METFORMIN TREATMENT IS ASSOCIATED WITH IMPROVED QUALITY OF LIFE AND OUTCOME IN PATIENTS WITH DIABETES AND ADVANCED HEART FAILURE (HFrEF)

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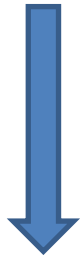
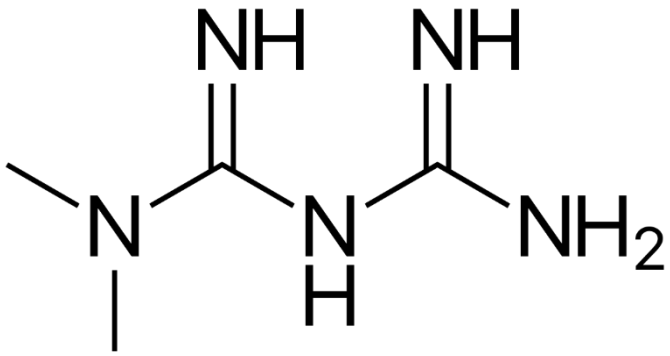
Prague, 28.11.2022

Metformin

Galegin
(too toxic)



Metformin



Galega officinalis

MET side effect

- **Lactate acidosis (LA)**

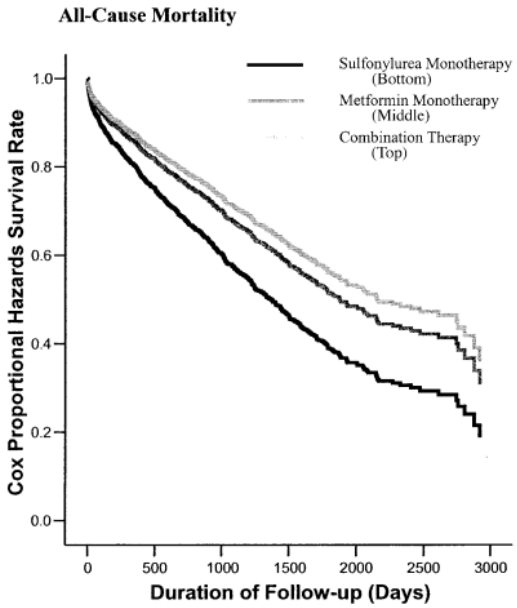
- **Phenformin**
  (used in the USA since 1957)
  LA 1: 4000
  → **1977 withdrew from the market**

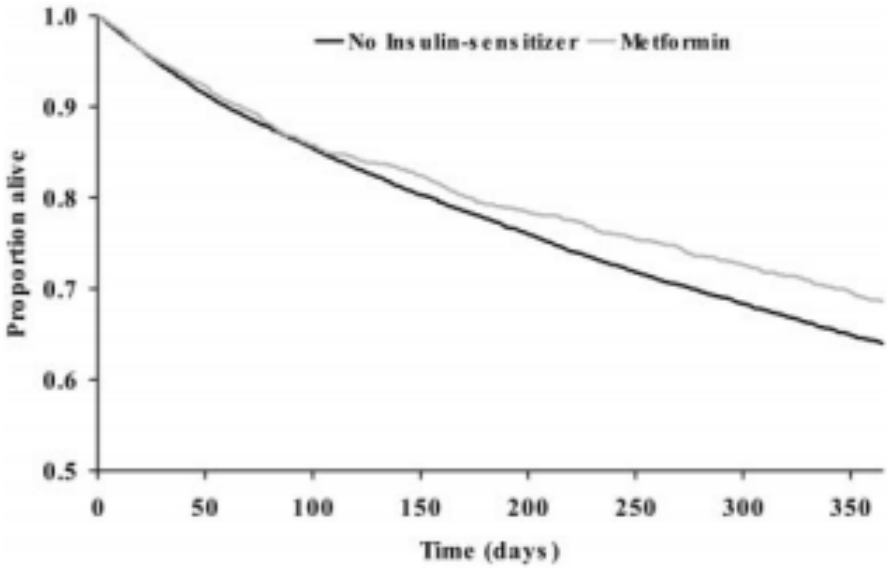
- **Metformin**
  LA 1: 40 000- 80 000
  → **Used in the USA since 1995**

Kreisberg et al. Clin Endocr Metab, 12 (1983), pp. 391-41

MET in patients with HF and DM

- **in HF considered contraindicated**
- **this recommendation was not really followed in everyday clinical practice**





Eurich et al. Diabetes Care 2005 Oct;28(10):2345-51

Masoudi et al. Circulation. 2005 Feb 8;111(5):583-90.

Metformin and lactic acidose (LA)

Cochrane Library:

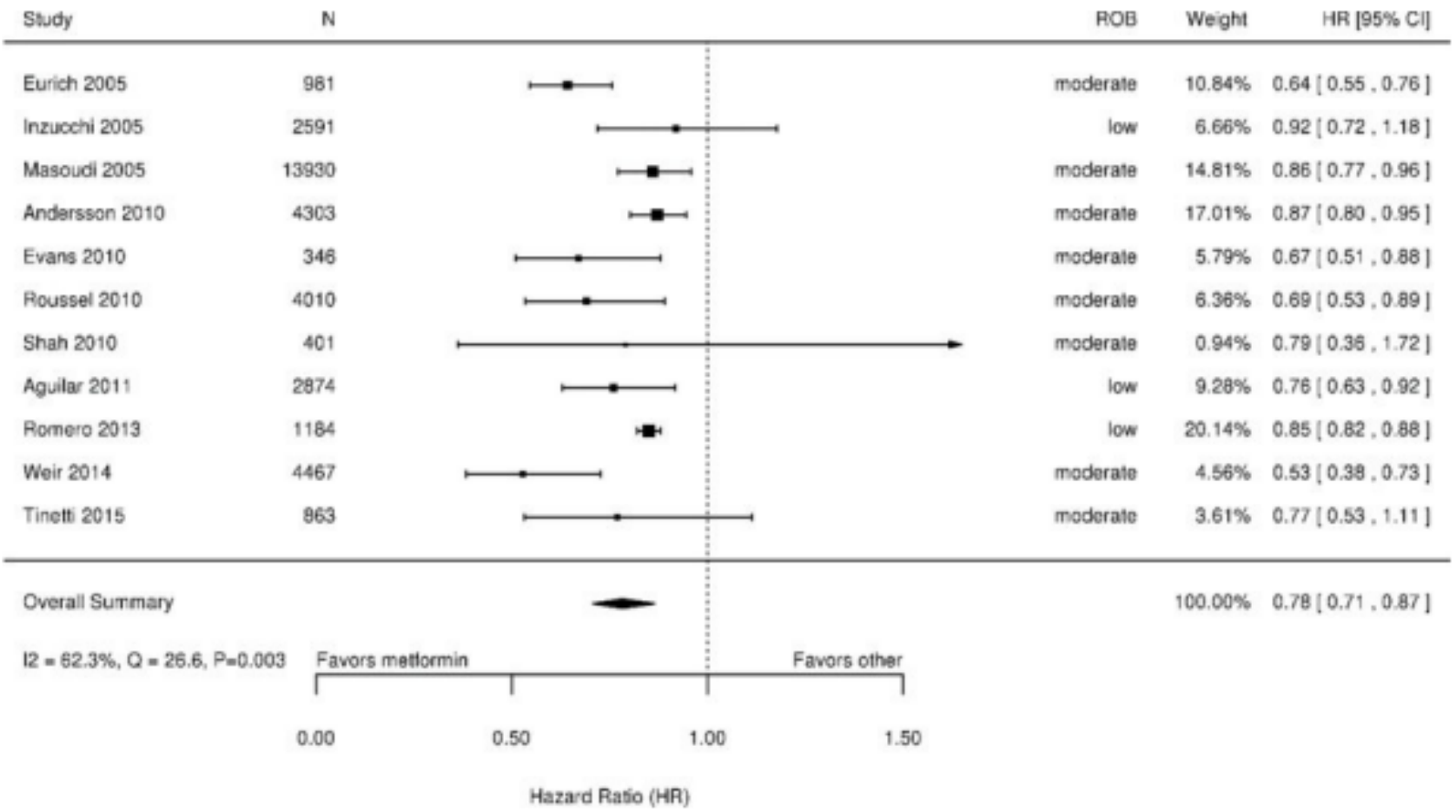
347 studies
70,490 patient-years MET+
55,451 patient-years MET-

