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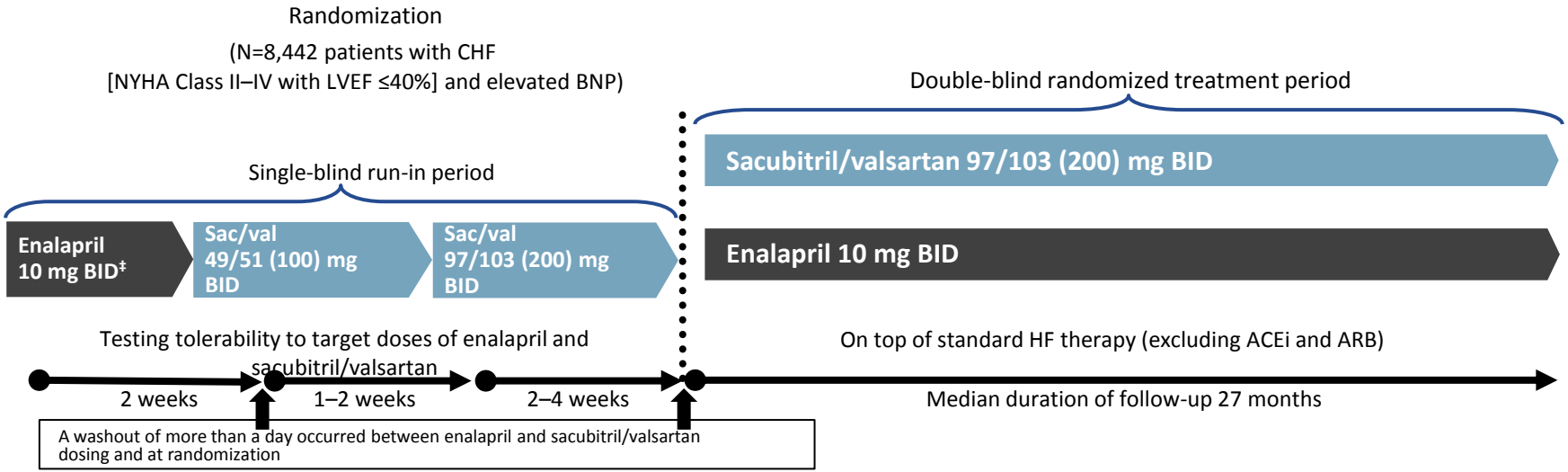
Duální inhibice RAAS: Ovlivní také poruchy srdečního rytmu u pacientů s HFrEF ?

Miloš Táborský

PARADIGM-HF: Study design



Primary outcome: CV death or HF hospitalization

‡Enalapril 5 mg BID for 1–2 weeks followed by enalapril 10 mg BID as an optional starting run-in dose for patients who are treated with ARB or with a low dose of ACEi.

1. McMurray et al. Eur J Heart Fail. 2013;15:1062-1073; 2. McMurray et al. Eur J Heart Fail. 2014;16:817-825; 3. McMurray et al. N Engl J Med. 2014;371:993-1004

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Hlasování 1:

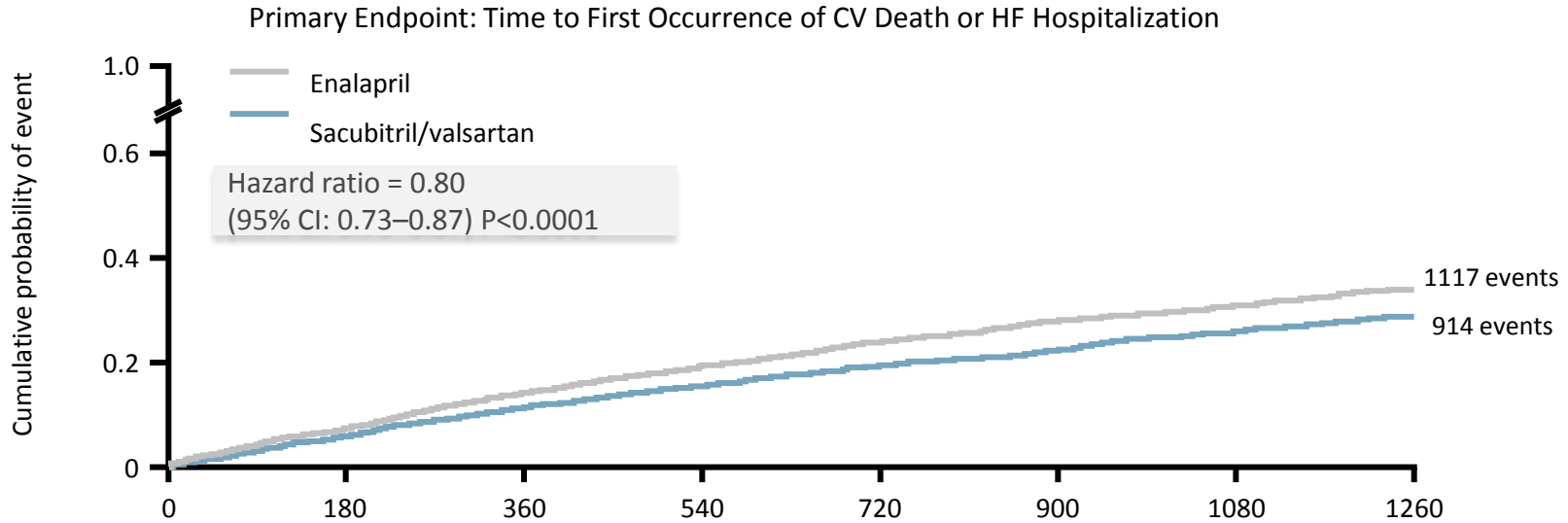
Sacubitril valsartan je indikován u pacientů s HFrEF :

