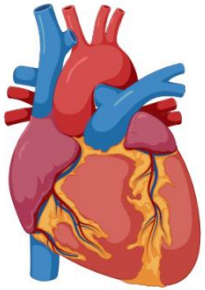
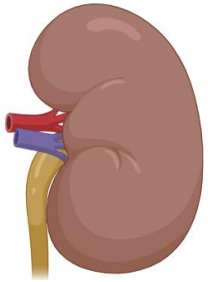
SELEKTIVNÍ BLOKÁDA ENDOTELINOVÉHO RECEPTORU TYPU A ZMÍRŇUJE SRDEČNÍ A RENÁLNÍ SELHÁNÍ U POTKANÍCH MODELŮ





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ČKS, 5.5.2024

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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

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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

Journal of Hypertension 2023, 41:99–114

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Received 1 May 2022 **Revised** 6 August 2022 **Accepted** 7 September 2022

DOI:10.1097/HJH.0000000000003307

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Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

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

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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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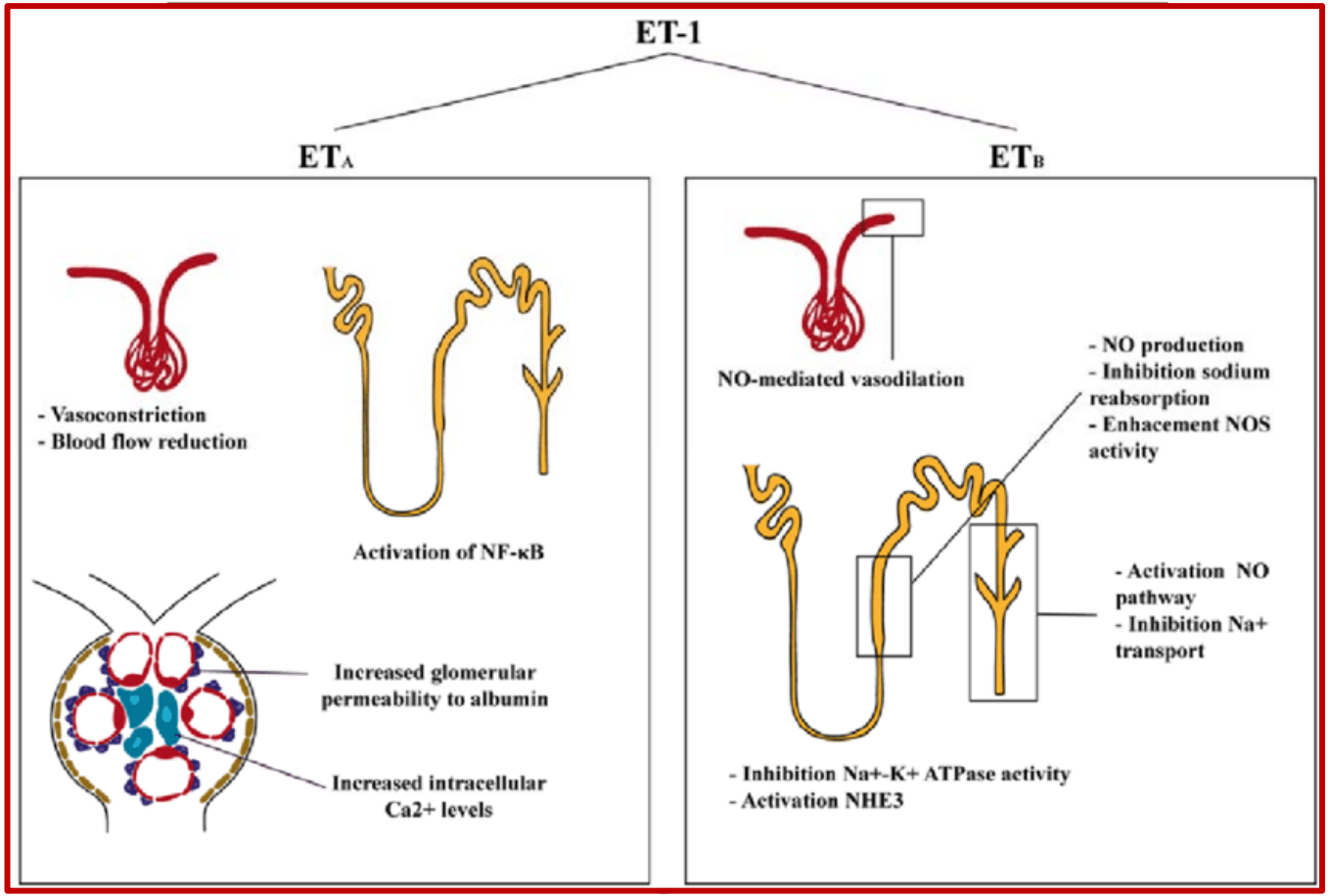
https://doi.org/10.1016/j.biopha.2022.114157
Received 16 September 2022; Received in revised form 11 December 2022; Accepted 21 December 2022
Available online 27 December 2022
0753-3322/

