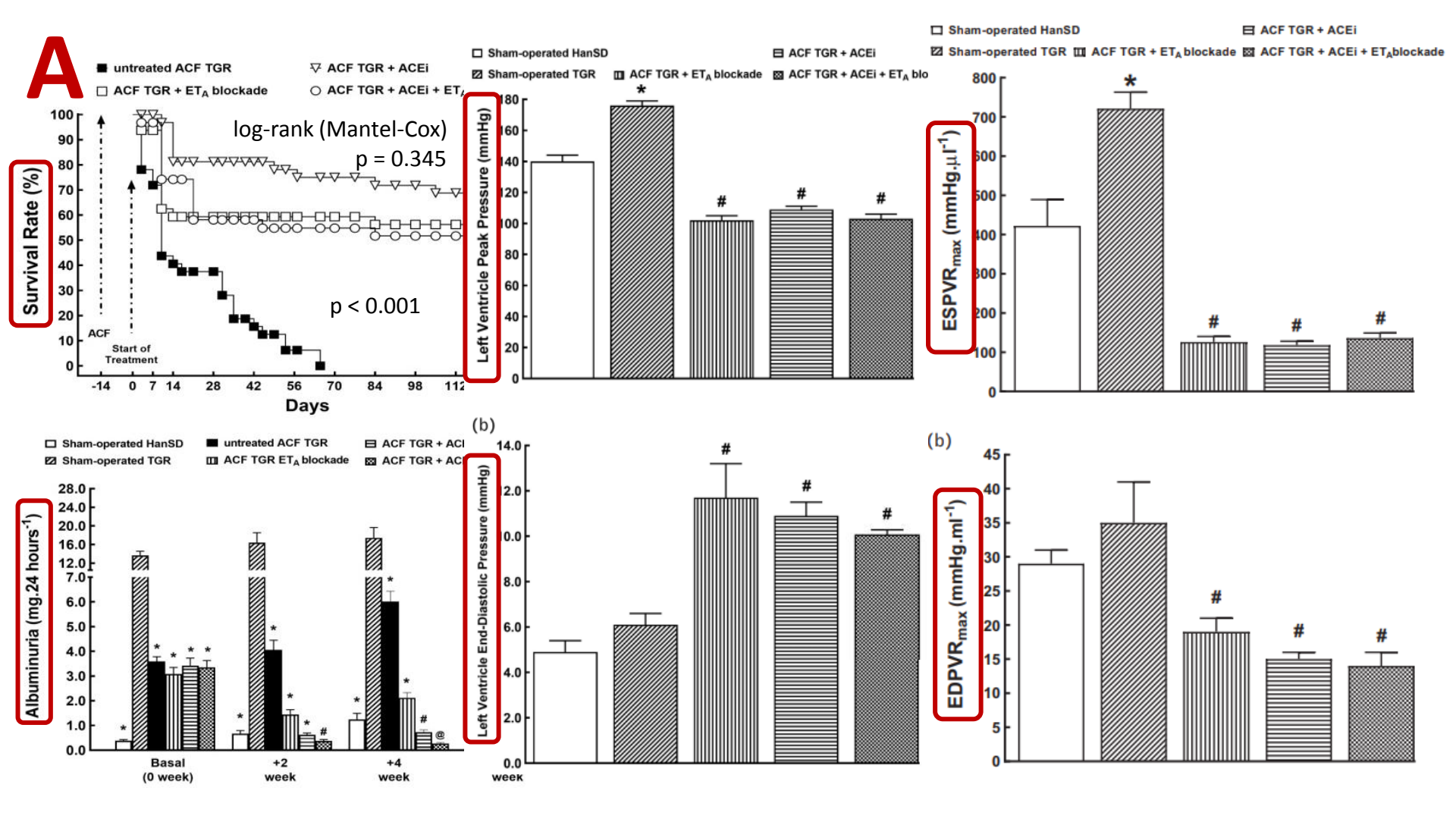


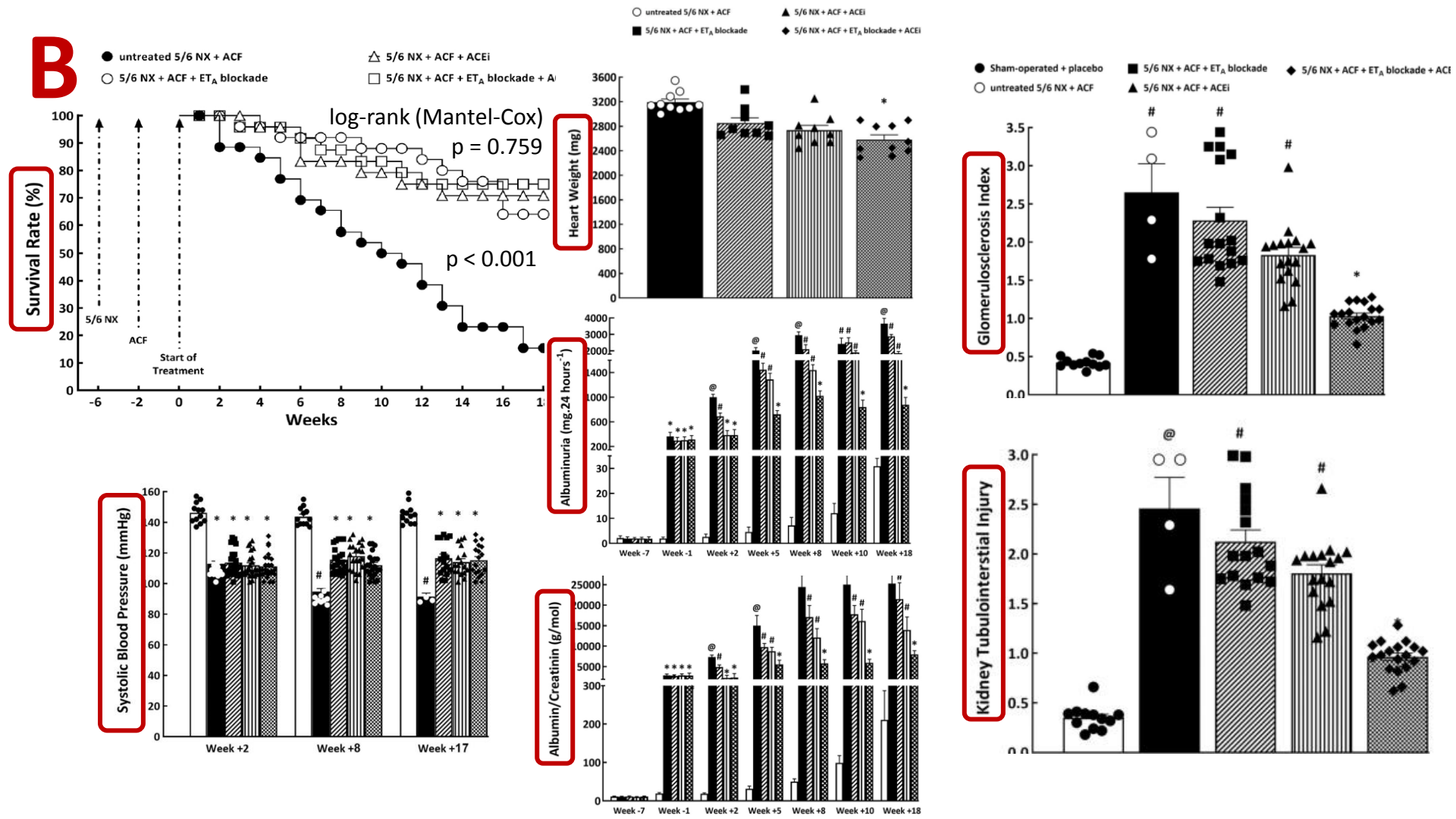
VJI l.sin.
anaesthetics, drugs, fluids

tracheostomy
invasive ventilation (reduction of respiratory artefacts)

art. carotis l.dx.
P-V catheter to LV

VJI l.dx.
Fogarty catheter to VCI (occlusions to preload reduction)


