



Program za napredovalo srčno popuščanje  
in transplantacije srca  
*KO za kardiologijo*  
*UKC Ljubljana*

# SRČNO POPUŠČANJE

## Obravnava komorbidnosti

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Maj 2024

# Komorbidnosti - pomembni del srčnega popuščanja

- bolezni koronarnih arterij
- kaheksija in **sarkopenija**
- rakave bolezni
- depresija, bolezni avtonomnega živčevja, možganske kapi
- sladkorna bolezen
- erektilna disfunkcija
- putika in artritis
- hipo- in hiperkalemija
- hiperlipidemija
- pomanjkanje železa in anemija
- ledvična bolezen
- pljučna bolezen
- debelost
- motnje spanja in sindrom apneje v spanju
- bolezni srčnih zaklopk
- arterijska hipertenzija

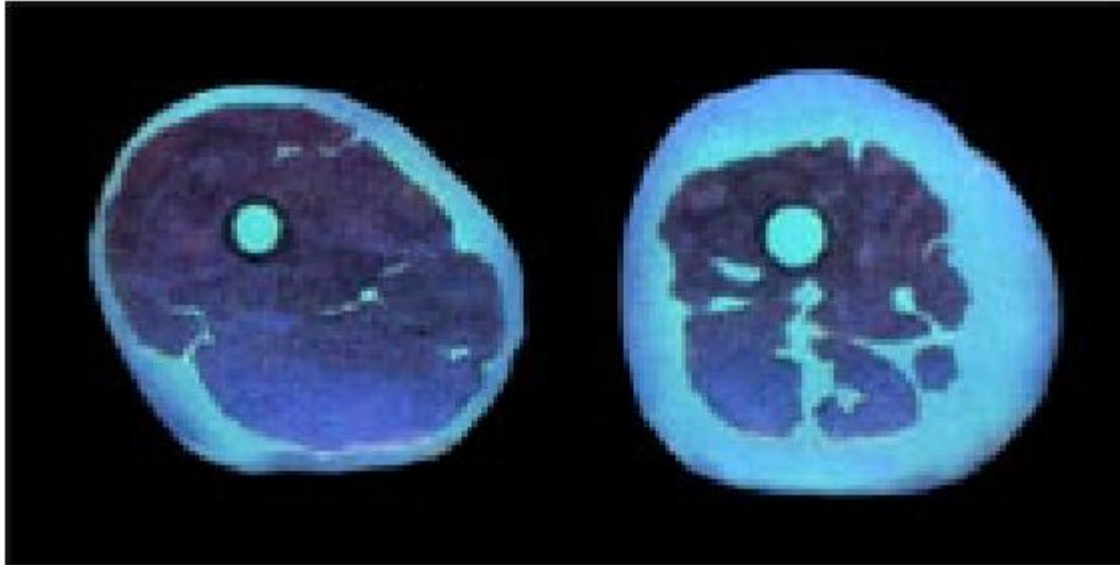
# O čem govorimo?

- Sarkopenija
- Slaba prehranjenost (malnutricija)
- Stradanje
- Miopenija
- Hiperkatabolizem
- Kaheksija
- Izguba TT
- Anoreksija



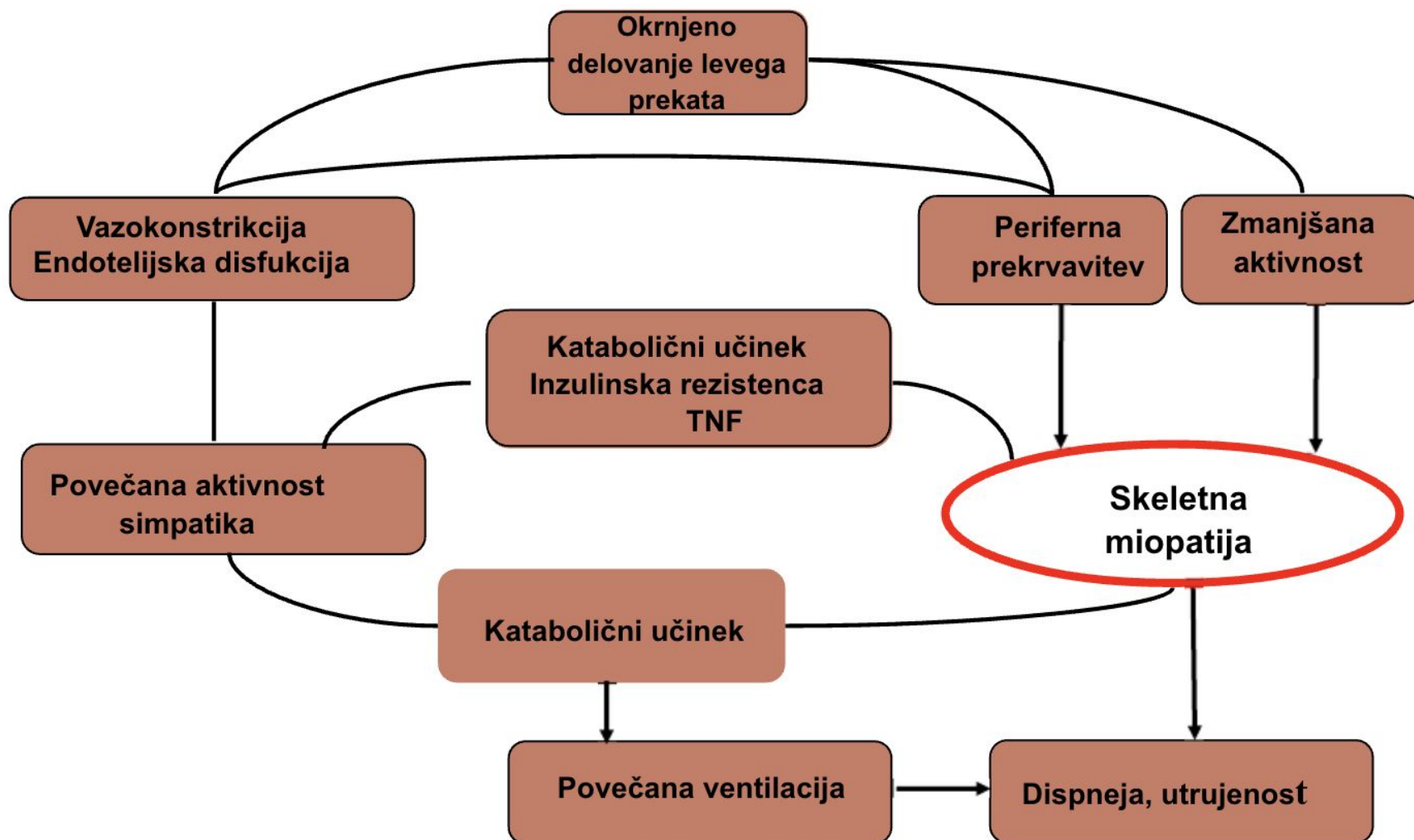
“Vse  
je  
to  
isto”

# Izguba tkiva in srčno popuščanje



- Zgodaj v poteku bolezni:  
Izguba mišične mase brez izgube telesnega tkiva
- Faza izgube telesnega tkiva:  
Vsa tkiva: mišično tkivo, maščobno tkivo, kosti

# Mišična teorija in vloga periferije



# Sarkopenija in srčno popuščanje

	All patients	Patients without muscle wasting (n = 161)	Patients with muscle wasting (n = 39)	P-value
Sex (m/f %)	79.5/20.5	75.8/24.2	94.9/5.1	0.007*
Age (years)	66.9 ± 10.4	66.0 ± 10.6	70.8 ± 8.3	0.01
Weight (kg)	86.7 ± 16.9	89.2 ± 15.9	76.3 ± 17.1	<0.0001
Body mass index (kg/m <sup>2</sup> )	28.8 ± 5.1	29.9 ± 4.7	24.5 ± 4.5	<0.0001
Cause of HF (ischaemic/non- ischaemic %)	50.5/49.5	45.9/54.1	69.2/30.8	0.02*
NYHA—class	2.3 ± 0.5	2.3 ± 0.6	2.5 ± 0.8	0.16
LVEF (%)	38.9 ± 13.5	39.8 ± 13.8	35.0 ± 11.6	0.05
HFrEF/HpEF (%)	68.8/31.2	65.1/34.9	83.8/16.2	0.03*
Sodium (mmol/L)	141.4 ± 3.5	141.6 ± 3.5	140.8 ± 3.3	0.23
Potassium (mmol/L)	4.5 ± 0.9	4.5 ± 0.6	4.3 ± 0.6	0.18
Creatinine (mg/dL)	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	0.78
Cholesterolin (mmol/L)	176.6 ± 52.5	177.8 ± 52.2	171.4 ± 54.1	0.49
Haemoglobin (g/dL)	13.4 ± 1.4	13.4 ± 1.4	13.2 ± 1.4	0.32
Leucocytes (/nL)	6.9 ± 1.9	6.9 ± 2.0	6.5 ± 1.9	0.28
Interleukin-1β (pg/mL)	0.26 ± 0.71	0.28 ± 0.80	0.21 ± 0.30	0.43
Interleukin-6 (pg/mL)	3.0 ± 4.4	2.6 ± 4.0	4.4 ± 5.4	0.001
Tumour necrosis factor-α (pg/mL)	8.2 ± 22.9	9.3 ± 25.5	4.0 ± 4.4	0.90