Endotelinový systém



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

Endotelinový systém

Antagonisté (blokátory) ET receptorů

- neselektivní (ET_A/ET_B) - bosentan (20:1)*, macitentan (50:1)*
- selektivní (ET_A) - ambrisentan (200:1)*, **atrasentan (1 200:1)**, zibotentan (10 000:1)
- další

* schváleno u PAH

X NÚ - periferní otoky, retence tekutin

(více u neselektivní blokády i ET_B – snížení průtoku krve ledvinou, retence Na, …)

Renální selhání (CKD)

- SONAR trial (2019) – atrasentan u DM nefropatie – redukce progrese CKD a ESKD
- ZENITH-CKD (2023) – zibotentan + dapagliflozin u CKD +/- DM – redukce albuminurie
- PROTECT (2023) – sparsentan (dual ET+ARB) vs. irbesartan u IgA nefropatie – redukce proteinurie a eGFR poklesu

Srdeční selhání (CHF)

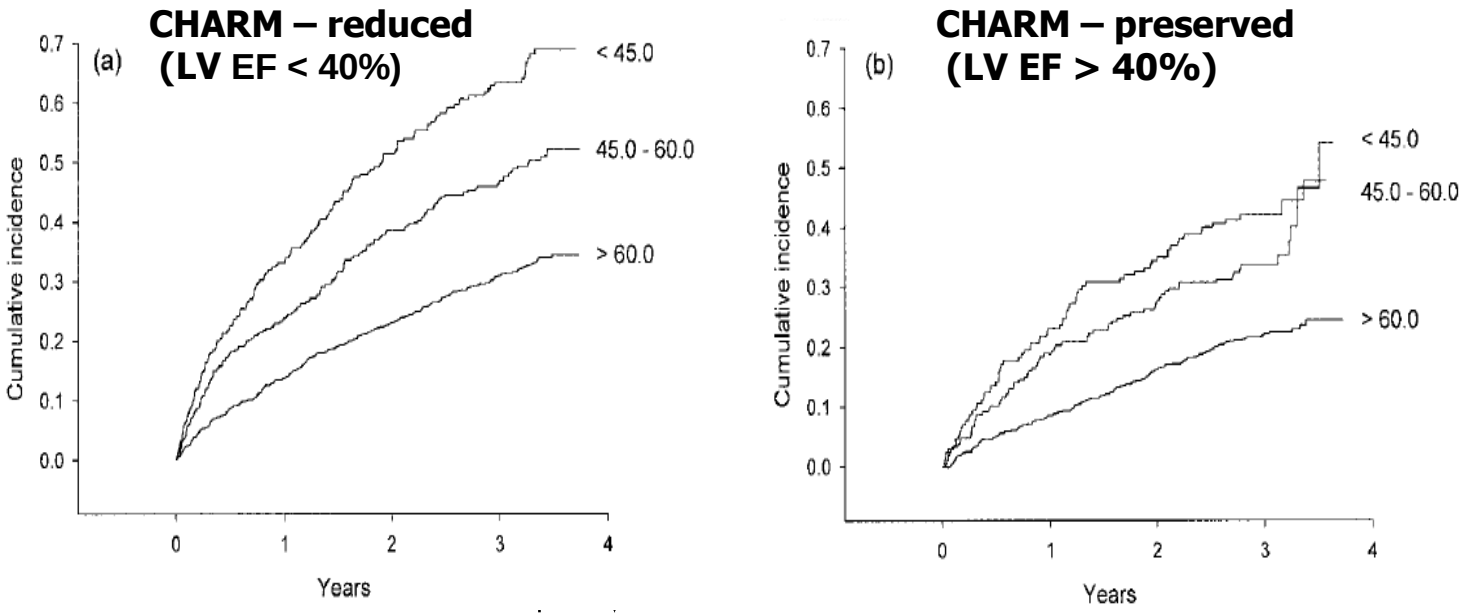
- hladina Big-ET a ET-1 významný negativní prognostický marker
- dosavadní klin. studie s ET blok. nepřesvědčivé (neselektivní, méně selektivní)
  - vyšší riziko NÚ vč. retence tekutin