LA incidence
4,3/ 100 000 patient-years MET+
5,4/ 100 000 patient-years MET-

→ there is no evidence whatsoever that MET therapy would be associated with increased risk of lactic acidose

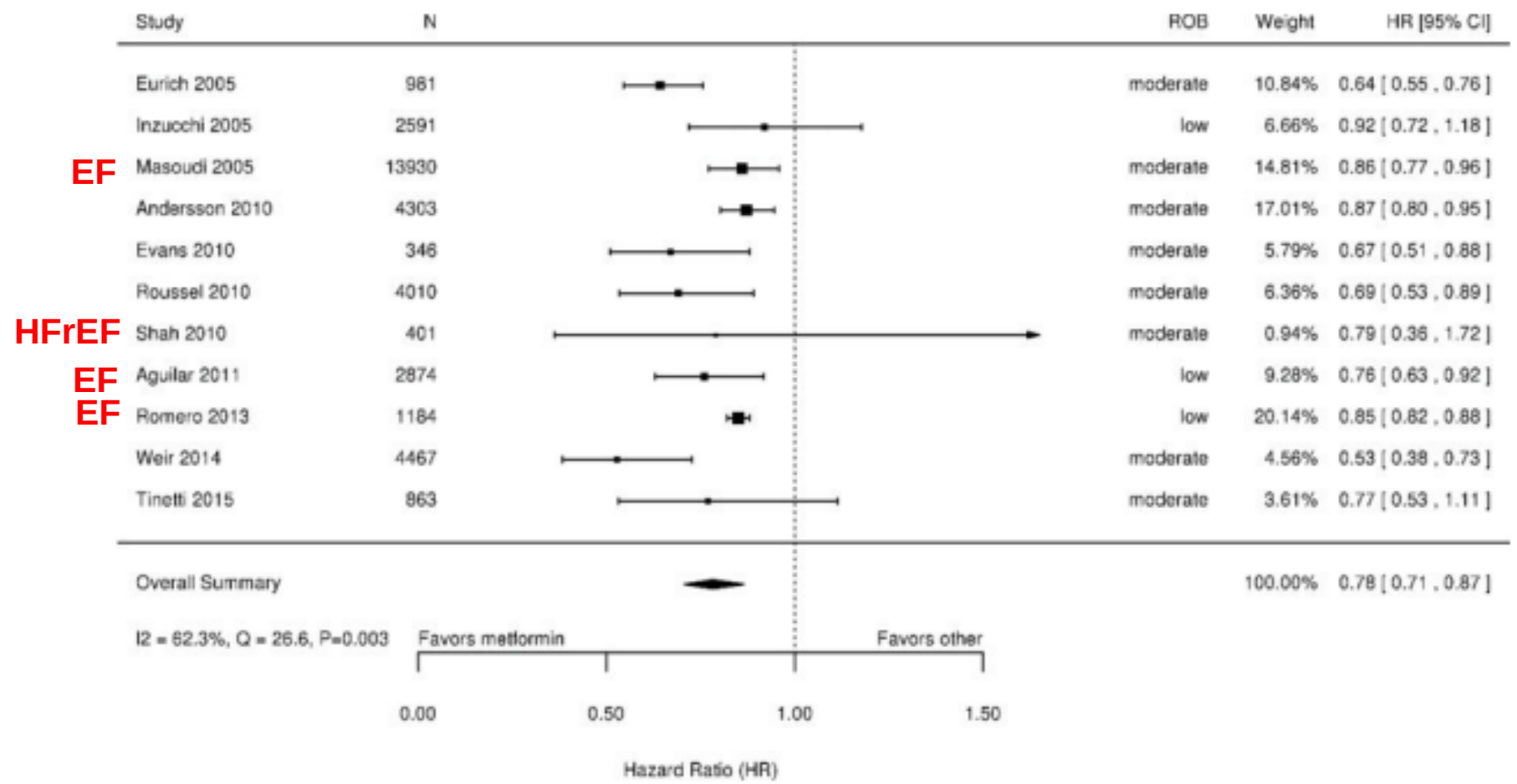
Salpeter et al. Cochrane Database Syst Rev 2010 Apr 14;2010(4): CD002967

MET in heart failure



Crowley et al. Ann Intern Med. 2017 Feb 7;166(3):191-200.

....BUT



→ **there is no randomized trial on MET in HF patients**

Crowley et al. Ann Intern Med. 2017 Feb 7;166(3):191-200.