A
untreated ACF TGR
ACF TGR + ACEi
ACF TGR + ETA blockade
ACF TGR + ACEi + ETA
Survival Rate (%)
log-rank (Mantel-Cox)
p = 0.345
p < 0.001
ACF
Start of Treatment
-14 0 7 14 28 42 56 70 84 98 112
Days
Sham-operated HanSD
Sham-operated TGR
ACF TGR + ETA blockade
ACF TGR + ACEi + ETA blo
Left Ventricle Peak Pressure (mmHg)
Sham-operated HanSD
Sham-operated TGR
ACF TGR + ACEi
ACF TGR + ETA blockade
ACF TGR + ACEi + ETAblockade
ESPVRmax (mmHg.µl-1)
(b)
Sham-operated HanSD
Sham-operated TGR
untreated ACF TGR
ACF TGR ETA blockade
ACF TGR + ACE
ACF TGR + AC
Albuminuria (mg.24 hours-1)
Basal (0 week)
+2 week
+4 week
Left Ventricle End-Diastolic Pressure (mmHg)
week
(b)
EDPVRmax (mmHg.ml-1)


B
untreated 5/6 NX + ACF
5/6 NX + ACF + ACEi
5/6 NX + ACF + ET$_A$ blockade
5/6 NX + ACF + ET$_A$ blockade + A
log-rank (Mantel-Cox)
p = 0.759
p < 0.001
Survival Rate (%)
5/6 NX
ACF
Start of Treatment
Weeks
Heart Weight (mg)
Albuminuria (mg.24 hours^{-1})
Week -7
Week -1
Week +2
Week +5
Week +8
Week +10
Week +18
Systolic Blood Pressure (mmHg)
Week +2
Week +8
Week +17
Albumin/Creatinin (g/mol)
Sham-operated + placebo
Glomerulosclerosis Index
Kidney Tubulointerstial Injury

	Placebo	ET_A blockade	ACE inhibitor	ET_A + ACE blockade
Survival	↓	↑↑	↑↑	↑↑

A

Original Article

Journal of Hypertension

OPEN

Endothelin type A receptor blockade attenuates aorto-caval fistula-induced heart failure in rats with angiotensin II-dependent hypertension

Petr Kala[a,b], Olga Gawrys[a,c], Matúš Miklovic[a], Zdenka Vanourková[a], Petra Skaroupková[a], Sárka Jíchová[a], Janusz Sadowski[c], Elzbieta Kompanowska-Jezierska[c], Agnieszka Walkowska[c], Josef Veselka[b], Miloš Táborsky[d], Hana Maxová[e], Ivana Vanecková[f], and Ludek Cervenka[a,d]

Objective: Evaluation of the effect of endothelin type A (ET_A) receptor blockade on the course of volume-overload heart failure in rats with angiotensin II-dependent hypertension.

Methods: Ren-2 renin transgenic rats (TGR) were used as a model of hypertension. Heart failure was induced by creating an aorto-caval fistula (ACF). Selective ET_A receptor blockade was achieved by atrasentan. For comparison, other rat groups received trandolapril, an angiotensin-converting enzyme inhibitor (ACEi). Animals first underwent ACF creation and 2 weeks later the treatment with atrasentan or trandolapril, alone or combined, was applied; the follow-up period was 20 weeks.

Results: Eighteen days after creating ACF, untreated TGR began to die, and none was alive by day 79. Both atrasentan and trandolapril treatment improved the survival rate, ultimately to 56% (18 of 31 animals) and 69% (22 of 32 animals), respectively. Combined ACEi and ET_A receptor blockade improved the final survival rate to 52% (17 of 33 animals). The effects of the three treatment regimens on the survival rate did not significantly differ. All three treatment regimens suppressed the development of cardiac hypertrophy and lung congestion, decreased left ventricle (LV) end-diastolic volume and LV end-diastolic pressure, and improved LV systolic contractility in ACF TGR as compared with their untreated counterparts.

Conclusion: The treatment with ET_A receptor antagonist delays the onset of decompensation of volume-overload heart failure and improves the survival rate in hypertensive TGR with ACF-induced heart failure. However, the addition of ET_A receptor blockade did not enhance the beneficial effects beyond those obtained with standard treatment with ACEi alone.