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

Kombinace CHF a CKD

Projekt CHARM (candesartan x placebo) u CHF

Celková a KV mortalita, HF hospitalizace



Efekt CKD na CHF prognózu

Mortalita v CHF studiích **2,3x vyšší** u **eGFR** < 60ml/min a **1,7x vyšší u albuminurie.**

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

Kombinace CHF a 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

Navzdory nejhorší prognóze, CKD pacienti většinou vyřazeni z CHF studií.
-> efekt standardní terapie?, dávkování?

Uptodate.com

Předchozí práce

1) ET_A blokátor zlepšuje přežívání animálního modelu CHF (ACF TGR)
na úroveň srovnatelnou s monoterapií ACEi.

2) ET_A blokátor zlepšuje morfologické a hemodynamické parametry u ACF TGR na úroveň ACEi,
u funkce a remodelace PK dokonce lepší.

Kala et al. Sjezd ČKS 2020

Hypotéza a cíle

Zvýšená aktivace endotelinového systému u CHF a v kombinaci s CKD
je dlouhodobě maladaptivní a podílí se na progresi obou onemocnění.

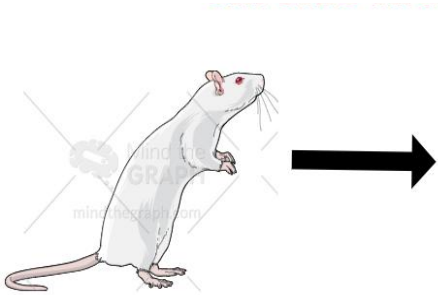
Kombinovaná chronická selektivní blokáda ET_A (atrasentan) spolu s ACE inhibitorem:

→ **A** zlepší přežívání TGR + ACF oproti monoterapii ACEi přes ovlivnění morfologických srdečních a hemodynamických parametrů a nebude způsobovat retenci tekutin

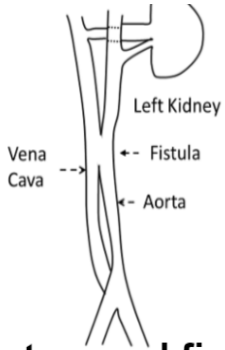
→ **B** zlepší přežívání HanSD + 5/6 Nx + ACF oproti monoterapii ACEi přes ovlivnění renální morfologie a funkce