1. Pouze u pacientů se sinusovým rytmem

2. Jak u pacientů se SR, tak i pacientů s FS

3. Indikace je bez ohledu na arytmický statut pacienta – SR, FS, NSKT, KT

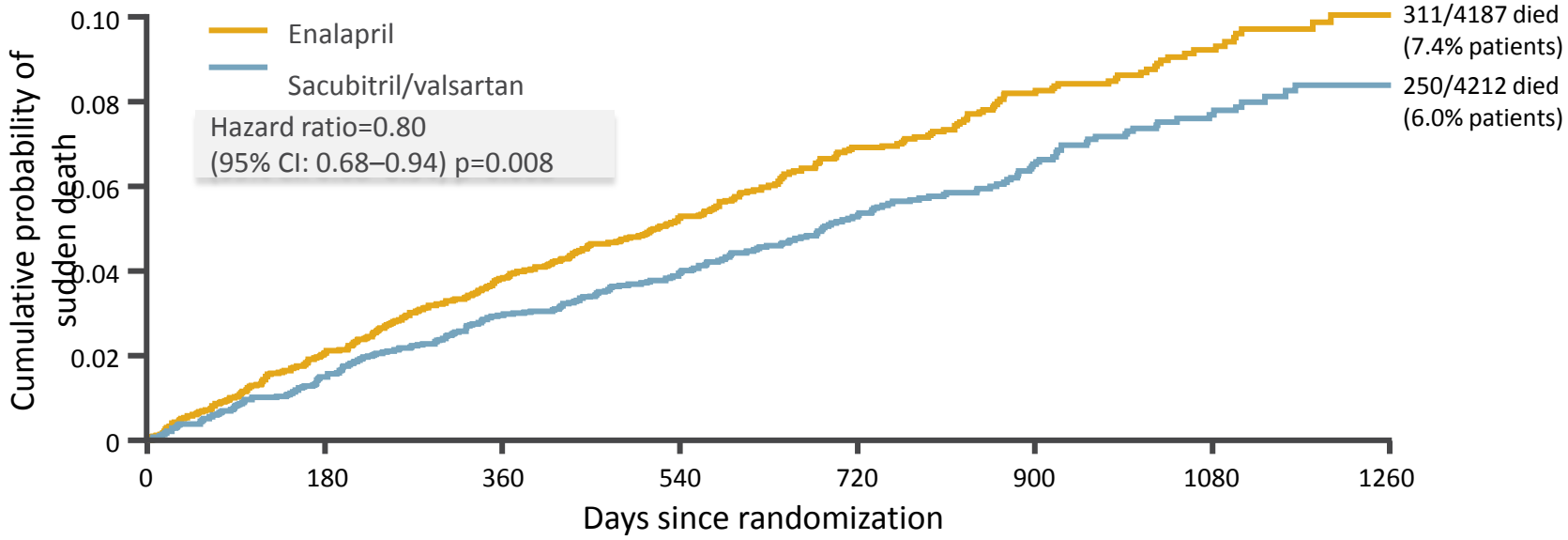
PARADIGM-HF: Sacubitril/valsartan reduced incidence of primary endpoint



No. at risk								
Sacubitril/valsartan	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

1. McMurray, et al. New Engl J Med. 2014;371:993-1004

Sacubitril/valsartan significantly reduced the risk of sudden death compared with enalapril

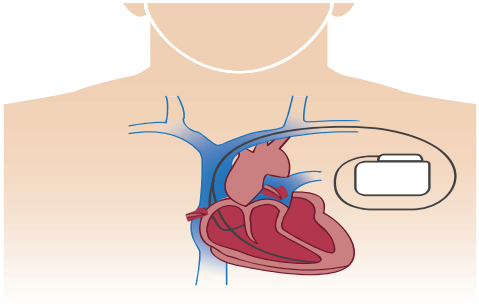


No. at risk				
Sacubitril/valsartan	4187	3891	2478	1005
Enalapril	4212	3860	2410	994

1. Desai et al. Eur Heart J 2015;36:1990-7; 2. McMurray, et al. New Engl J Med. 2014;371:993-1004

The benefit of sacubitril/valsartan on sudden death was independent of ICD use

- ICD and CRT-D use in PARADIGM-HF was 15% and 5%[1,2] respectively, similar to that in other recent HFrEF trials.[3,4] While the patients with an ICD had a lower overall risk of sudden death, their use did not eliminate risk completely
- The sacubitril/valsartan treatment effect on sudden death was not influenced by the presence of defibrillator devices[2]
- Among patients with an ICD, use of sacubitril/valsartan reduced the relative risk of sudden death by 51% compared with enalapril[2]



PARADIGM-HF	Sudden death n (%)	Hazard ratio, sac/val vs. enalapril (95% CI)
– ICD	7.3% (525/7156)	0.82 (0.69–0.98)
Enalapril*	8% (287/3592)	n/a
Sac/val*	6.7% (238/3564)	n/a
+ ICD	2.9% (36/1243)	0.49 (0.25–0.98)
Enalapril*	3.9% (24/620)	n/a
Sac/val*	1.9% (12/623)	n/a

*This was a post hoc analysis; * Novartis data on file*

1. McMurray et al. 2014. Eur J Heart Fail. 2014;16:817-25; 2. Desai et al. Eur Heart J. 2015;36:1990-7; 3. Swedberg et al. Lancet. 2010;376:875-85; 4. Zannad et al. N Engl J Med 2011;364:11-21

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Hlasování 2:

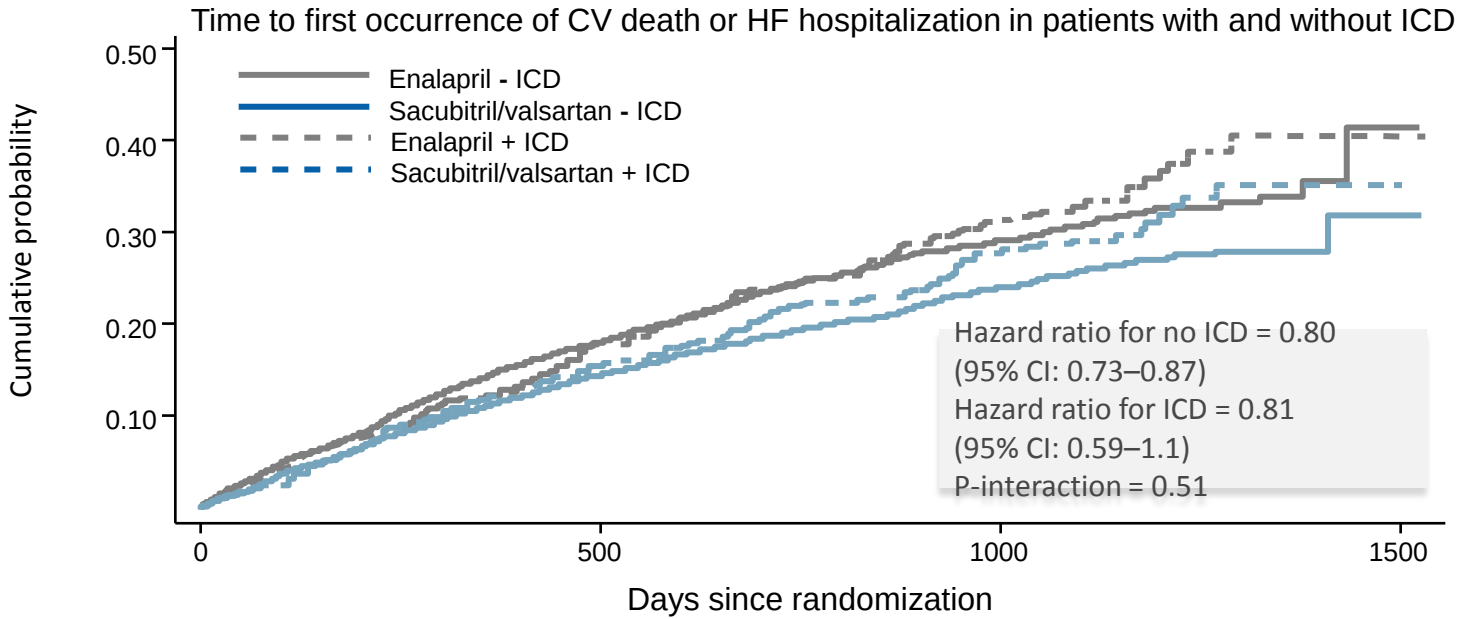
Kolika pacientům se symptomatickým HFrEF s opt. Farmakoterapií je v ČR implantován/vyměněn ICD ?

1. 2500

2. 3400

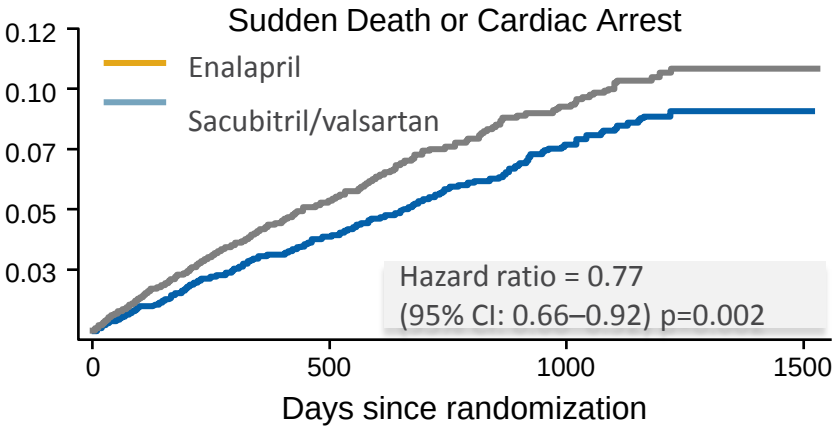
3. 4200

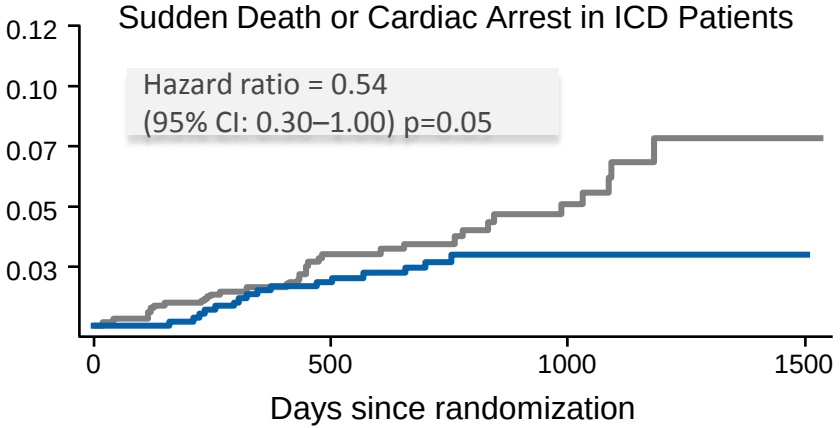
Sacubitril/valsartan reduced the risk of CV death or HF hospitalization compared with enalapril, irrespective of ICD use



Novartis data on file

Sacubitril/valsartan reduced the risk of sudden death or cardiac arrest compared with enalapril, irrespective of ICD use