Prevalenca 39/200 = 19.5%

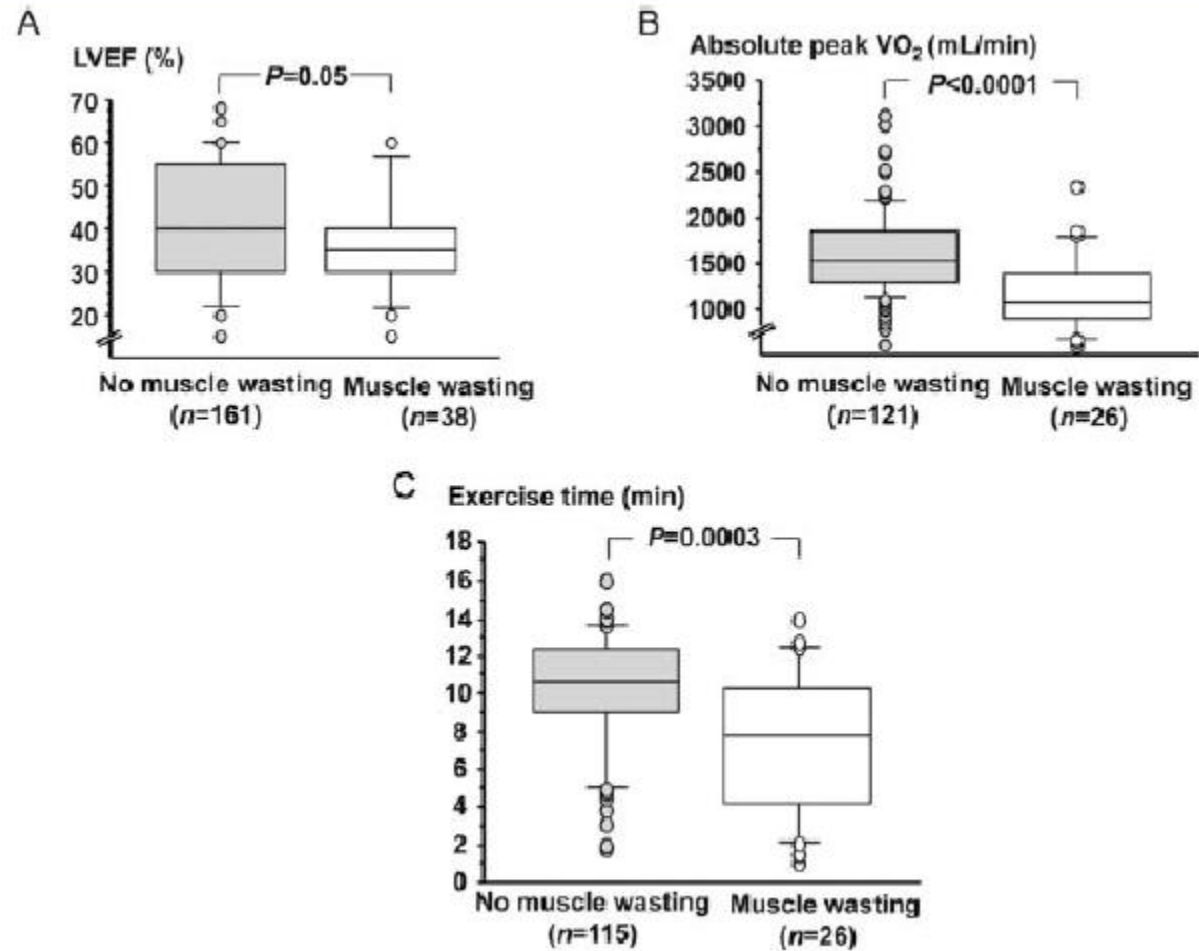
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Tumour necrosis factor-α (pg/mL)	8.2 ± 22.9	9.3 ± 25.5	4.0 ± 4.4	0.90