Keywords: endothelin system, hypertension, Ren-2 renin transgenic rat, renin–angiotensin system, volume-overload heart failure

Abbreviations: ACE, angiotensin-converting enzyme; ACF, aorto-caval fistula; ACEi, angiotensin-converting enzyme inhibitor; ANG II, angiotensin II; ANG 1–7, angiotensin-(1–7); $(+dP/dt)_{max}$, maximum rates of pressure rise; $(-dP/dt)_{max}$, maximum rates of pressure fall; ESPVR, end-systolic pressure–volume relationship; ET_A, endothelin type A; ET-1, endothelin 1; HanSD, Hannover Sprague-Dawley rats; LV, left ventricle; LVEDP, left ventricle end-diastolic pressure; LVEDV, left ventricle end-diastolic volume; PRSW, preload recruitable stroke work; RAAS, renin–angiotensin–aldosterone system; RV, right ventricle; SNS, sympathetic nervous system; TGR, Ren-2 renin transgenic rats; TPR, total peripheral resistance

INTRODUCTION

Over the past 40 years, substantial progress has been made in the treatment of acute coronary syndromes. However, many surviving patients still develop substantial myocardial damage eventually leading to heart failure [1]. Heart failure has become a major public health problem [2,3]; despite the availability of multiple therapeutic measures and recent pharmacological advances, the prognosis remains bleak [2,4–7]. Inappropriately activated renin–angiotensin–aldosterone system (RAAS) is crucial for the progression of heart failure and blockade thereof has become a cornerstone component of the treatment. However, in the advanced phase of heart failure its effectiveness is limited [2,6–9], which was conspicuous in patients who had been hypertensive before the onset of

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B

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Endothelin type A receptor blockade increases renoprotection in congestive heart failure combined with chronic kidney disease: Studies in 5/6 nephrectomized rats with aorto-caval fistula

Petr Kala[a,b,*], Zdenka Vaňourková[b], Petra Škaroupková[b], Elżbieta Kompanowska-Jezierska[c], Janusz Sadowski[c], Agnieszka Walkowska[c], Josef Veselka[a], Miloš Táborský[d], Hana Maxová[e], Ivana Vaněčková[f], Luděk Červenka[b,d]

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ARTICLE INFO

Keywords:
Congestive heart failure
Chronic kidney disease
Endothelin system
Endothelin receptor type A
Aorto-caval fistula
5/6 nephrectomy

ABSTRACT

Background: Association of congestive heart failure (CHF) and chronic kidney disease (CKD) worsens the patient's prognosis and results in poor survival rate. The aim of this study was to examine if addition of endothelin type A (ET_A) receptor antagonist to the angiotensin-converting enzyme inhibitor (ACEi) will bring additional beneficial effects in experimental rats.

Methods: CKD was induced by 5/6 renal mass reduction (5/6 NX) and CHF was elicited by volume overload achieved by creation of aorto-caval fistula (ACF). The follow-up was 24 weeks after the first intervention (5/6 NX). The treatment regimens were initiated 6 weeks after 5/6 NX and 2 weeks after ACF creation.

Results: The final survival in untreated group was 15%. The treatment with ET_A receptor antagonist alone or ACEi alone and the combined treatment improved the survival rate to 64%, 71% and 75%, respectively, however, the difference between the combination and either single treatment regimen was not significant. The combined treatment exerted best renoprotection, causing additional reduction in albuminuria and reducing renal glomerular and tubulointerstitial injury as compared with ACE inhibition alone.

Conclusions: Our results show that treatment with ET_A receptor antagonist attenuates the CKD- and CHF-related mortality, and addition of ET_A receptor antagonist to the standard blockade of RAS by ACEi exhibits additional renoprotective actions.

1. Introduction

Congestive heart failure (CHF) presents an extreme burden to the public healthcare worldwide. Almost 40% of CHF patients die within 1 year from the diagnosis and 70% within 5 years, even under adequate modern therapy [1,2]. The incidence and prevalence of chronic kidney disease (CKD) is also increasing [3] and CKD is one of the strongest risk factors for the development of CHF [4,5]. CHF coexists with CKD in approximately half of CHF patients [4–8]. Unfortunately, patients with estimated glomerular filtration rate $\leq$ 30 ml/min/1.73 m^2 have now largely been excluded from randomized control trials in HF, which limits the information on patients with combined CHF and CKD [4,5,7,8]. Therefore, although the patients with combined CHF and advanced CKD represent probably the highest cardiovascular risk population, their exclusion from CHF trials is a serious deontological error. Even the newest guidelines of the European Society of Cardiology for the treatment of CHF admit that there is little direct evidence to support any recommendation for the treatment of these patients [7,9]. Obviously,

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Thank you for your attention

Petr Kala