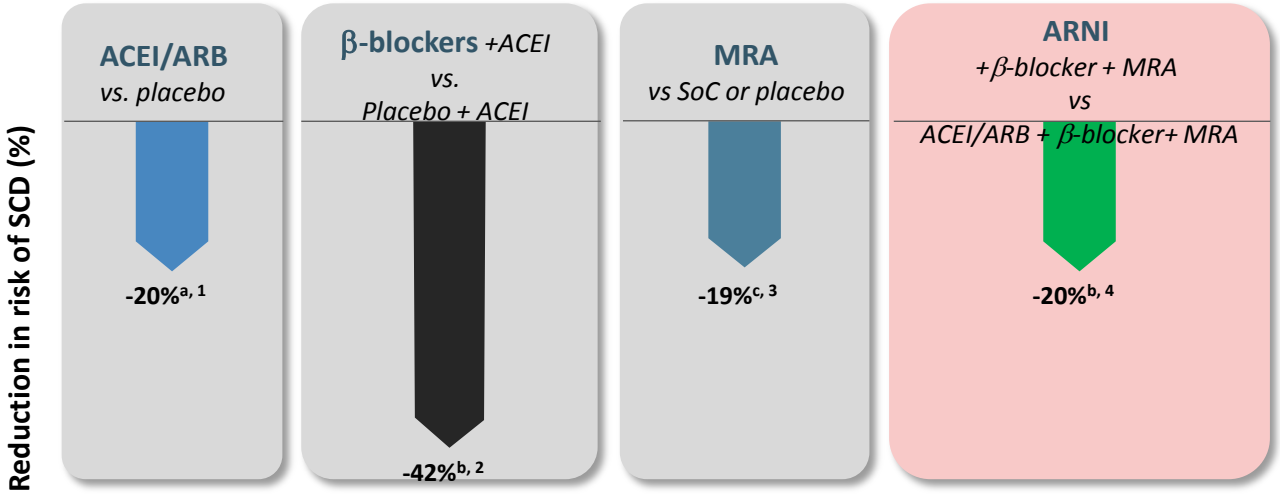


P-interaction for efficacy of sacubitril/valsartan and ICD = 0.21

Novartis data on file.

Effect of sacubitril/valsartan on sudden death compared with ARB and ACE inhibitors

- Optimization of pharmacotherapy reduces the risk of SCD in patients with HF
- Among GDMT, the efficacy of β-blockers and ARNI in reducing SCD is strongly supported by evidence from RCTs



[a]Meta-analysis in patients with prior MI; [b]RCT; [c]meta-analysis

1. Domanski et al., JACC, 1999; 598-604; 2. CIBIS II Investigators, Lancet, 1999; 353:9-13; 3. Le et al., PLoS One, 2016; 11(2):e0145958; 4. Desai et al. Eur Heart J. 2015;36:1990–7

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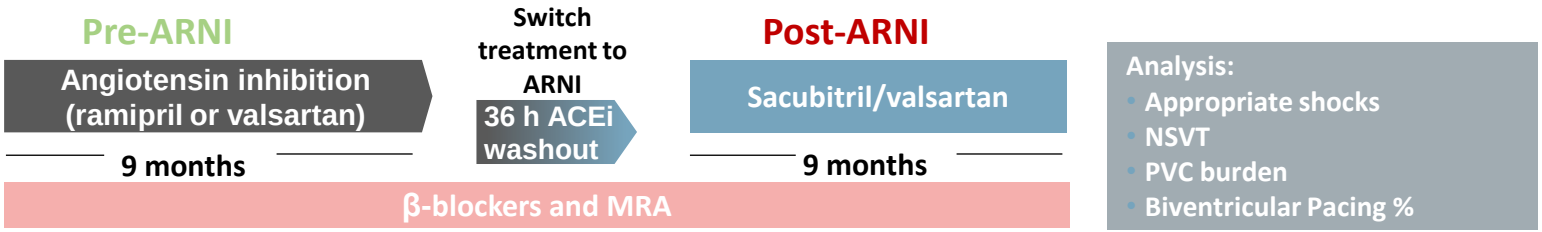
Effects of angiotensin-neprilysin inhibition as compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices

de Diego et al. Heart Rhythm 2018;15(3):395-402

Study design and patient population



Patient population:

120 HFrEF patients with ICD or ICD-CRT referred to cardiology HF/arrhythmia outpatient clinic:

- HF symptoms with NYHA class ≥II despite optimal medical therapy, including initiation and titration of ACEi (ramipril) or ARB (valsartan), β-blockers, and MRA if tolerated
- LVEF ≤40%
- Under home monitoring of an ICD
- Patients serve as their own control by design

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Patient characteristics pre- and post-intervention (1/3)

- Observational study design; patients served as their own controls
- Patients were on optimal medical therapy (OMT) throughout the study period

	Pre-ARNI (n = 120)	Post-ARNI (n = 120)	P value
Clinical characteristics			
Age (yrs)	69 ± 8	70 ± 8	NS
Male	91 (76)	91 (76)	NS
Ischemic cardiopathy	98 (82)	98 (82)	NS
Hypertension	75 (62)	75 (62)	NS
Diabetes	36 (30)	36 (30)	NS
Hypercholesterolemia	62 (52)	63 (52)	NS
Renal insufficiency (filtration rate <60 mL/min)	48 (40)	48 (40)	NS
Rhythm			
Sinus rhythm	85 (71)	84 (70)	NS
Paroxysmal AF	17 (14)	12 (10)	.07
Permanent AF	35 (29)	36 (30)	NS

Values are given as mean ± SD, n (%), or %.