Meformin u HFrEF a DM

Trials

BioMed Central

Research

Open Access

Metformin treatment in diabetes and heart failure: when academic equipoise meets clinical reality

Dean T Eurich*[1], Ross T Tsuyuki[2], Sumit R Majumdar[1,2], Finlay A McAlister[1,2], Richard Lewanczuk[2], Marcelo C Shibata[2] and Jeffrey A Johnson[1]

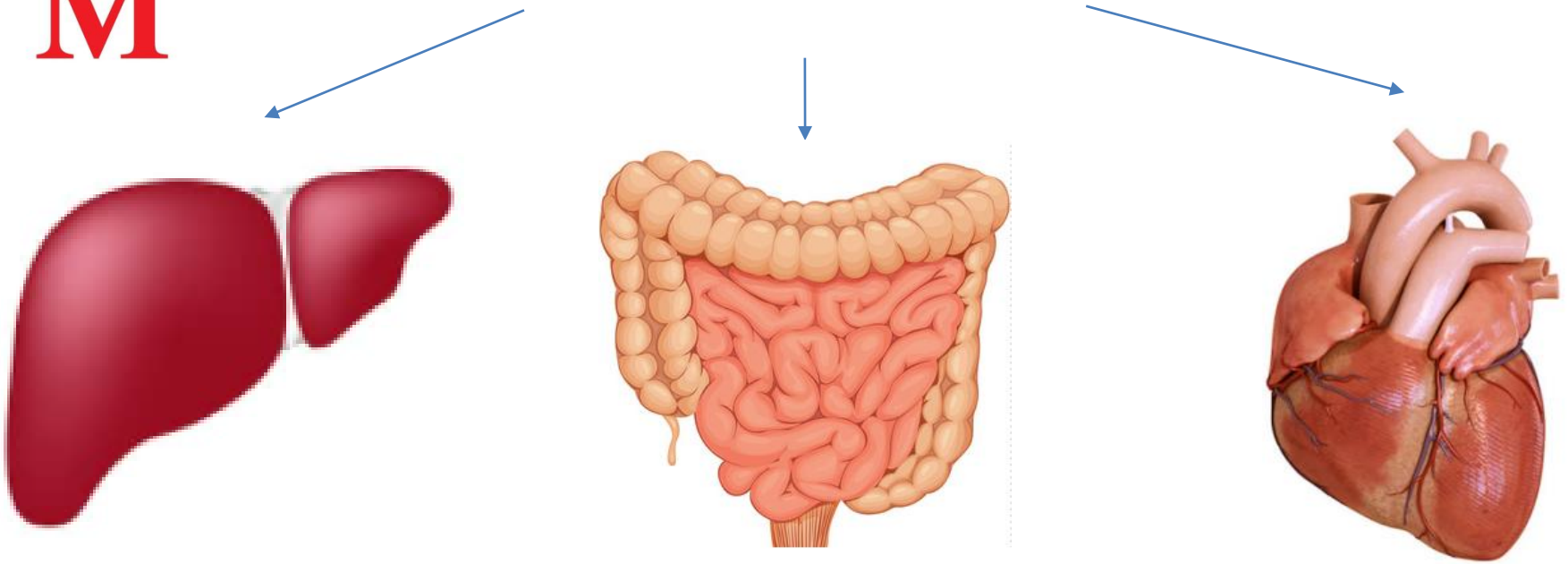
Study Design: The pilot study was a randomized double blinded placebo controlled trial. Patients with HF and type 2 diabetes were screened in hospitals and HF clinics in Edmonton, Alberta, Canada (population ~1 million). Major exclusion criteria included the current use of insulin or high dose metformin, decreased renal function, or a glycosylated hemoglobin <7%. Patients were to be randomized to 1500 mg of metformin daily or matching placebo and followed for 6 months for a variety of functional outcomes, as well as clinical events.

Results: Fifty-eight patients were screened over a six month period and all were excluded. Because of futility with respect to enrollment, the pilot study was abandoned. The mean age of screened patients was 77 (SD 9) years and 57% were male. The main reasons for exclusion were: use of insulin therapy (n = 23; 40%), glycosylated hemoglobin <7% (n = 17; 29%) and current use of high dose metformin (n = 12; 21%). Overall, contraindicated metformin therapy was the most commonly prescribed oral antihyperglycemic agent (n = 27; 51%). On average, patients were receiving 1,706 mg (SD 488 mg) of metformin daily and 12 (44%) used only metformin.

Conclusion: Despite uncertainty in the scientific literature, there does not appear to be clinical uncertainty with regards to the safety or effectiveness of metformin in HF making a definitive randomized trial virtually impossible.

Trials 2009, **10**:12 doi:10.1186/1745-6215-10-12

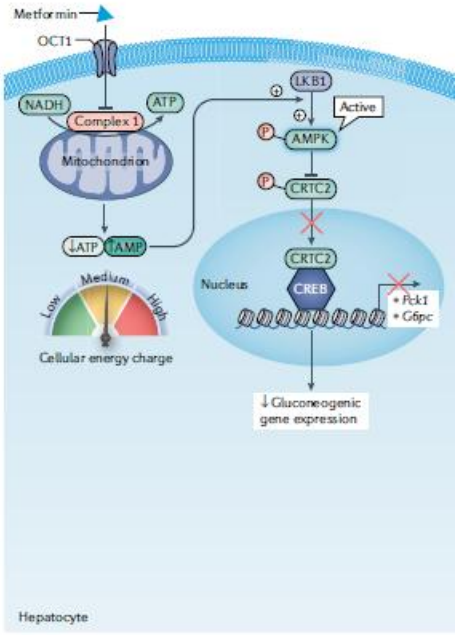
Pleiotropní efekt metforminu



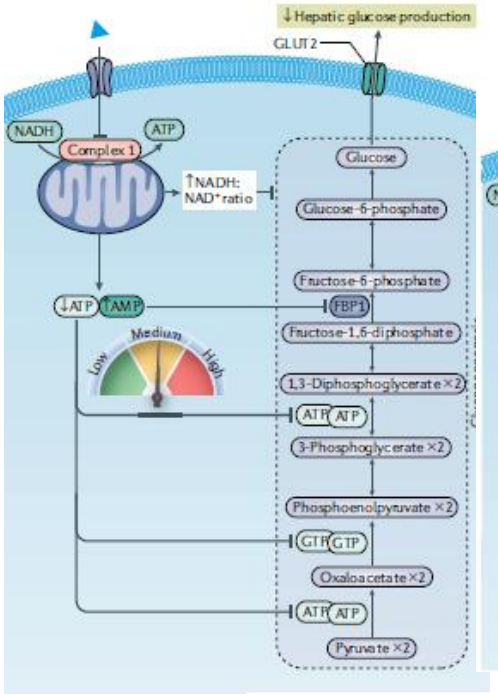
Metformin: mechanism of action

Target organ: liver → inhibition of mitochondrial complex I
→ inhibition of gluconeogenesis

