IRA - METFORMINA CORRELATA

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Uso di Metformina

Nel 1994 FDA:

- **Nella malattia renale o disfunzione renale (creatinemia ≥ 1,5 mg/dl (maschi) , ≥ 1,4mg/dl (donne))**
- **Nei pazienti ≥ 80 anni con alterata clearance della creatinina**

Nel 2016 FDA & EMA:

- **In tutte le età**
- **eGFR ≥ 30 mL/min/1.73 m^2**

Lipska et al. Citizen Petition to the US Food and Drug Administration to Change Prescribing Guidelines: The Metformin Experience. Circulation 2016

Acidosi Lattica Associata alla Metformina (MALA)

Risk of Lactic Acidosis or Elevated Lactate Concentrations in Metformin Users With Renal Impairment: A Population-Based Cohort Study

Willemijn L. Eppenga,[1,2] Arief Lalmohamed,[3,4] Arjen F. Geerts,[3] Hieronymus J. Derijks,[2,3] Michel Wensing,[1] Antoine Egberts,[3,4] Peter A.G.M. De Smet,[1,5] and Frank de Vries[3,6,7]

Diabetes Care 2014;37:2218–2224 | DOI: 10.2337/dc13-3023

Table 1—Baseline characteristics of current metformin users and nonusers among patients using NIADs

Characteristics	Current metformin users (*N* = 223,968)	Nonusers (*N* = 34,571)
Follow-up, years (mean [SD])[a]	4.3 (2.8)	4.9 (3.0)
Female sex	105,561 (47.1)	15,007 (43.4)
Age, years (mean [SD])	60.1 (14.8)	67.8 (14.5)
18–49	51,394 (22.9)	4,221 (12.2)
50–59	49,018 (21.9)	4,997 (14.5)
60–69	59,363 (26.5)	7,899 (22.8)
70–79	45,689 (20.4)	9,558 (27.6)
≥80	18,504 (8.3)	7,896 (22.8)
Most recent renal function (mL/min/1.73 m^2) in the previous year[b]		
<30	586 (0.3)	955 (2.8)
30–59	29,742 (13.3)	7,436 (21.5)
≥60	132,344 (59.1)	14,235 (41.2)
Unknown	61,296 (27.4)	11,945 (34.6)

Endpoint: Acidosi lattica

- Livelli plasmatici lattato > 5mmol/l
- Diagnosi di acidosi lattica

Risk of Lactic Acidosis or Elevated Lactate Concentrations in Metformin Users With Renal Impairment: A Population-Based Cohort Study

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Table 2—Risk of lactic acidosis or elevated lactate concentrations in current, recent, and past metformin users compared with never users of metformin

	Risk of lactic acidosis or elevated lactate concentration			
Metformin use	Person-years, *n*	Events, *n*	Age-/sex-adjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Never use				
Past use				
Recent use				
Current us				

L'incidenza di Acidosi Lattica nei pazienti in terapia con metformina era di 7,4 per 100,000 persone/anno vs. 2,2 per 100,000 persone/anno che non erano in terapia con Metformina

Current metformin users are stratified by renal function. [a]Adjusted for age, sex, BMI, a history of heart failure, and use of renin-angiotensin-aldosterone system inhibitors and other NIADs/insulin in the previous 6 months. Chronic liver disease and sepsis were not included in the final model because there were too few exposed patients. [b]Renal function records in the previous week are excluded. [c]This substratum included 8,849 person-years, with one event that could not be subdivided further because the patient only had a READ code for chronic kidney disease stage 3 (30–59 mL/min/1.73 m^2).

Risk of Lactic Acidosis or Elevated Lactate Concentrations in Metformin Users With Renal Impairment: A Population-Based Cohort Study

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	Risk of lactic acidosis or elevated lactate concentration			
Metformin use	Person-years, *n*	Events, *n*	Age-/sex-adjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Substratification of current users by most recent renal function (mL/min/1.73 m^2) in the previous year[b]				
≥60	547,731	29	2.42 (0.58–10.1)	2.87 (0.67–12.3)
<60	126,881	21	7.56 (1.77–32.2)	6.37 (1.48–27.5)
30–59[c]	124,275	19	7.09 (1.98–27.9)	5.94 (1.55–24.7)
45–59	89,976	13	6.60 (1.49–29.2)	6.06 (1.37–27.1)
30–44	25,450	5	7.98 (1.61–39.6)	5.47 (1.05–28.5)
<30	2,605	2	35.1 (4.90–249)	25.7 (3.57–185)
≥45	644,861	43	3.30 (0.79–13.8)	3.16 (0.75–13.3)
<45	29,751	7	8.97 (1.85–43.4)	6.74 (1.34–33.8)
Unknown	68,539	5	3.33 (0.65–17.2)	4.51 (0.85–23.8)