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Patient characteristics pre- and post-intervention (2/3)

- Patients were on OMT throughout the study period
- An improvement in NYHA functional class and a reduction in the dose of diuretic treatment were observed post-ARNI

	Pre-ARNI (n = 120)	Post-ARNI (n = 120)	P value
Medical treatment	100% ACEi or ARB	100% sacubitril-valsartan	
β-blocker	98%	98%	NS
Mineraloid antagonist	97%	97%	NS
Antiarrhythmic drug	30%	29%	NS
Oral diuretic	75%	52%	<.03
Device			
ICD only	56%	56%	NS
ICD + CRT	44%	44%	NS
Primary prevention	65%	65%	NS
Secondary prevention	35%	35%	NS
Clinical data NYHA functional class (I–IV)	2.4 ± 0.4	1.5 ± 0.7	<.0002

Values are given as mean ± SD, n (%), or %.

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Patient characteristics pre- and post-intervention (3/3)

- There was a significant increase in LVEF and LVEDD post-ARNI[1], suggesting both functional and structural improvements in cardiac tissue[1-3]
- Levels of pro-BNP were lowered post-ARNI[1], suggesting a reduction in myocardial wall stress and a lower likelihood of ICD shocks[1,4]

	Pre-ARNI (n = 120)	Post-ARNI (n = 120)	P value
Echocardiographic data			
LVEF (%)	30.4 ± 4	35.1 ± 8	<.01
LVEDD (mm)	61 ± 5	58 ± 6	<.01
Examination data			
Systolic blood pressure (mmHg)	121 ± 38	107 ± 39	<.02
Diastolic blood pressure (mmHg)	73 ± 23	64 ± 26	<.006
Heart rate average (bpm)	67 ± 7	64 ± 5	<.006
Blood tests			
Potassium level (mEq/L)	4.4 ± 0.5	4.7 ± 0.5	<.03
Pro-BNP (pg/mL)	1971 ± 1530	1172 ± 955	<.01
Glomerular filtration rate (mL/min)	55 ± 19	57 ± 19	NS

Values are given as mean ± SD, n (%), or %

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402; 2. Al-Khatib et al. Circulation. 2017;000:e000–e000. DOI: 10.1161/CIR.0000000000000549; 3. Tomaselli , Zipes. Circ Res. 2004;95:754-63; 4. Levine et al. Heart Rhythm 2014;11:1109–1116

Effect of sacubitril/valsartan on home monitoring parameters

Treatment with sacubitril/valsartan was associated with a significant improvement in biventricular pacing, which indicates a reduction in PVC burden (correlated with the reduction in pro-BNP)[1]

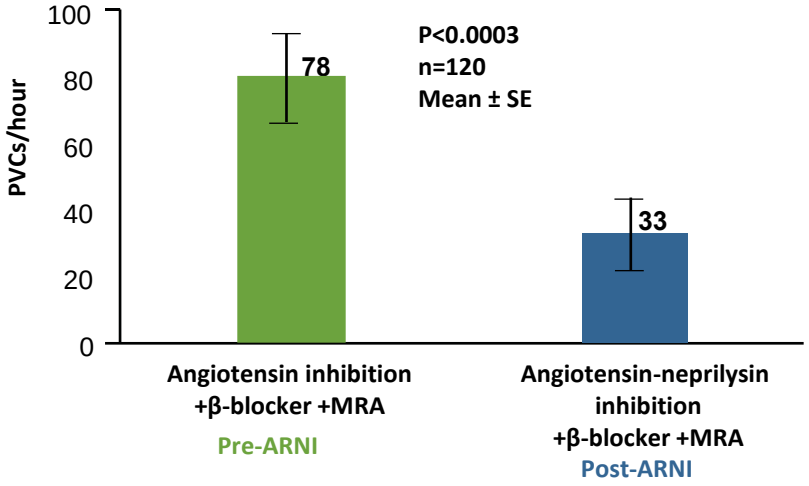
Treatment with sacubitril/valsartan was associated with a reduction in the number of both appropriate and total ICD shocks required, which may positively impact patient QoL[1-3]

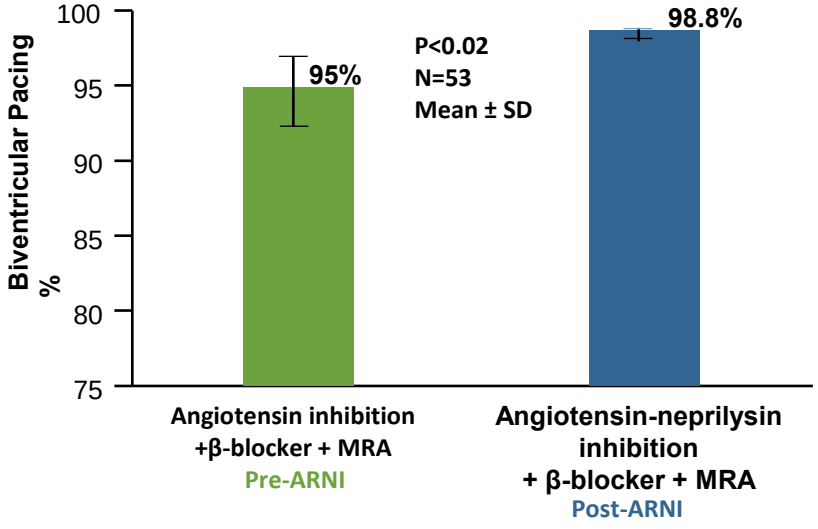
	ACEi/ARB (n = 120)	ARNI (n = 120)	P value
Follow-up (months)	9	9	
Biventricular pacing (n = 53)			
Biventricular pacing (%)	95 ± 6	98.8 ± 1.3	<0.02
Biventricular pacing <90%	5	0	0.07
ICD shocks (n = 120)			
Appropriate ICD shocks	8	1	<0.03
Inappropriate ICD shocks	3	1	1
Total ICD shocks (appropriate + inappropriate)	11	2	<0.01
Appropriate shocks or biventricular pacing <90%	13	1	<0.002

Values are given as n or mean ± SD unless otherwise indicated

1. de Diego C, et al. Heart Rhythm. 2018;15(3):395-402; 2. Passman R et al. Arch Intern Med 2007;167(20):2226-32. 3. Mark DB et al. New Engl J Med. 2008;359(10):999-1008.