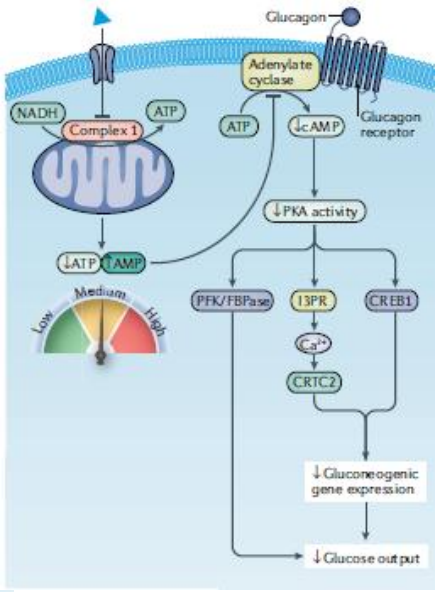
Inhibition of transcription of genes stimulating gluconeogenesis



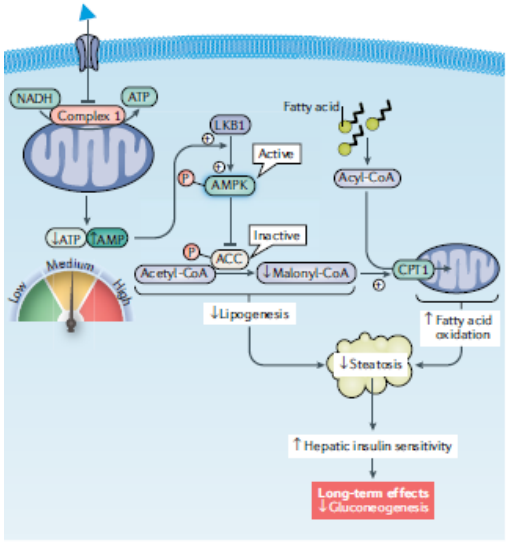
Inhibition of gluconeogenesis due to energy depletion



Decrease of gluconeogenesis stimulated by glucagon

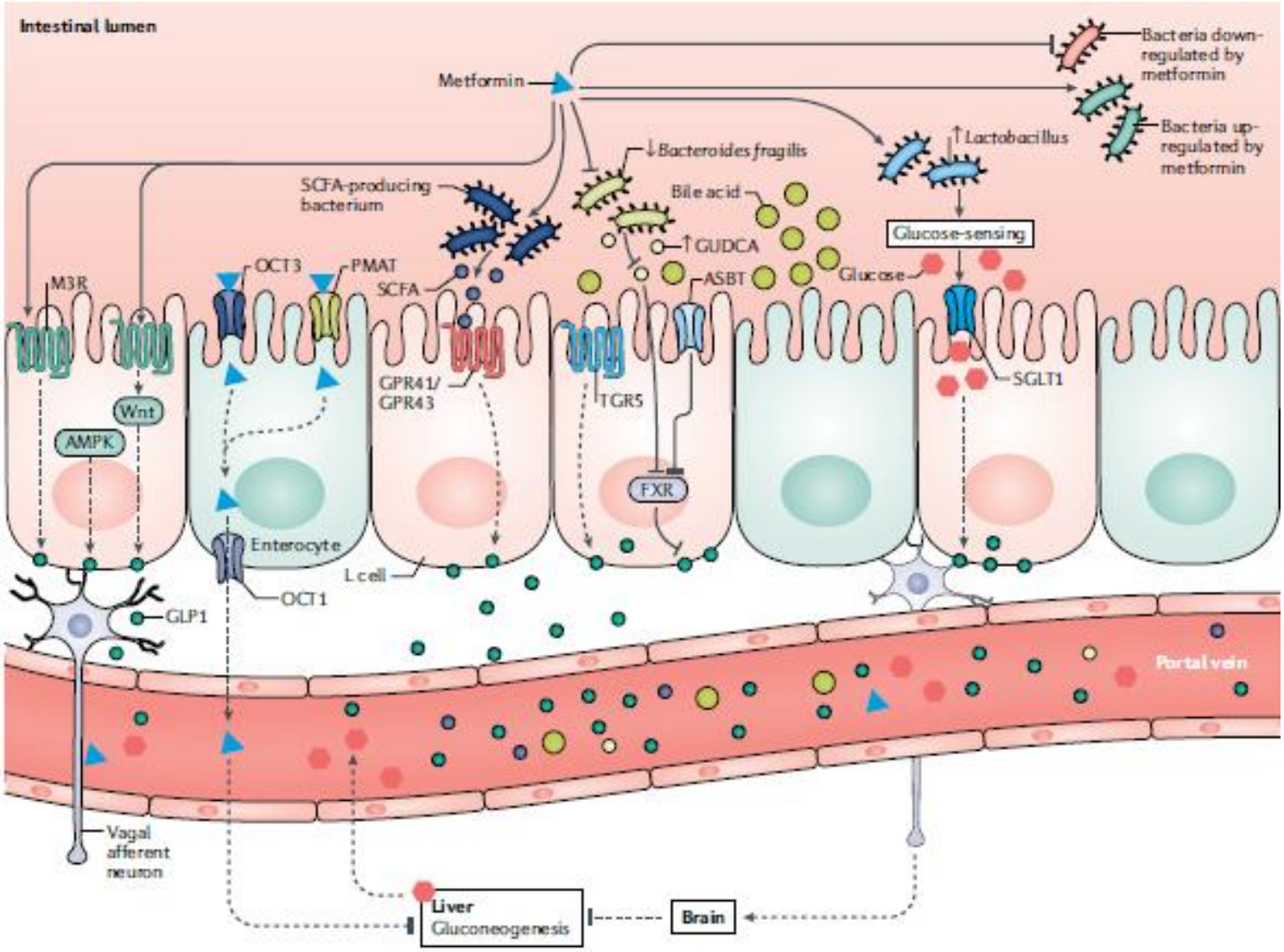


Insulin sensitivity improvement



Foretz et al. Nat Rev Endocrinol. 2019 Oct;15(10):569-589.

Metformin: complex action in the gut



Foretz et al. Nat Rev Endocrinol. 2019 Oct;15(10):569-589.

MET in HF guidelines: 2016

Recommendations	Class [a]	Level [b]	Ref [c]
Iron deficiency			
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A	469, 470
Diabetes			
Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.	IIa	C	440 ,441

Ponikowski P et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, Eur Heart J. 2016 Jul 14;37(27):2129-2200

MET in HF guidelines: 2021

Metformin is thought to be safe in patients with HF, compared with insulin and sulfonylureas, based on observational studies.[651,652] However, it is not recommended in patients with an eGFR <30 mL/min/1.73 m^2 or hepatic impairment because of the risk of lactic acidosis. It has not been studied in controlled outcome trials, to date.[6,646]

McDonagh et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Aug 27:ehab368. doi: 10.1093/eurheartj/ehab368.