Prevalenca 39/200 = 19.5%



# Sarkopenija in srčno popuščanje

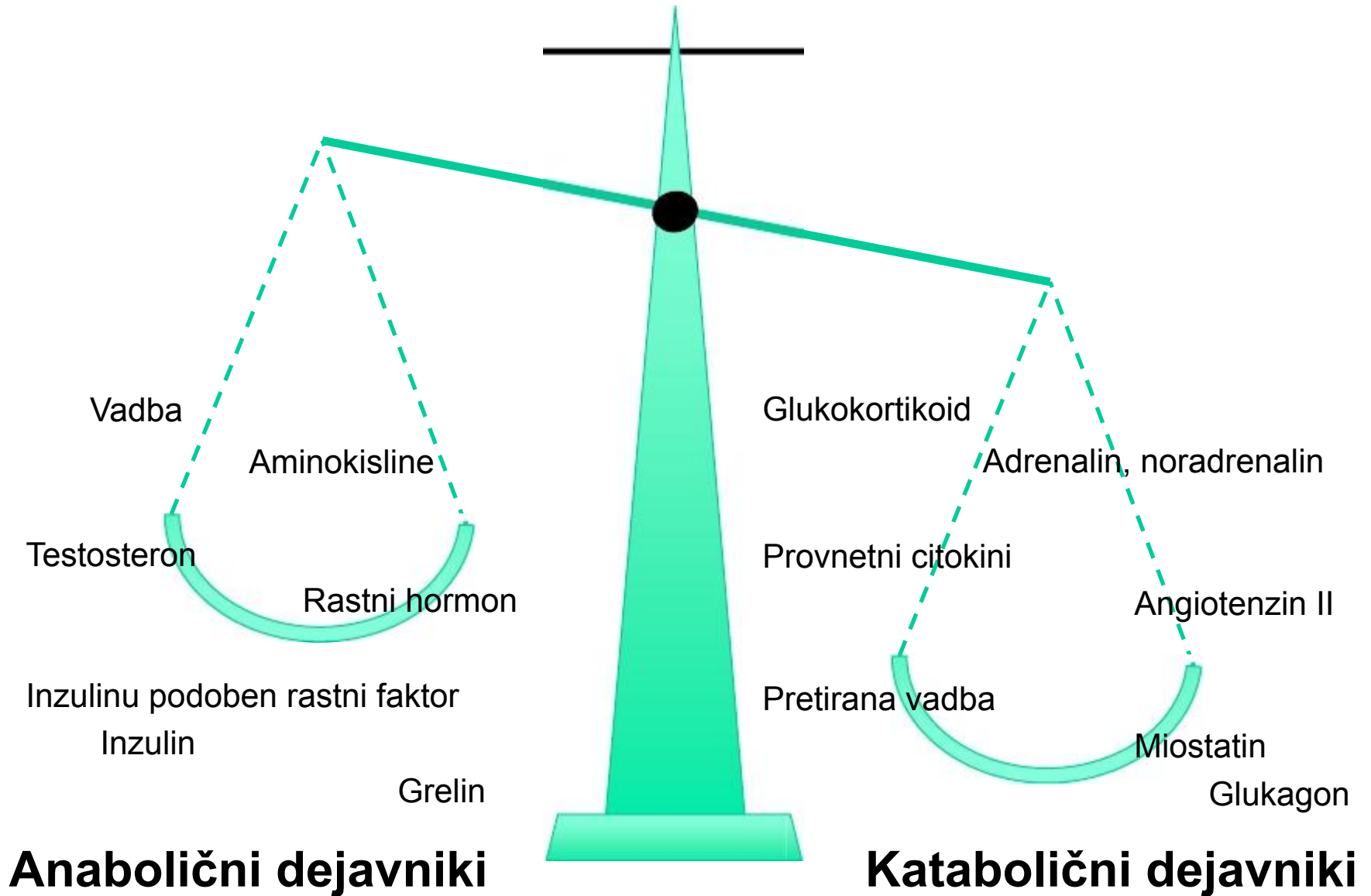




# Sarkopenija in srčno popuščanje

	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (per year increase)	1.07	1.03–1.12	0.0004	1.09	1.03–1.15	0.005
Sex (female)	3.48	1.47–8.25	0.005	9.72	2.84–33.26	0.0003
BMI (per kg/m <sup>2</sup> increase)	0.86	0.79–0.93	0.0002			
Overweight or obesity (present)	0.25	0.11–0.59	0.002			
NYHA (per 1 class increase)	4.20	2.23–7.93	<0.0001	2.61	0.96–7.08	0.06
Atrial fibrillation (present)	1.37	0.65–2.86	0.41			
Hb (per 1 g/dL increase)	0.59	0.45–0.78	0.0002	0.77	0.55–1.07	0.12
Anaemia (present)	3.79	1.82–7.92	0.0004			
LVEF (per 1% increase)	0.98	0.95–1.00	0.039	0.95	0.91–0.98	0.005
6-min walk test (per 10 m increase)	0.91	0.87–0.94	<0.0001	0.95	0.90–1.00	0.04
Lean mass, legs (per 500 g increase)	0.81	0.75–0.87	<0.0001			
Appendicular lean mass (per 500 g increase)	0.85	0.80–0.90	<0.0001			
Muscle wasting (present)	5.07	1.90–13.50	0.0012	6.53	1.56–27.37	0.01
Coronary artery disease (present)	2.06	1.05–4.03	0.03			
Diabetes mellitus (present)	0.93	0.45–1.94	0.85			
Chronic obstructive pulmonary disease (present)	2.55	0.83–7.88	0.10			
Number of co-morbidities (per 1 increase) <sup>2</sup>	1.41	1.02–1.95	0.04	1.33	0.79–2.26	0.29

# Anabolično - katabolično neravnovesje



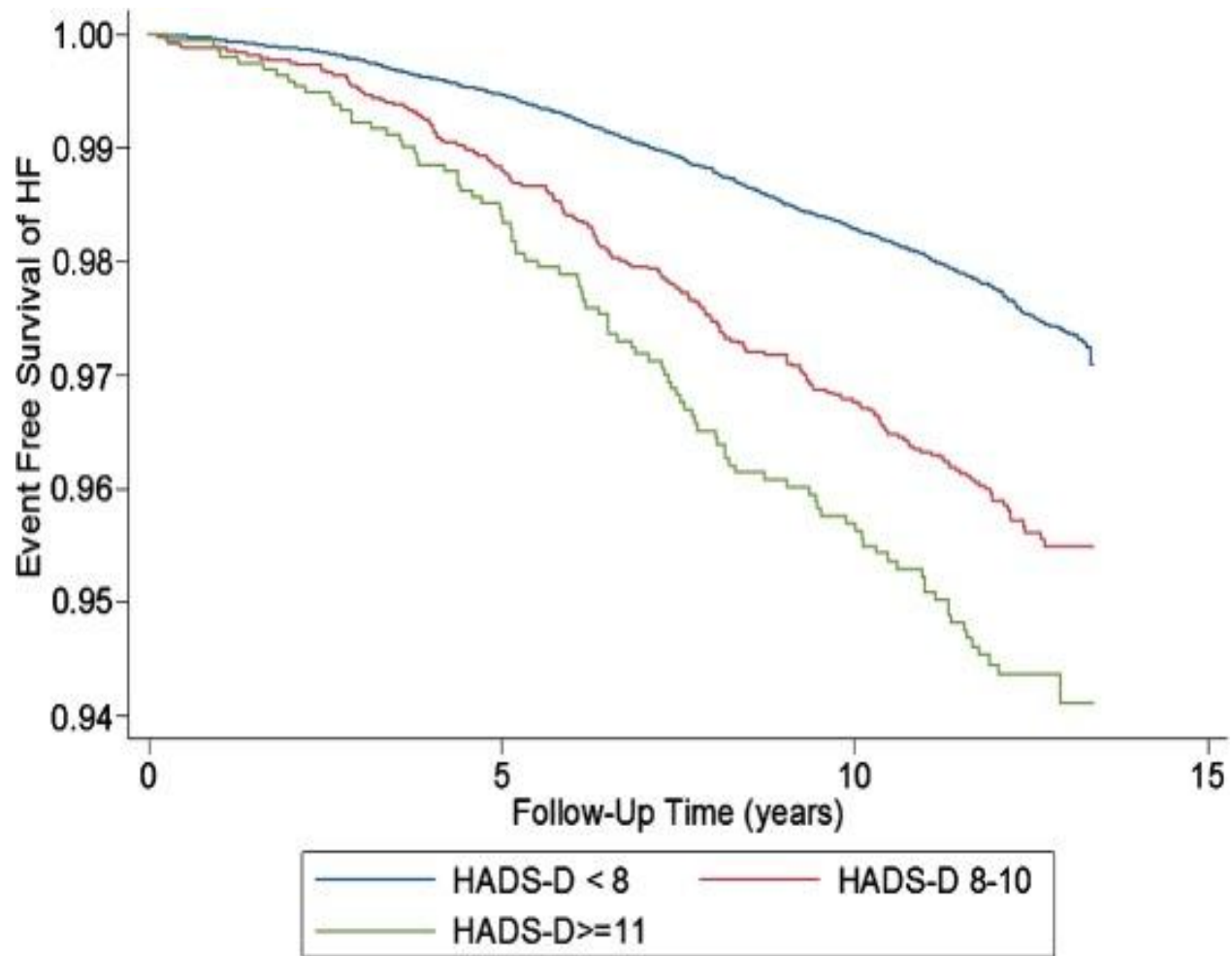
# Sarkopenija - priporočila

body weight and BMI.<sup>684,698,701,702</sup> So far, the most effective strategy for sarcopenia treatment is resistance exercise training, possibly combined with a protein intake of 1–1.5 g/kg/day.<sup>698,703</sup> Drug treatments, including anabolic compounds like testosterone, growth hormone, ghrelin receptor agonists, were tested in small studies, showing favourable results mostly in terms of exercise capacity and muscle strength.<sup>697,703–705</sup> There are no data showing a favourable impact of sarcopenia treatment on outcomes. However, exercise training has favourable effects in patients with HF (see section 9.4).<sup>95,323–329</sup>

# Komorbidnosti - pomembni del srčnega popuščanja

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# Depresija in tveganje za srčno popuščanje





# Depresija in srčno popuščanje

**Table 2. Heart Failure and Risk of Depression Estimated Using Cox Regression**

Sample	Hazard Ratio (95% Confidence Interval)		P-Value
	Depressive Symptoms and Syndromes*	Depressive Syndromes Only†	
<b>Complete sample (n = 5,095)</b>			
Age and sex adjusted	1.36 (1.03–1.81)	.03	1.54 (1.06–2.24) .02
Fully adjusted‡	1.41 (1.03–1.94)	.04	1.66 (1.09–2.52) .02
<b>Persons without history of depression (n = 3,454)</b>			
Age and sex adjusted	1.41 (0.93–2.13)	.10	1.79 (1.05–3.04) .03
Fully adjusted‡	1.64 (1.04–2.58)	.03	2.07 (1.15–3.72) .01