A decrease in PVC burden after sacubitril/valsartan was associated with an increase in biventricular pacing %, compared with ACEi/ARB





The increments seen in biventricular pacing with sacubitril/valsartan (3.8%) could have significant impact on symptomatic improvement and on mortality

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Sacubitril/valsartan significantly increased time of survival free from appropriate ICD shocks, compared with ACEi/ARB[1]

- The most common mechanism of sudden death in patients with an ICD was VT/VF treated with an appropriate shock followed by EMD[2]
- ICD patients suffer from poorer psychological well-being following shocks, which impacts QoL[3-5]

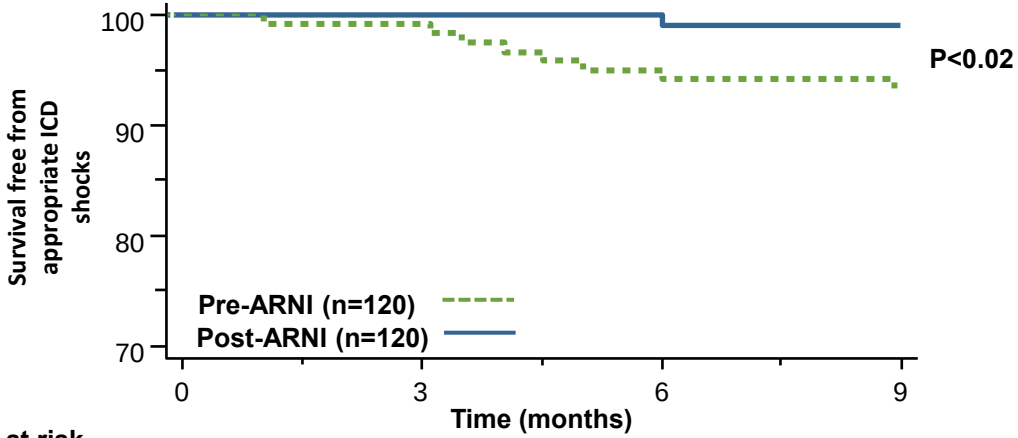


Figure from de Diego et al

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402; 2. Mitchell et al. J Am Coll Cardiol. 2002;39:1323–8; 3. Tomzik et al. Front Cardiovasc Med. 2015;234. doi: 10.3389/fcvm.2015.00034; 4. Passman, et al. Arch Intern Med 2007;167(20):2226-32.
5. Mark et al. New Engl J Med. 2008;359(10):999-1008; Figure from de Diego et al

Sacubitril/valsartan significantly lowers number of episodes and duration of NSVT and sustained VT[1]

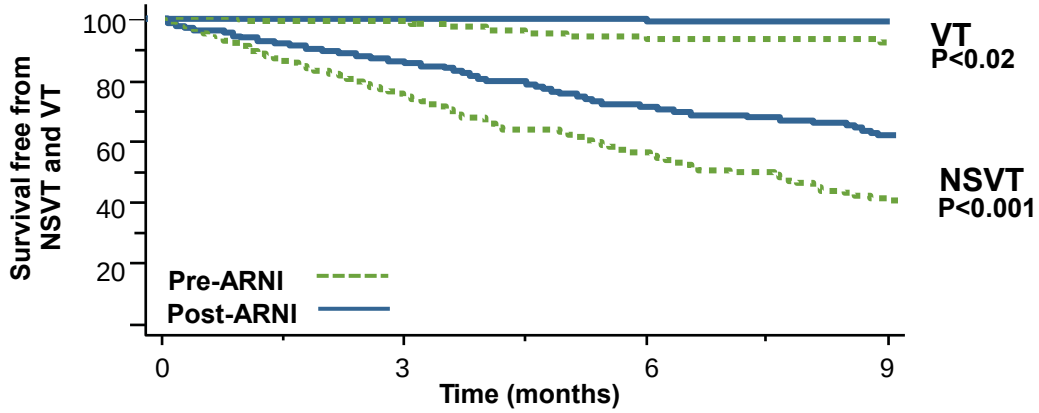
The reduction in ventricular arrhythmias contributed to the reduction in ICD shocks, and suggests a potential mechanistic source for the reduction in sudden death seen in the PARADIGM-HF trial[1-3]

	ACEi/ARB (n = 120)	ARNI (n = 120)	P value
Type of appropriate ICD shocks			
VF by intracardiac recordings	2	0	
VT by intracardiac recordings	6	1	
Ventricular arrhythmias (n = 120)			
Sustained VT	8	1	<0.03
NSVT (episodes/patient)	15 ± 1.7	5.4 ± 0.5	<0.002
NSVT	71	45	<0.0001
NSVT duration (s)	8 ± 2.5	5.4 ± 1.6	<0.001
PVCs/hour (mean ± SEM)	78 ± 15	33 ± 12	<0.003
Atrial arrhythmias (n = 85)			
Paroxysmal AT/AF ≥30 seconds	17	12	0.07

Values are given as n or mean ± SD unless otherwise indicated

1. de Diego C, et al. Heart Rhythm. 2018;15(3):395-402; 2. McMurray JJV, et al. New Engl J Med. 2014;371:993-1004; 3. Desai AS, et al. Eur Heart J. 2015;36:1990-7.