Goals of the study

- analyze the effect of MET therapy in patients with advanced HFrEF and DM
- prospectivelly enrolled patients
- patients were thoroughly examined @ baseline

Patients

847 pacients with advanced HFrEF

67,7% NYHA III/IV (EFLK **23.6 %, 44,9%** with moderate/severe RV dysfunction)

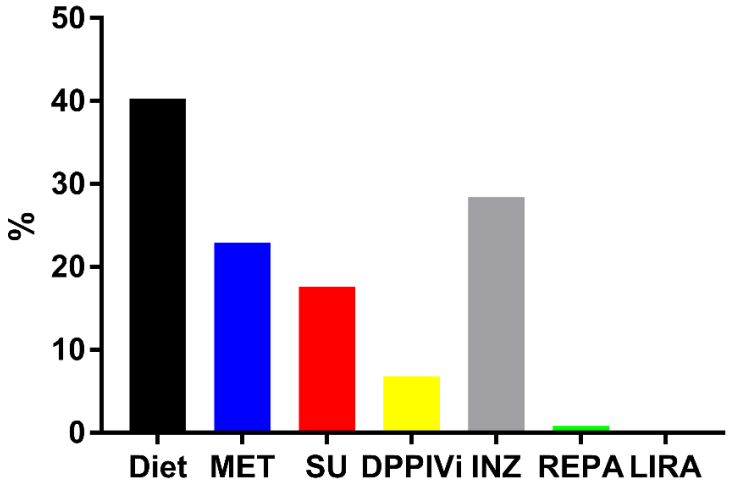
87,7% beta-blocker, **78,8%** ACEi/ARB, **77%** MRA, **59,4%** ICD

467 non-DM, **380** DM > **290** without MET**, 87** with MET

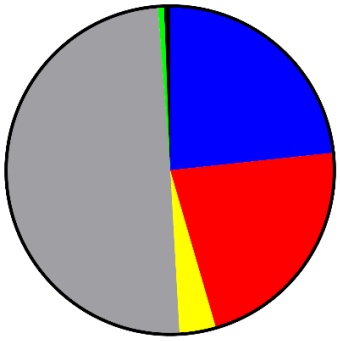
FU **1126** days (IQRs 410; 1781)
515 patients (60.8%) experienced an outcome
> death / urgent heart transplantation/ MSP implantation

IK+E M

DM treatment

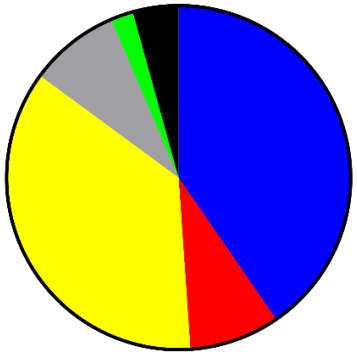


One drug
(N= 167)



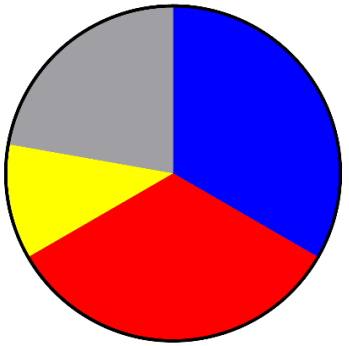
- MET
- SU
- DPPIVi
- INZ
- REPA
- LIRA

Two drugs
(N= 47)



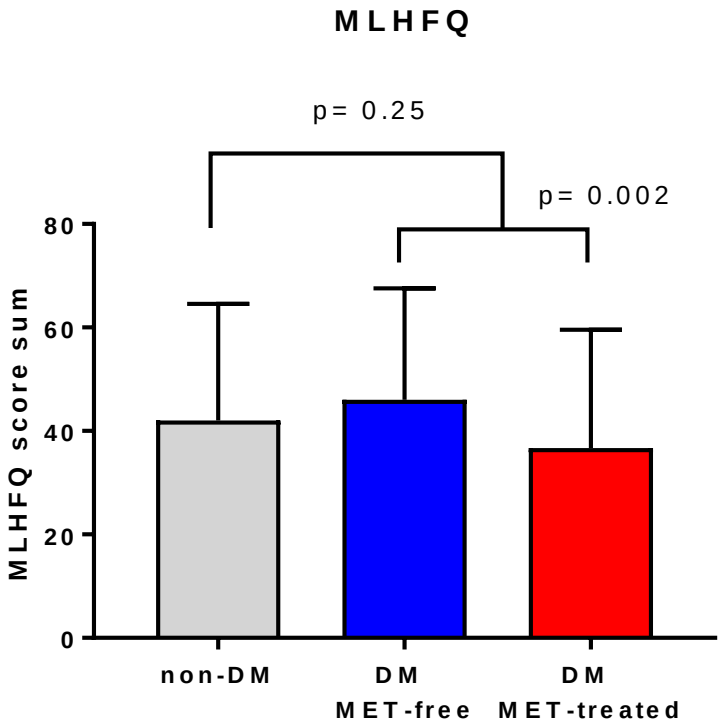
- MET+SU
- MET+DPPIVi
- MET+INS
- SU+DPPIVi
- SU+INS
- DPPIVi+INS

Three drugs
(N= 9)



- MET+DPPIVi+SU
- MET+DPPIVi+INS
- MET+DPPIVi+REPA
- SU+DPPIVi+INS

MET in advanced HFrEF: QoL



	r	P
BNP *(ng.L^{-1})*	0.006	**<0.0001**
BMI *(kg.m^{-2})*	0.82	**0.0007**
eGFR *(ml.min^{-1}.1.73m^{-2})*	0.01	0.85
MET *(present vs. absent)*	- 9.2	**0.003**
SU derivatives *(present vs. absent)*	1.2	0.73
DPPIVi *(present vs. absent)*	-7.9	0.12
Insulin *(present vs. absent)*	-1.4	0.62