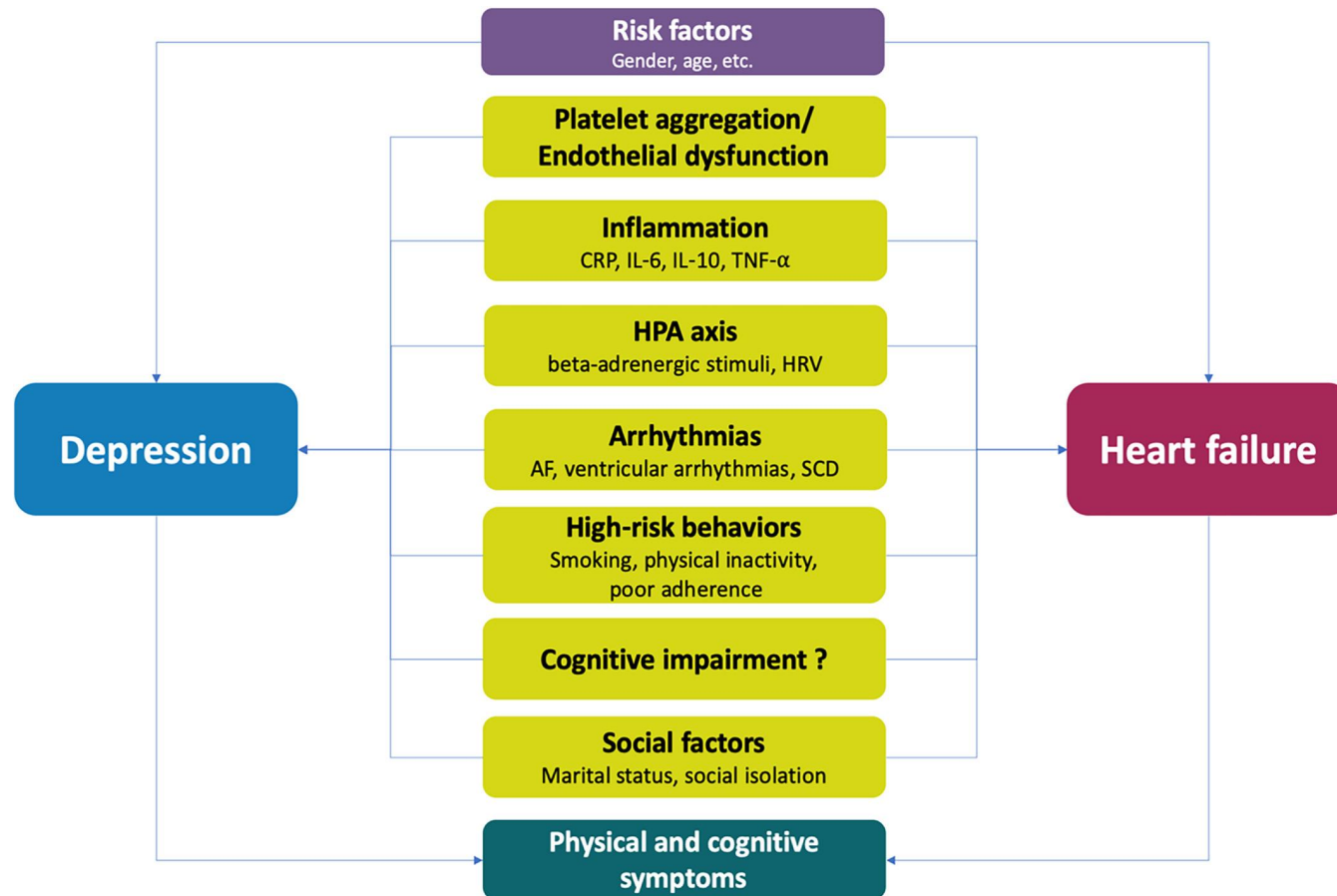
# Depresija in srčno popuščanje

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# Mehanizmi



# Depresija - priporočila

There is still no consensus on the best therapy for HF patients with depression. Psychosocial intervention may improve depressive symptoms but has no effect on prognosis of depressed patients with HF.<sup>839</sup> Depressive symptoms may improve with selective serotonin reuptake inhibitors but trials specifically designed to assess the effect of these drugs in patients with HF and depression have failed to show any significant benefit over placebo on both symptoms and outcomes.<sup>840,841</sup> Interestingly, patients improved also in the placebo arm showing the importance of better care in these patients. Both trials showed the safety of sertraline and escitalopram, respectively.<sup>840,841</sup> Tricyclic antidepressants should be avoided for the treatment of depression in HF as they may cause hypotension, worsening HF, and arrhythmias.<sup>837,838</sup>

# Komorbidnosti - pomembni del srčnega popuščanja

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# Sladkorna bolezen tipa 2 in srčno popuščanje

Patients with T2D are at risk for atherosclerotic events like MIs, which result in HFrEF due to myocardial wall damage<sup>1</sup>

Patients with T2D are also at risk of HF due to direct inflammatory effect in the microvascular and myocardium with subsequent fibrosis<sup>2</sup>

atherosclerotic  
mediated

atherosclerotic  
independent

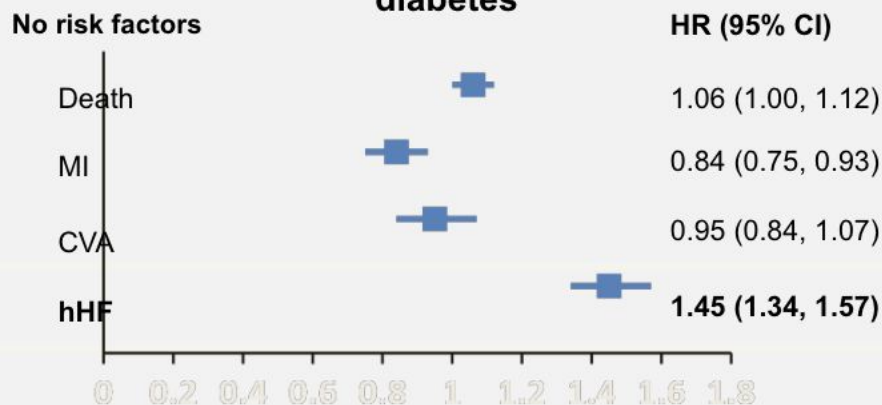
**SRČNO  
POPUŠČANJE**

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; T2D, type 2 diabetes.

1. de Simone G, et al. J Hypertens. 2010;28(2):353–360. 2. Redfield MM. N Engl J Med. 2016;375:1868-1877.

# Sladkorna bolezen tipa 2 in dejavniki tveganja

## Risk of event in patients with T2D with no other risk factors out of range compared to patients without diabetes

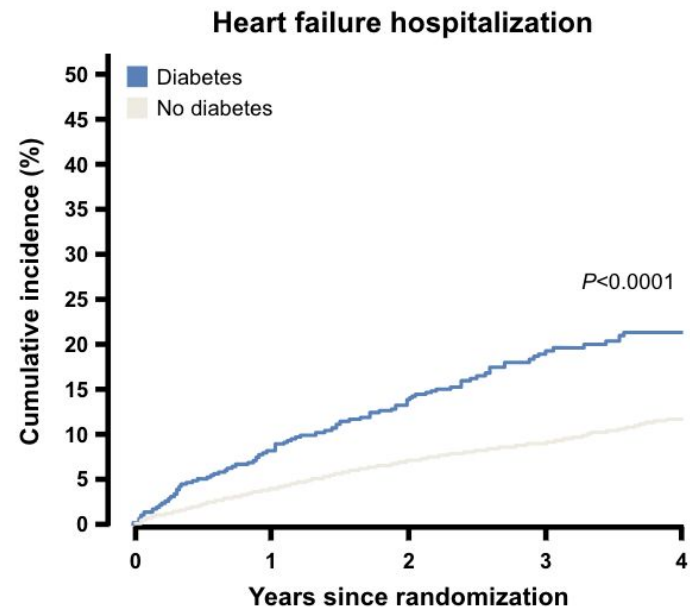
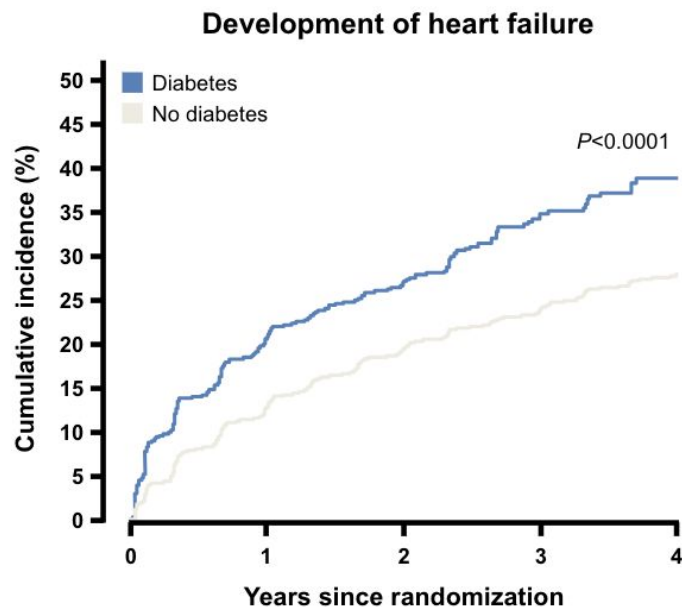


- In this analysis the risk of hHF in patients with T2D (n=271,174) was compared to those without T2D (n=1,355,870)
- The following risk factors were either not present or within guideline range: systolic and diastolic BP, LDL-C, albuminuria and tobacco use
- A substantial risk for hHF remained among patients who had all the variables within target range

**On average, the patients with T2D had a 45% increase in the risk of hHF, despite other major risk factors in guideline recommended range or absent**

BP, blood pressure; CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; hHF, hospitalisation for HF; HR, hazard ratio; LDL-C, low density-lipoprotein cholesterol; MI, myocardial infarction; T2D, type 2 diabetes. Rawshani A, et al. N Engl J Med. 2018;379:633-644.