Sacubitril/valsartan significantly increased time of survival free from VT and NSVT, compared with ACEi/ARB



Number at risk (VT)

ARNI	120	120	120	120	119	119
ACEi/ARB	120	119	119	115	113	113

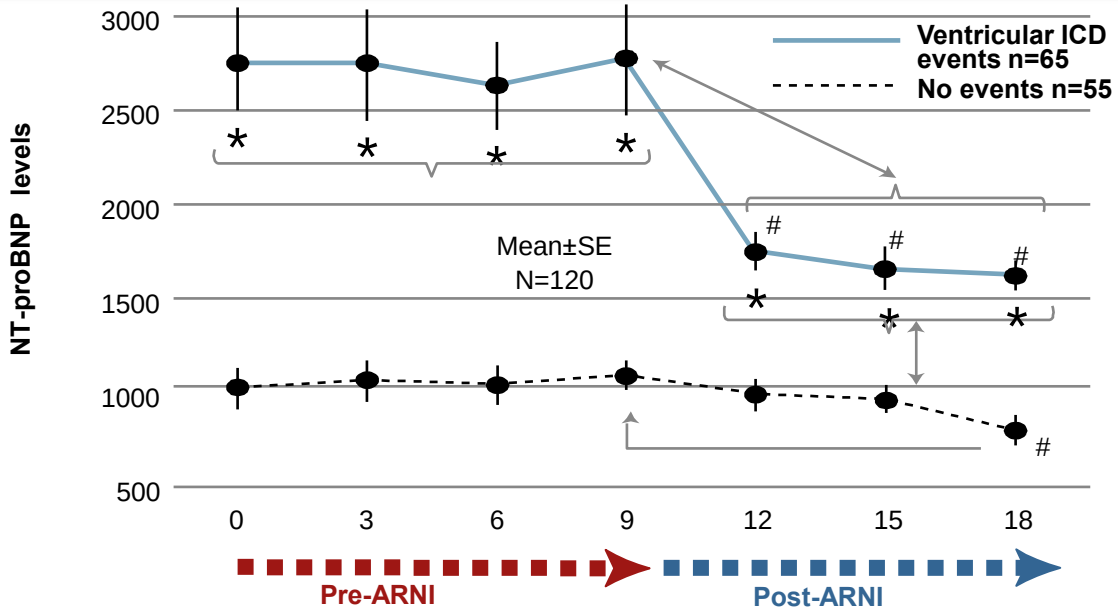
Number at risk (NSVT)

ARNI	120	111	103	95	86	82
ACEi/ARB	120	104	90	77	67	59

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Sacubitril/valsartan decreases NT-proBNP in patients with VA ICD events

- Prior to switching to sacubitril/valsartan (pre-ARNI), NT-proBNP levels were significantly elevated in patients with VA ICD events compared with patients without VA
- Following the switch to sacubitril/valsartan (post-ARNI), both groups experienced a decrease in NT-proBNP levels, though this effect was more pronounced in the VA ICD group



1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

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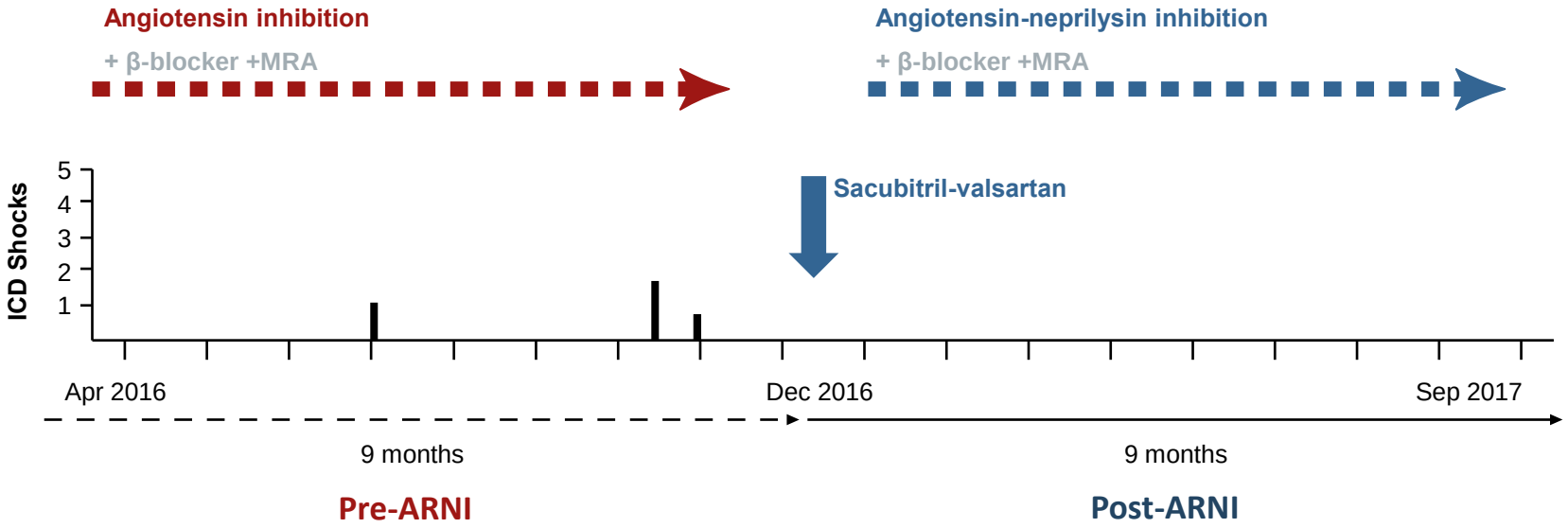
Hlasování č. 3:

Kazuistika

- 59 letý pacient poinfarktovou dysfunkcí LK, EF 0,28, EDD 62, LBBB, symptomatickým HFrEF, maximalizovanou farmakoterapií srdečního selhání včetně sacubitril valsartanu. Na EKG SR, LBBB, biventrikulární ICD s Home Monitoringem.
- Přichází ke konzulataci do ambulance srdečního selhání – v ambulanci malé regionální nemocnice mu bylo po 6 M léčby vysazeno ošetřujícím lékařem Entresto v uptitrované dávce 49/51 se zdůvodněním, že je nyní NYHA II a má NTpro BNP 98 pg/ml a musí tedy užívat ACEi.
- Je tento postup lege artis ?