A

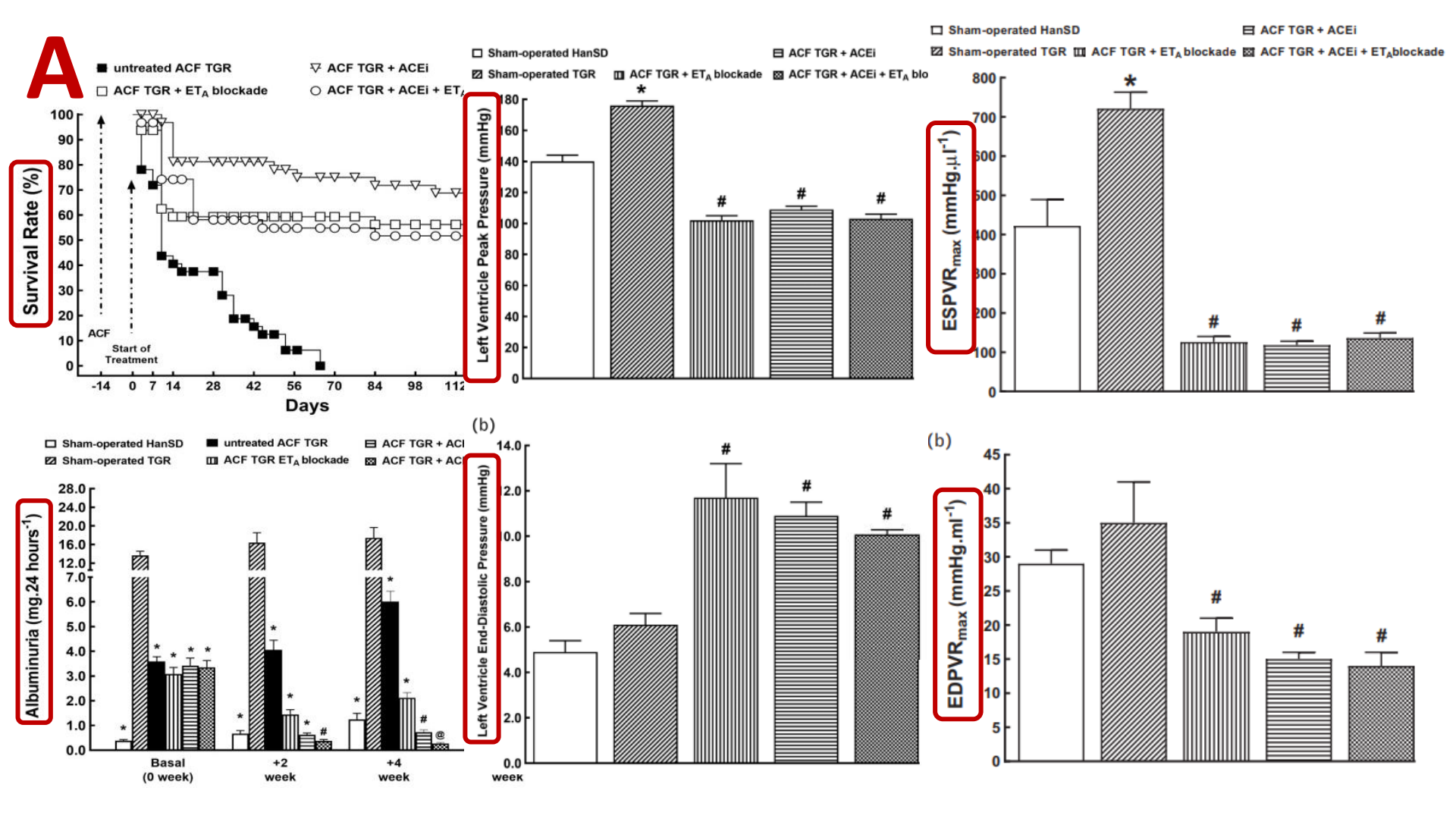
Model CHF

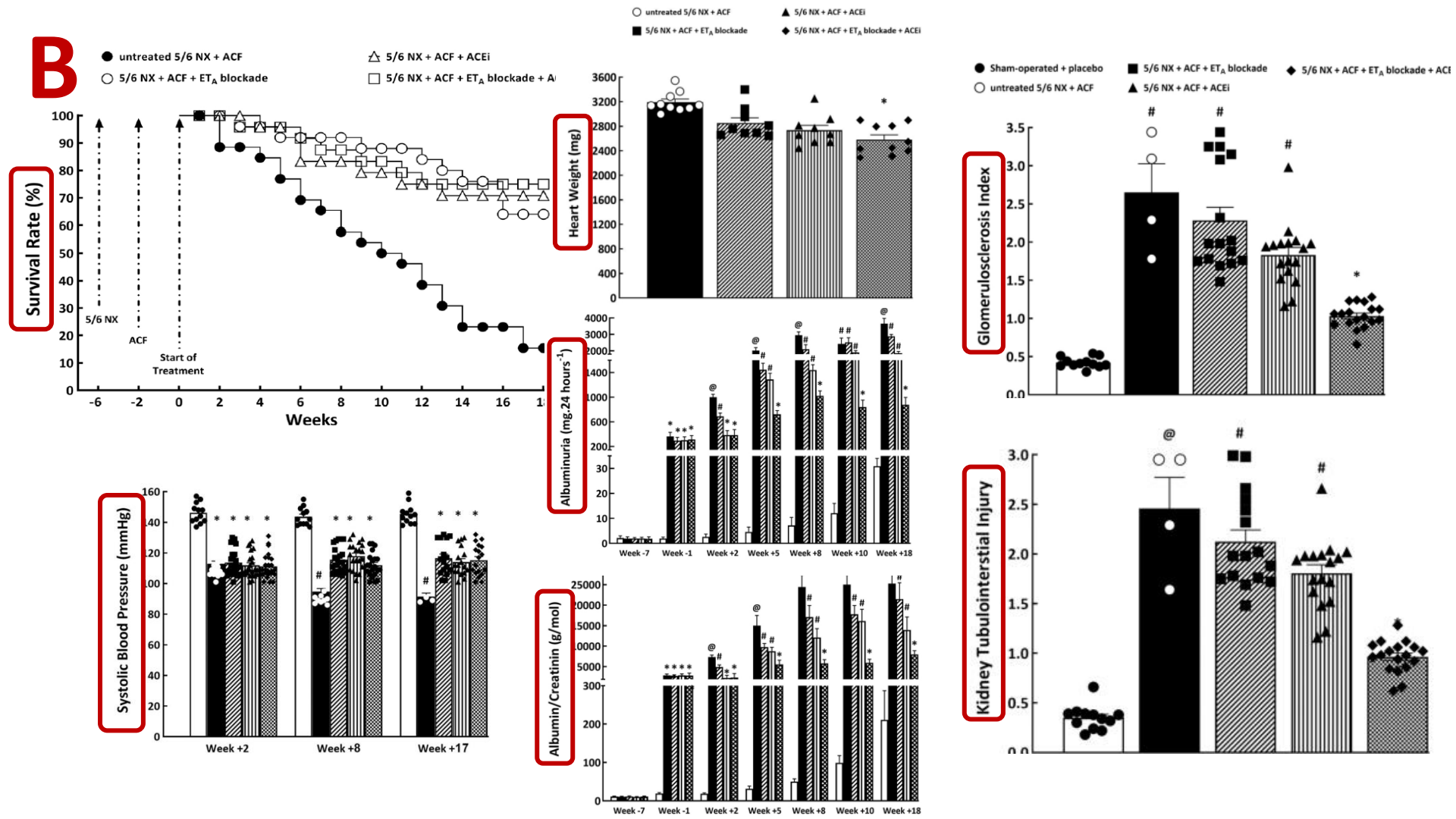


TGR rat
(hypertensive)



aorto-caval fistula
(ACF)


A
untreated ACF TGR
ACF TGR + ACEi
ACF TGR + ETA blockade
ACF TGR + ACEi + ETA
Survival Rate (%)
ACF
Start of Treatment
Days
Sham-operated HanSD
Sham-operated TGR
ACF TGR + ETA blockade
ACF TGR + ACEi + ETA blo
Left Ventricle Peak Pressure (mmHg)
ESPVRmax (mmHg.μl-1)
(b)
Albuminuria (mg.24 hours-1)
Basal (0 week)
+2 week
+4 week
Left Ventricle End-Diastolic Pressure (mmHg)
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 + ACEi
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 blokátor	ACE inhibitor	ET_A + ACE blokáda
Přežívání	↓	↑↑	↑↑	↑↑
Remodelace LK	↑	↓	↓↓	↓↓
Srdeční funkce	↓	↑↑	↑↑	↑↑
Albuminurie	↑	↓	↓↓	↓↓↓
Poškození ledvin	↑	↓	↓↓	↓↓↓

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2. LF UK

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2. LF UK A FN MOTOL

Děkuji za pozornost

Petr Kala