Poleg tega, da je sladkorna bolezen tipa 2 dejavnik tveganja za razvoj srčnega popuščanja, poveča tudi hospitalizacije zaradi srčnega popuščanja.





# Hospitalizacije in prognoza srčnega popuščanja

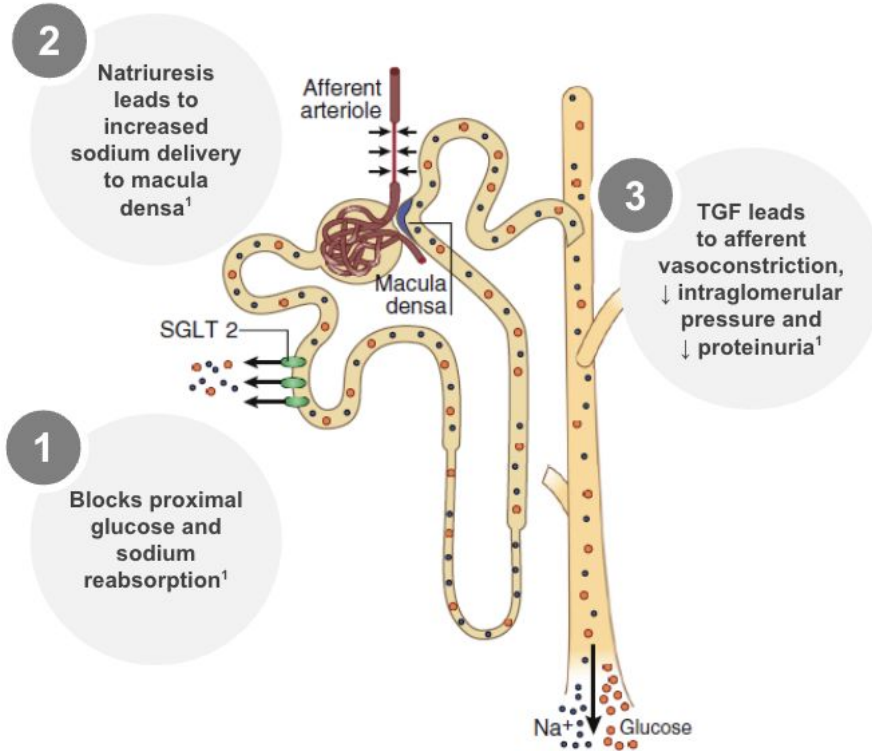
- HF hospitalizations represent a marker for significant adverse subsequent prognosis.<sup>1</sup>
- Thus HF hospitalization prevention overall, and especially in high risk patients, represent an important therapeutic goal.



HF, heart failure; 1. Solomon SD et al. *Circulation*. 2007;116:1482-1487; 2. Carson PE et al. *JACC: Heart Failure* Jun 2015, 3 (6) 429-441.



# Zaviralci SGLT2



## Effects mediated by SGLT2i in the kidney

### Natriuresis

- ↓ blood pressure<sup>1</sup>
- ↓ plasma volume<sup>1</sup>
- ↓ afterload<sup>3</sup>
- ↓ preload<sup>3</sup>
- ↓ LV wall stress<sup>3</sup>
- ↓ intraglomerular hypertension<sup>1</sup>
- ↓ intraglomerular hyperfiltration<sup>1</sup>

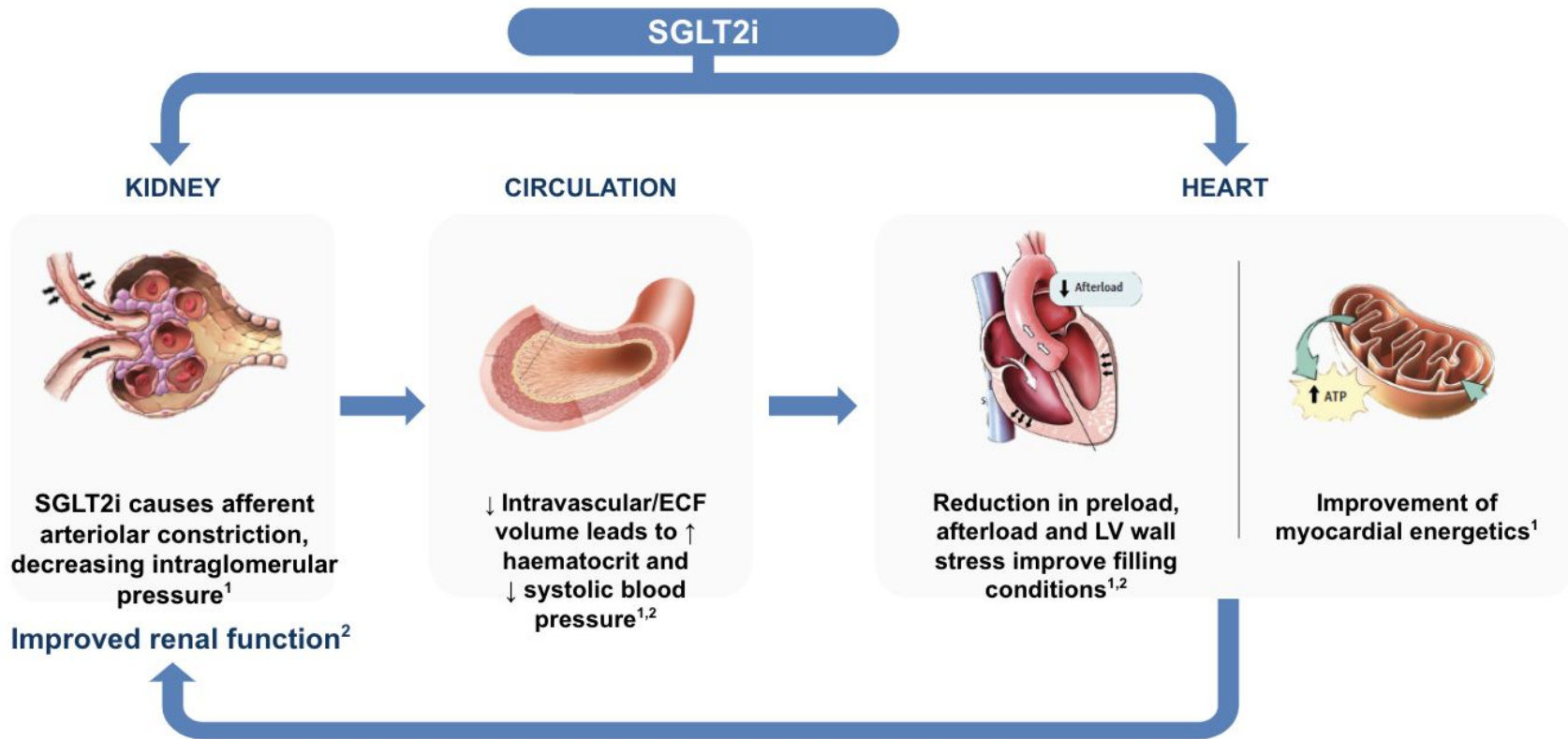
### Glucoresis

- ↓ HbA1c<sup>1</sup>
- ↓ total body fat mass<sup>1</sup>
- ↓ plasma uric acid<sup>1</sup>

SGLT2, sodium-glucose cotransporter 2; TGF, tubuloglomerular feedback.