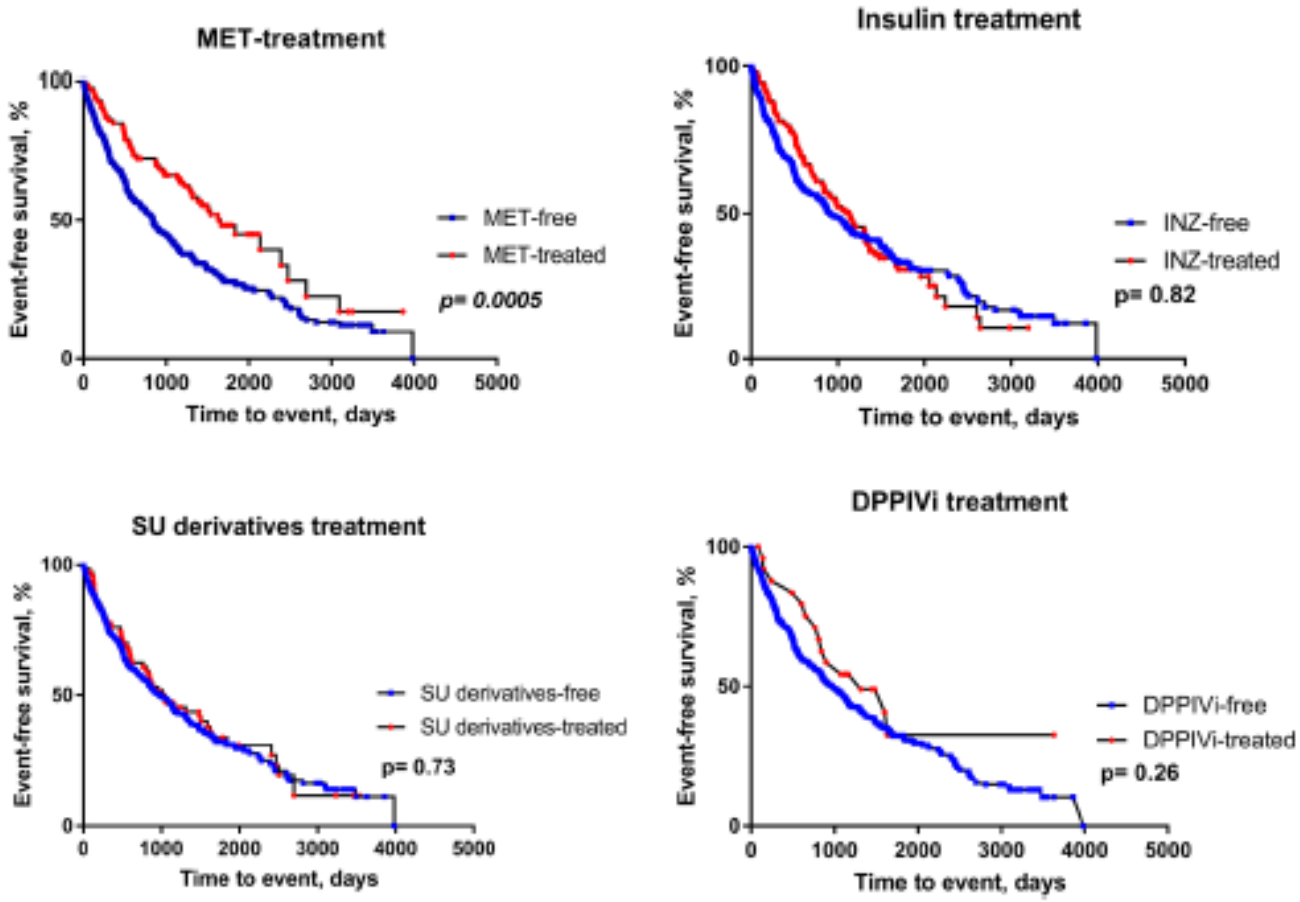
MET therapy associated with better quality of life (even after adjustation for confounders)

Benes et al. Sci Rep. 2022 Jul 29;12(1):13038

QoL

	No insulin	**Insulin**	
MLHFQ sum	44 (28; 60)	44 (29; 61)	0.92
MLHFQ somatic	22 (12; 27)	21 (12; 29)	0.70
MLHFQ emotional	6 (2; 12)	6 (3; 10)	0.70
	No SU derivatives	**SU derivatives**	
MLHFQ sum	45 (29; 61)	39 (22.5; 55.5)	0.25
MLHFQ somatic	22 (13; 28)	20 (10; 26)	0.20
MLHFQ emotional	6 (2; 11)	5 (1; 12)	0.55
	No DPPIV-inhibitors	**DPPIV-inhibitors**	
MLHFQ sum	44 (29; 61)	38 (14; 51)	0.07
MLHFQ somatic	22 (13; 28)	18 (6; 24)	0.08
MLHFQ emotional	6 (2; 12)	5 (0; 8)	0.10

MET u pokročilého HFrEF



MET treatment associated with better survival

Benes et al. Sci Rep. 2022 Jul 29;12(1):13038

Cox regression analysis

	Univariable analysis		
	HR	95% CI	p
MET treatment *(present vs. absent)*	0.57	0.41- 0.78	**0.0003**
Insulin treatment *(present vs. absent)*	0.97	0.74- 1.26	0.82
SU derivatives treatment *(present vs. absent)*	0.95	0.68- 1.28	0.61
DPPIV-inhibitors treatment *(present vs. absent)*	0.73	0.41- 1.21	0.24