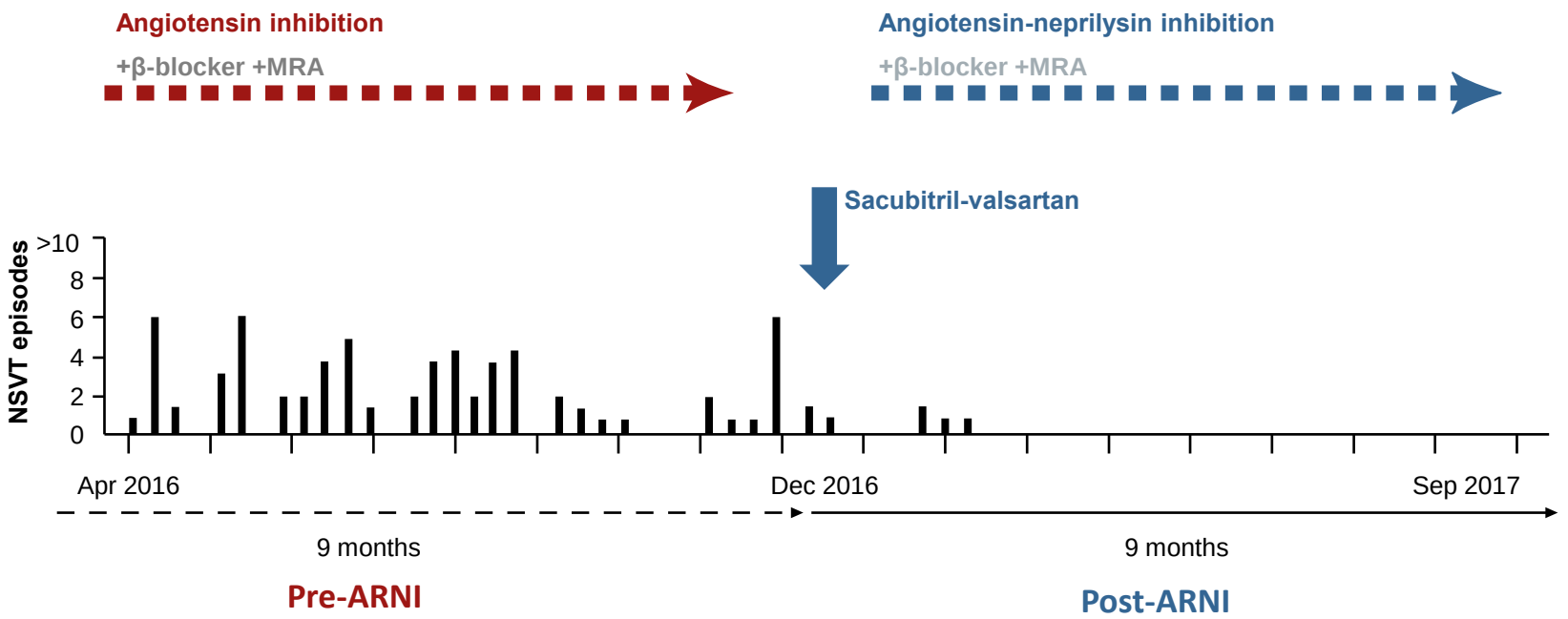
1. Ano
2. Ne

Fewer appropriate ICD shocks in a sample patient post-ARNI



1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Fewer NSVT episodes in a sample patient post-ARNI

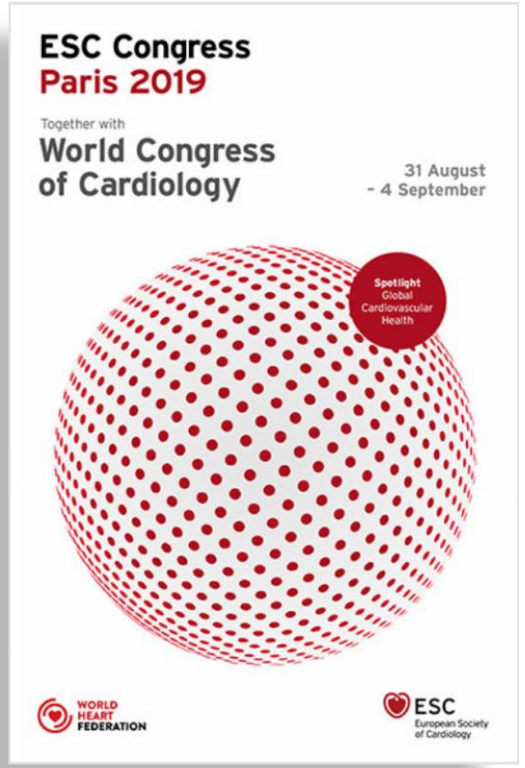


1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Abstrakt ESC 2019

Táborský M, Aiglová R et al.

The effect of sacubitril-valsartan on ventricular tachycardias in pts with HFrEF and ICD therapy.



SPC Entresto