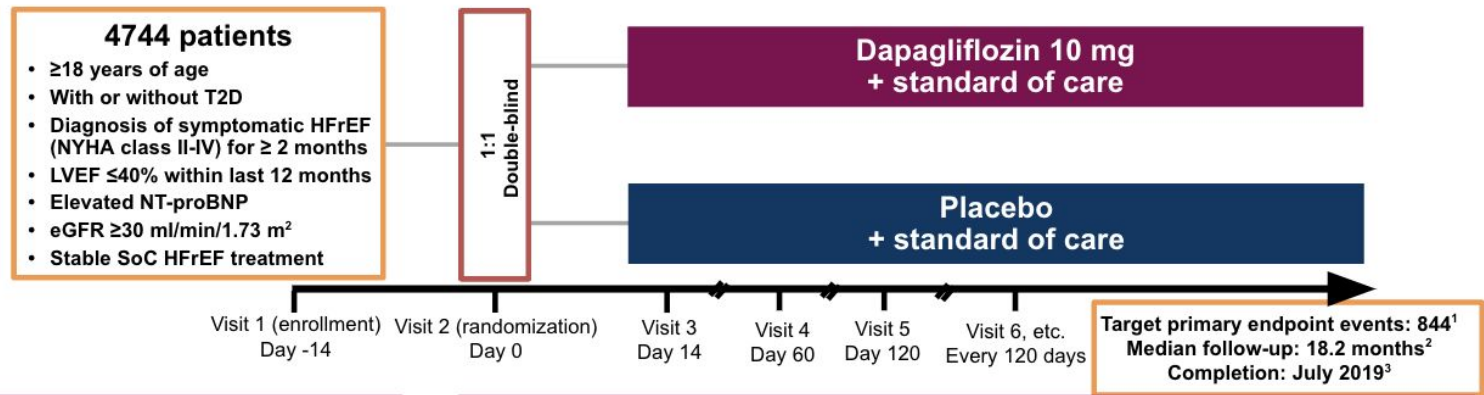
1. Rajasekeran H, et al. *Kidney Int.* 2016;89:524-526. 2. Alicic RZ, et al. *Clin J Am Soc Nephrol.* 2017;12:2032-2045. 3. Verma S. *JAMA Cardiol.* 2017;(9):939-940.

# Mehanizmi za razlago kardioresenalne zaščite z zaviralci SGLT2



ECF, extracellular fluid; LV, left ventricular; SGLT2, sodium-glucose cotransporter 2.  
1. Verma S, et al. JAMA Cardiol. 2017;2:939-940. 2. Sattar N, et al. Diabetologia. 2016;59:1333-1339.

# Raziskava: Assessing Dapagliflozin in Patients with Chronic HFrEF With or Without T2D



## Primary Endpoint

- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit



## Secondary Endpoints

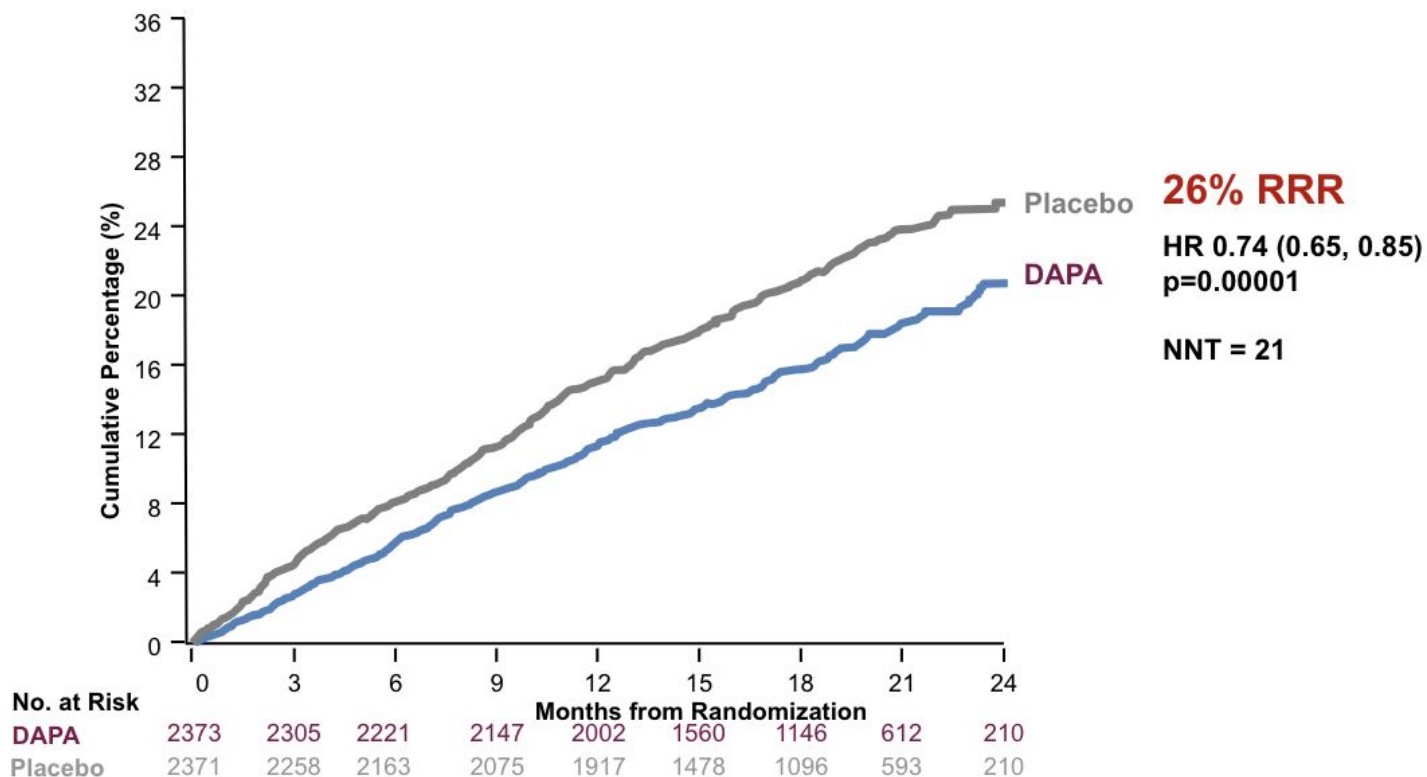
- Time to first occurrence of either of the components of the composite: CV death or hHF
- Total number of (first and recurrent) hHF and CV death
- Change from baseline measured at 8 months in the total symptom score of the KCCQ
- Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD or renal death
- Time to death from any cause

CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = glycated hemoglobin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction;

hHF = hospitalization for heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; SoC = standard of care; T2D = type 2 diabetes.

1. McMurray JJV et al. Article and supplementary appendix. Eur J Heart Fail. 2019;21:665-675; 2. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France; 3. Study NCT03036124. ClinicalTrials.gov website. Accessed August 19, 2019. 4. McMurray JJV et al. Eur J Heart Fail. 2019;doi: 10.1002/ejhf.1548. Accessed July 16, 2019.

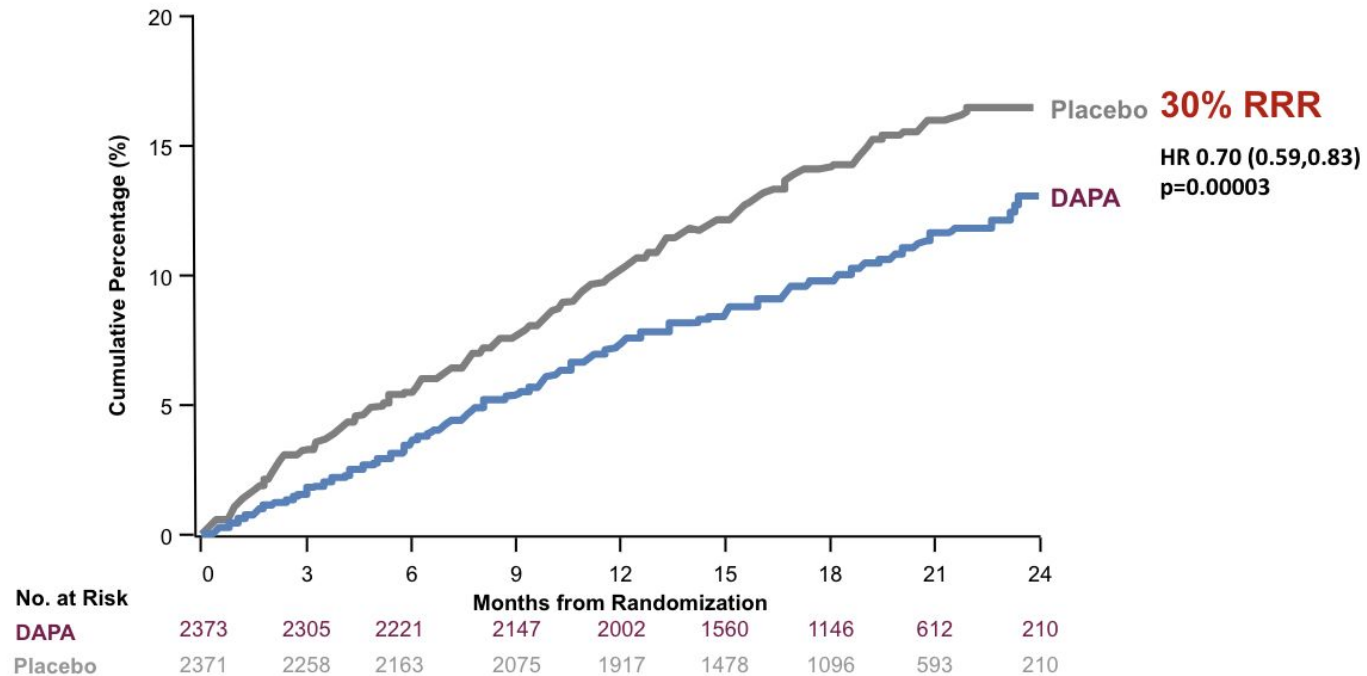
# Srčno-žilna smrt, hospitalizacije ali poslabšanje srčnega popuščanja



DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat.

1. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

# Poslabšanje srčnega popuščanja



DAPA = Dapagliflozin; HF = Heart failure; HR = Hazard ratio.

McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

# Sladkorna bolezen - priporočila

## Recommendations for the treatment of diabetes in heart failure

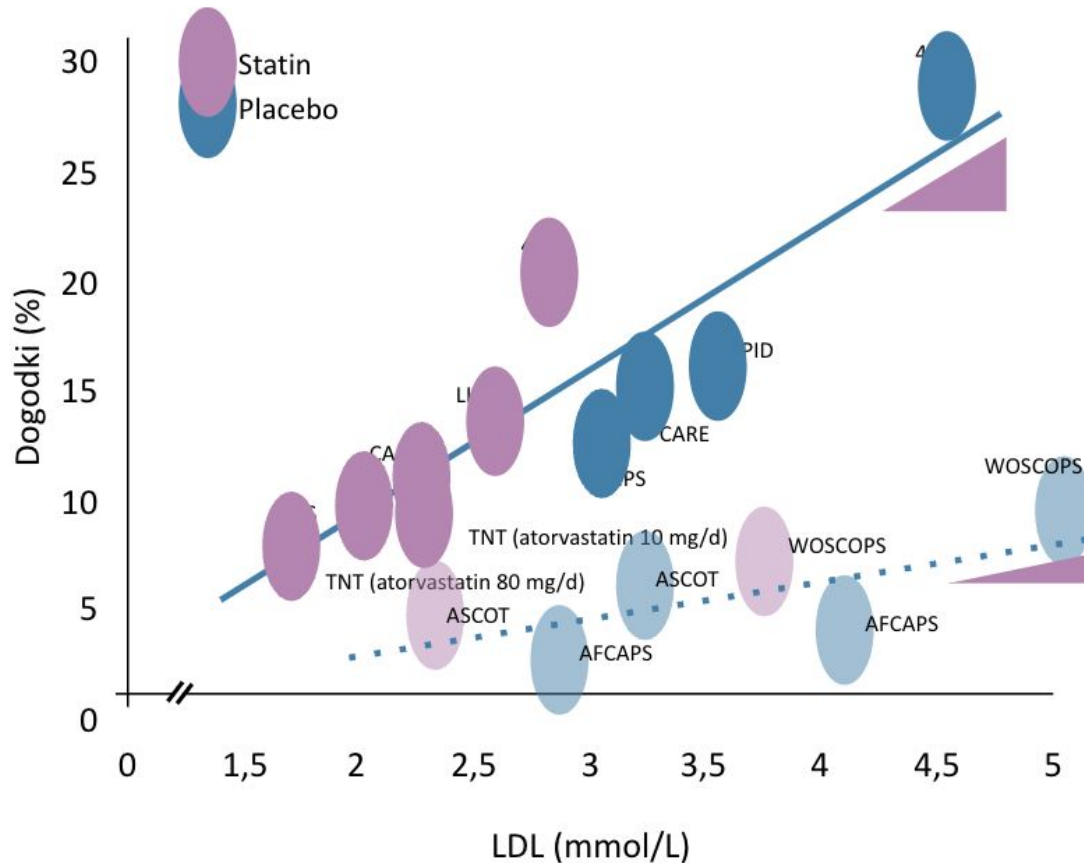
Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death. <sup>293–297</sup>	I	A
SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death. <sup>108,109,136</sup>	I	A

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# Statini in ishemična bolezen srca



## Prelomne raziskave s statini:

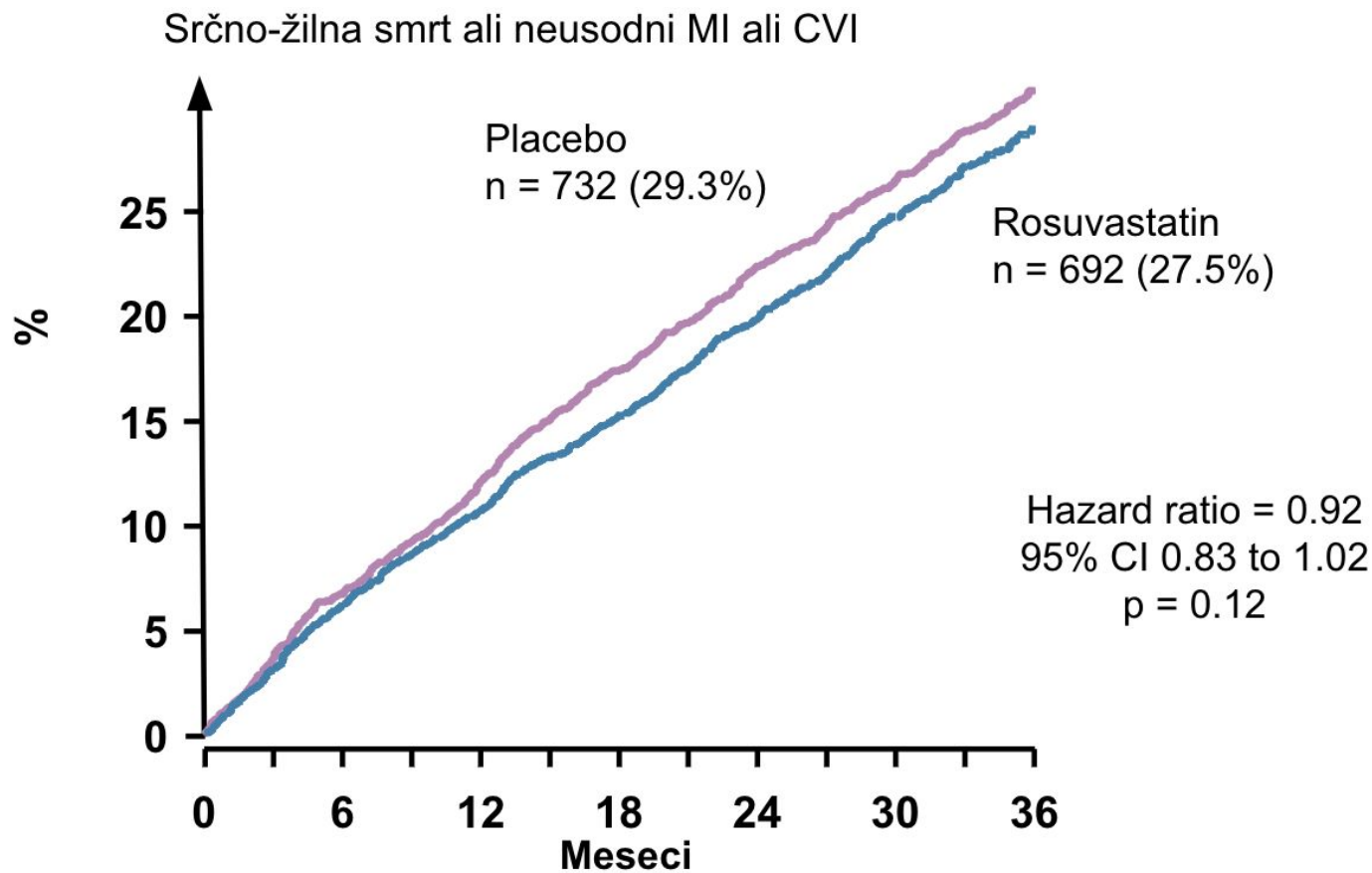
pomembno zmanjšanje usodnih in neusodnih kardiovaskularnih dogodkov v primarni in sekundarni preventivi.



Nobena od teh raziskav ni proučevala učinkovitosti pri srčnem popuščanju.