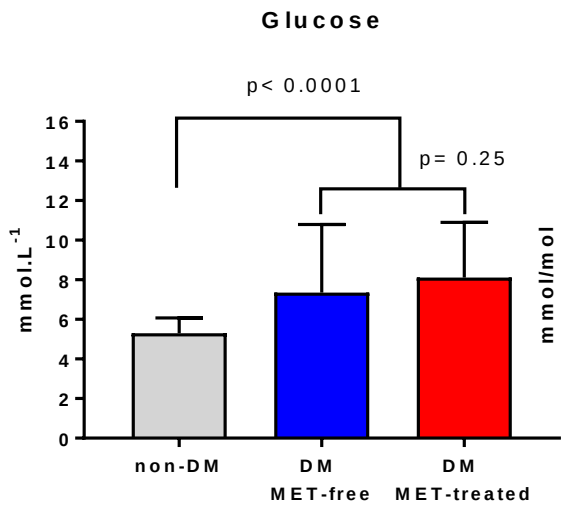
MET treated patients

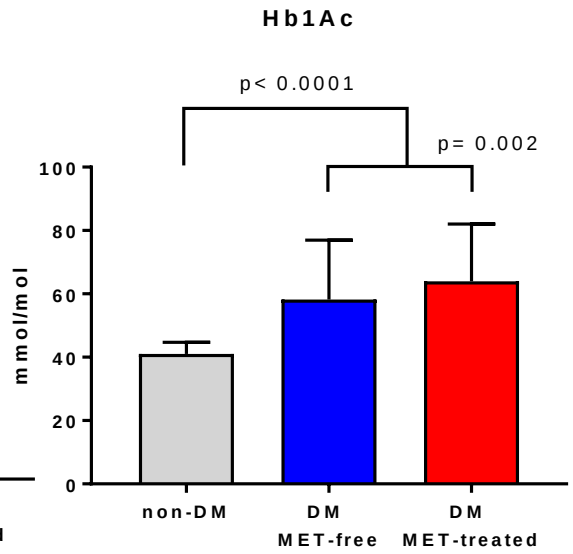
	Whole cohort (n= 847)	Non-DM (n= 467)	DM (n= 380)	P	DM-nonMET (n= 290)	DM+MET (n= 87)	P
Age *(years)*	57.40± 11.28	55.03± 11.94	60.31± 9.65	**<0.0001**	60.14± 9.63	60.92± 9.85	0.51
Males *(%)*	82.8	81.6	84.2	0.31	83.5	86.2	0.53
HF etiology *(% CAD)*	50.2	41.6	60.8	**<0.0001**	59.4	65.1	0.34
BMI *(kg.m^{-2})*	27.82 ± 5.09	26.94± 4.55	28.9± 5.50	**<0.0001**	28.27± 5.31	30.98± 5.61	**<0.0001**
BNP *(ng.l^{-1})*	466 (208; 1077)	381 (162; 948)	613 (264; 1187)	**<0.0001**	642 (334; 1354)	400 (148; 920)	**0.0002**
Hemoglobin *(g.l^{-1})*	140.85± 18.18	142.00± 18.36	139.49± 17.90	**0.049**	140.09± 18.13	138.00± 16.39	0.34
eGFR (*ml. min^{-1}.1.73m^{-2}*)	68.91± 22.50	72.55± 22.55	64.59± 21.69	**<0.0001**	63.34± 22.12	69.26± 19.76	**0.03**

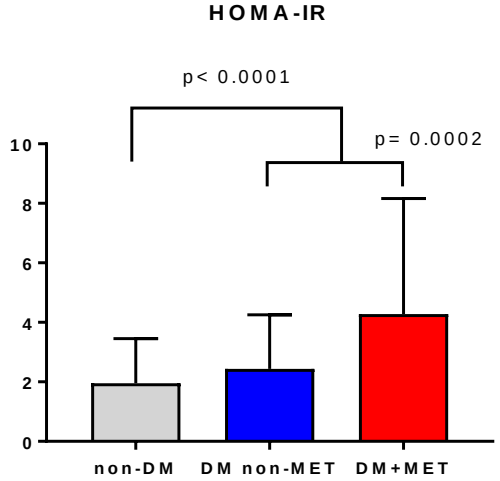
Multivariable Cox

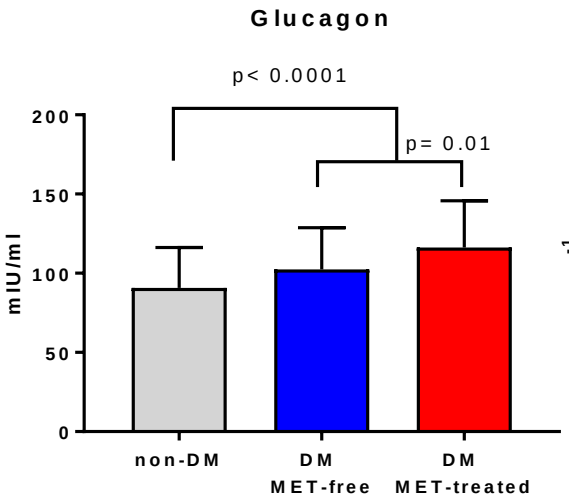
		HR	95% CI	p
Model 1	MET *(present vs. absent)*	0.57	0.41- 0.78	**0.0003**
Model 2	MET *(present vs. absent)*	0.63	0.45- 0.87	**0.004**
	BMI *($kg.m^{-2}$)*	0.97	0.94- 0.99	**0.005**
Model 3	MET *(present vs. absent)*	0.64	0.46- 0.88	**0.007**
	BMI *($kg.m^{-2}$)*	0.97	0.94- 0.99	**0.01**
	eGFR *($ml.min^{-1}.1.73m^{-2}$)*	0.995	0.989- 1.0006	0.08
Model 4	MET *(present vs. absent)*	0.70	0.50- 0.98	**0.035**
	BNP *($ng.L^{-1}$)*	1.00056	1.0004- 1.0007	**<0.0001**
	BMI *($kg.m^{-2}$)*	0.99	0.97- 1.018	0.51
	eGFR *($ml.min^{-1}.1.73m^{-2}$)*	0.996	0.991- 1.002	0.24