# Statini in srčno popuščanje

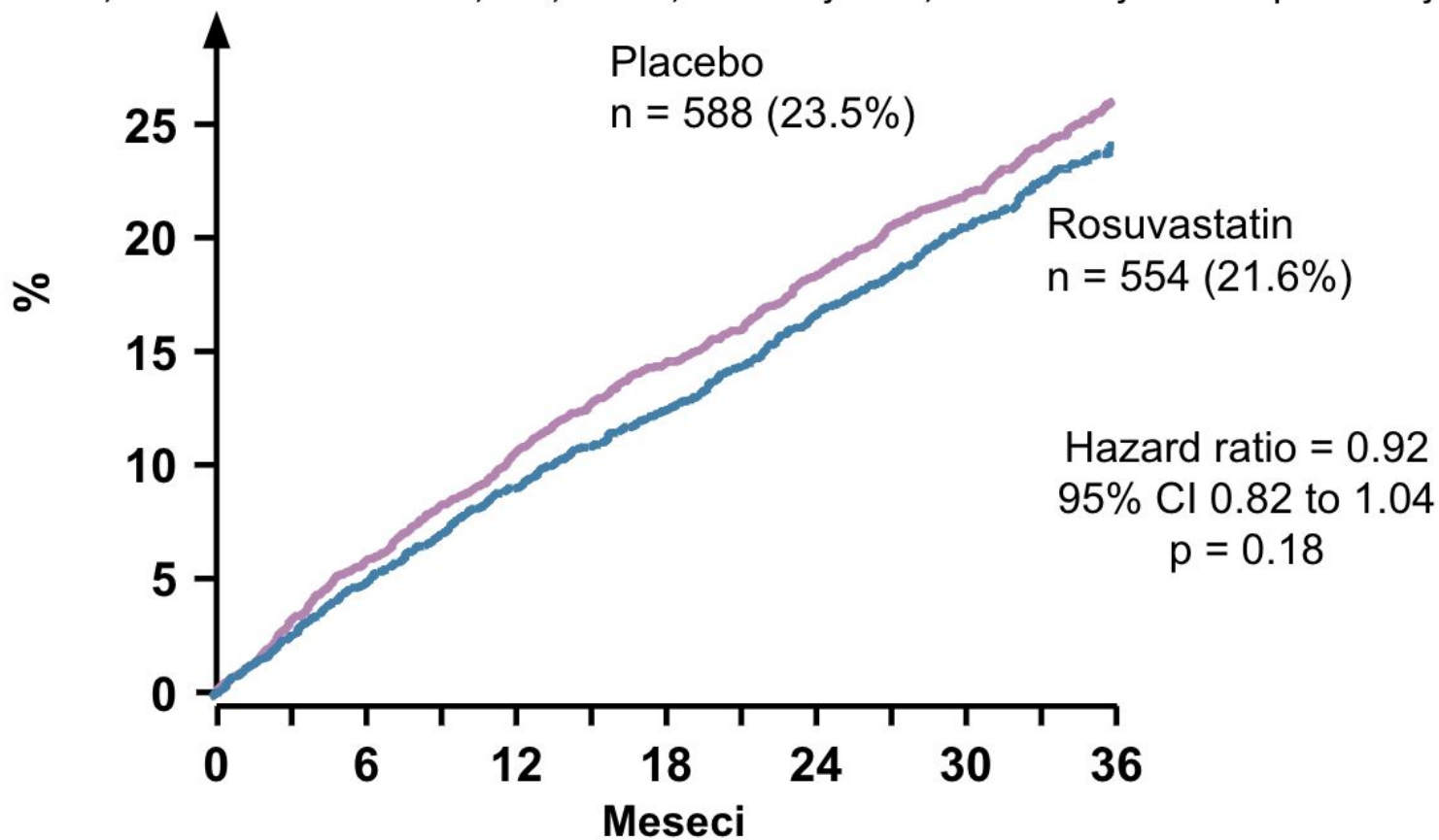
## Raziskava CORONA



# Statini in srčno popuščanje

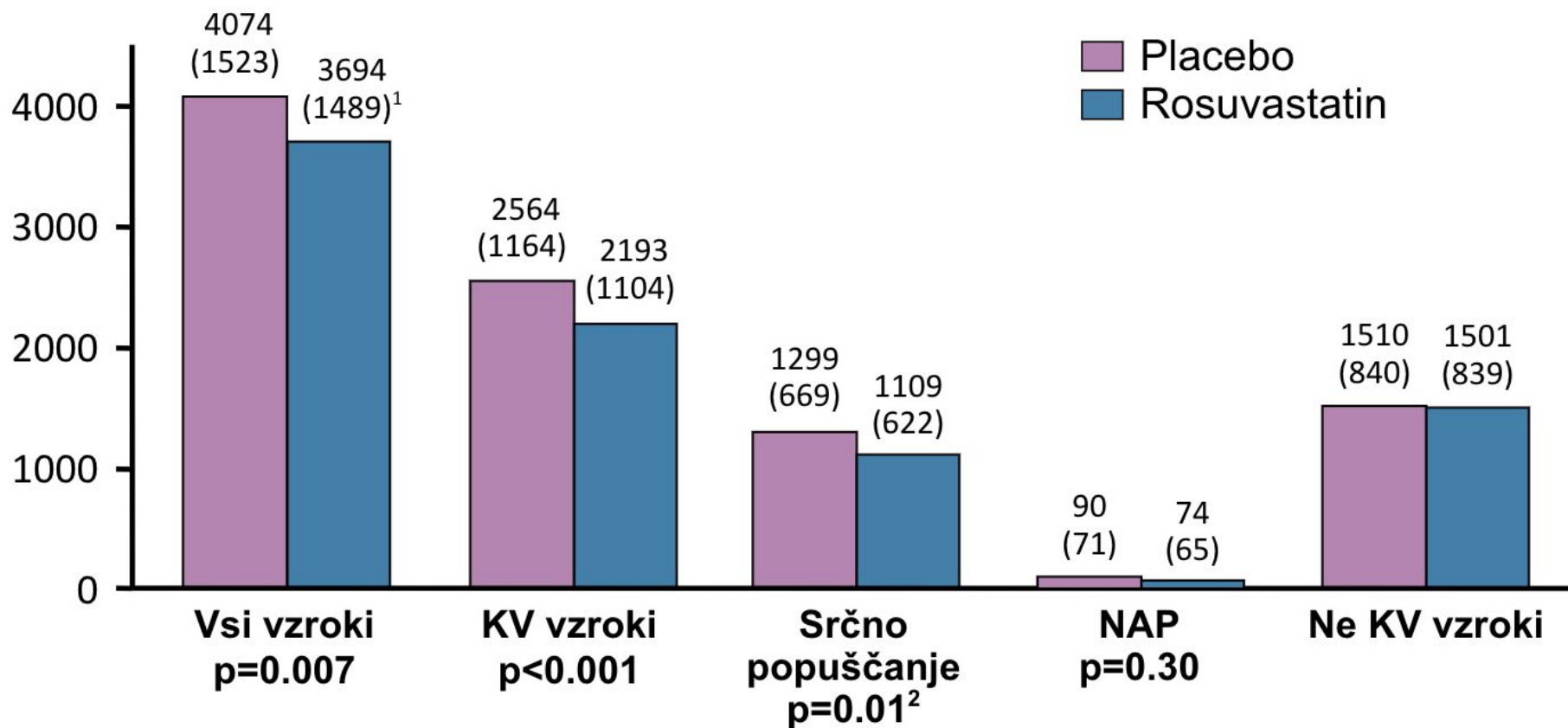
## Raziskava CORONA

NSS, fatal or non-fatal MI, PCI, CABG, aktivacija ICD, reanimacija ali hospitalizacija zaradi NAP



# Statini in srčno popuščanje

Raziskava CORONA - Hospitalizacije



# Hiperlipidemija - priporočila

<b>Recommendations</b>	<b>Class<sup>a</sup></b>	<b>Level<sup>b</sup></b>
Cholesterol-lowering therapy with statins is not recommended (but is not harmful either) in patients with heart failure in the absence of other indications for their use.	<b>III</b>	<b>A</b>
n-3 PUFAs 1 g/day may be considered for addition to optimal treatment in patients with heart failure.	<b>IIb</b>	<b>B</b>
Cholesterol-lowering treatment is not recommended in patients with aortic valvular stenosis without CAD in the absence of other indications for their use.	<b>III</b>	<b>A</b>

# Zaključek

- Novejše smernice kardioloških združenj dajejo več poudarka na komorbidnosti pri srčnem popuščanju.
- Medsebojno učinkovanje
- Za številne komorbidnosti nimamo podatkov o tem, kako njihovo zdravljenje vpliva na prognozo srčnega popuščanja.