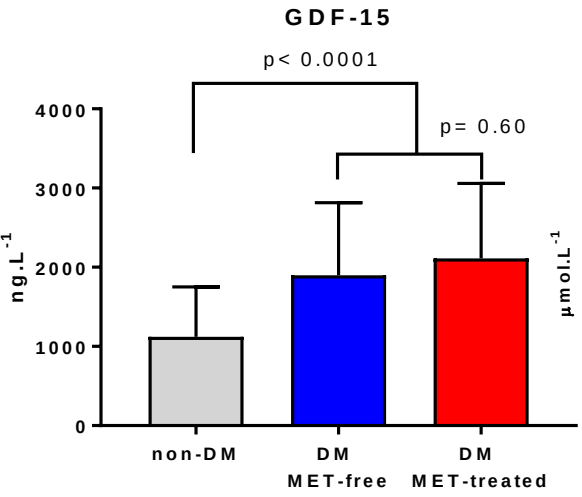
Metabolic profile

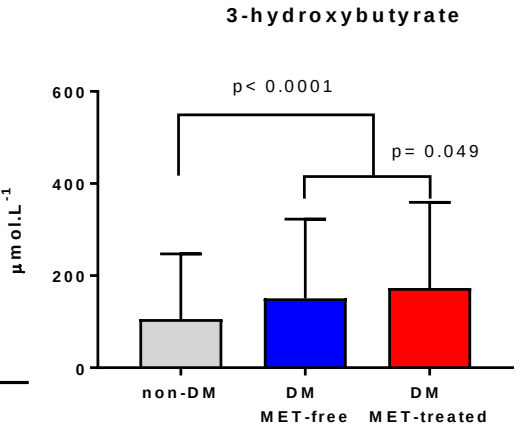




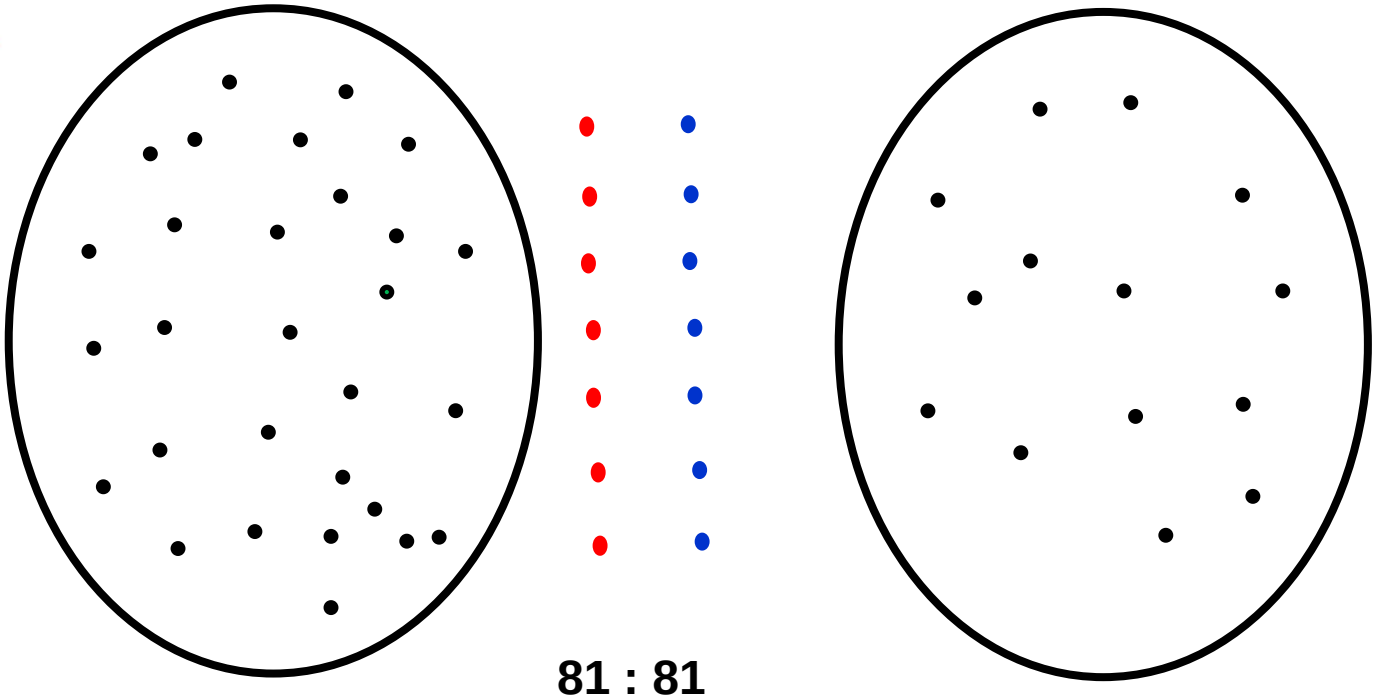








Propensity matching



81 : 81

17 variables:

DM – MET
n= 290

DM + MET
n= 87

Age, sex, NYHA functional class, BMI, eGFR, LVEF,
RV dysfunction grade, MiR and TriR severity, BNP, BB treatment,
RAAi, ICD, CRT, uric acid level, PAD/incretin treatment,
insulin treatment

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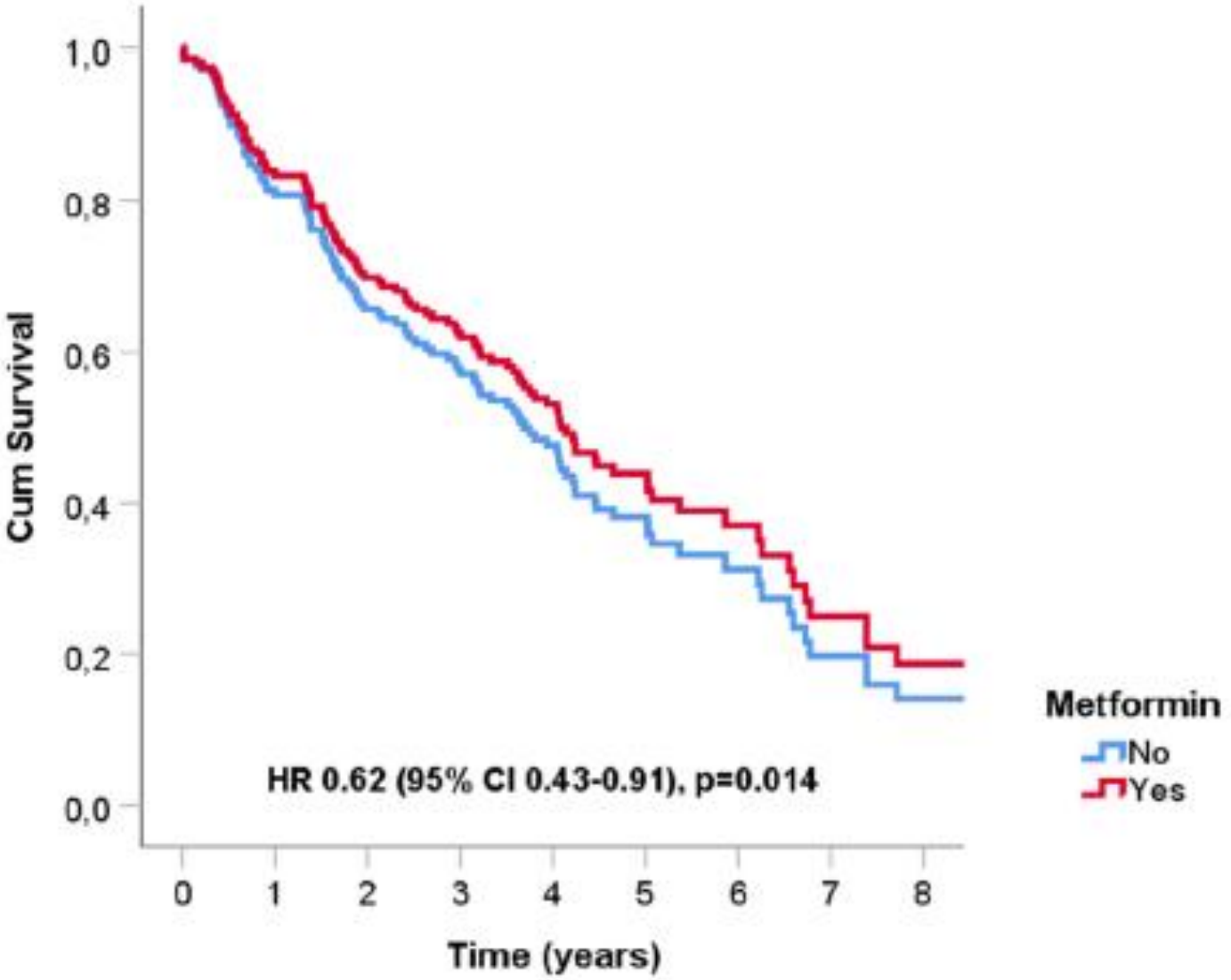
MET-treatment propensity matching



Benes et al. Sci Rep. 2022 Jul 29;12(1):13038

Conclusion

MET treatment in DM patients with advanced HFrEF was associated with:

- better quality of life

- improved outcome

… by mechanisms beyond improved DM compensation