Current metformin users are stratified by renal function. [a]Adjusted for age, sex, BMI, a history of heart failure, and use of renin-angiotensin-aldosterone system inhibitors and other NIADs/insulin in the previous 6 months. Chronic liver disease and sepsis were not included in the final model because there were too few exposed patients. [b]Renal function records in the previous week are excluded. [c]This substratum included 8,849 person-years, with one event that could not be subdivided further because the patient only had a READ code for chronic kidney disease stage 3 (30–59 mL/min/1.73 m^2).

Table 3—Risk of lactic acidosis or elevated lactate concentration in current metformin users stratified by cumulative exposure or re

- ✓ Il rischio di Acidosi Lattica è sei volte più alto nei pazienti in terapia con Metformina e ridotta funzionalità renale
- ✓ Tale rischio si raddoppia nei pazienti in terapia cronica e nei pazienti con recente terapia ad alto dosaggio e ridotta funzionalità renale

Metf				
Neve				
Curre				8)
Subst				
<7				5)
Renal function ≥60 mL/min/1.73 m²	460,012	23	2.28 (0.54–9.65)	2.73 (0.63–11.9)
Renal function <60 mL/min/1.73 m²	108,561	16	6.72 (1.55–29.2)	5.54 (1.26–24.4)
Unknown	60,071	4	3.03 (0.56–16.5)	4.25 (0.76–23.7)
≥730 g of metformin/year	114,506	12	4.78 (1.07–21.4)	6.14 (1.35–28.0)
Renal function ≥60 mL/min/1.73 m²	87,719	6	3.12 (0.63–15.4)	3.94 (0.78–20.0)
Renal function <60 mL/min/1.73 m²	18,320	5	12.4 (2.42–64.1)	11.8 (2.27–61.5)
Unknown	8,468	1	5.38 (0.49–59.3)	6.96 (0.62–78.0)
Substratification of current users by most recent prescribed daily dose of metformin and renal function[b]				
≤2 g of metformin/day	658,391	46	3.19 (0.77–13.1)	3.78 (0.90–15.8)
Renal function ≥60 mL/min/1.73 m²	483,674	24	2.27 (0.54–9.58)	2.71 (0.63–11.7)
Renal function <60 mL/min/1.73 m²	113,530	17	6.84 (1.58–29.6)	5.66 (1.29–24.8)
Unknown	61,187	5	3.73 (0.72–19.2)	5.19 (0.98–27.4)
>2 g of metformin/day	84,759	9	4.85 (1.05–22.4)	6.40 (1.35–30.3)
Renal function ≥60 mL/min/1.73 m²	64,057	5	3.56 (0.69–18.4)	4.59 (0.87–24.3)
Renal function <60 mL/min/1.73 m²	13,350	4	13.7 (2.51–74.7)	13.0 (2.36–72.0)
Unknown	7,352	0		

[a]Adjusted for age, sex, BMI, a history of heart failure, and use of renin-angiotensin-aldosterone system inhibitors and other NIADs/insulin in the previous 6 months. Chronic liver disease and sepsis were not included in the final model because there were too few exposed patients.
[b]Substratification by most recent renal function in the previous year; renal function records in the previous week excluded.

Diabetes Care 2014;37:2218–2224 | DOI: 10.2337/dc13-3023

Fattori di Rischio per MALA nell'anziano diabetico

⬇ Clearance lattato

Insufficienza Epatica

Aumentata produzione

Scompenso cardiaco
⬇ perfusione tissutale
Sepsi

Insufficienza Renale

⬇

⬇ Clearance Metformina

I livelli plasmatici di Metformina variano secondo il grado di funzionalità renale?

Livelli plasmatici della Metformina secondo la funzionalità renale

DIABETES CARE, VOLUME 33, NUMBER 6, JUNE 2010

Serum metformin levels in impaired renal function

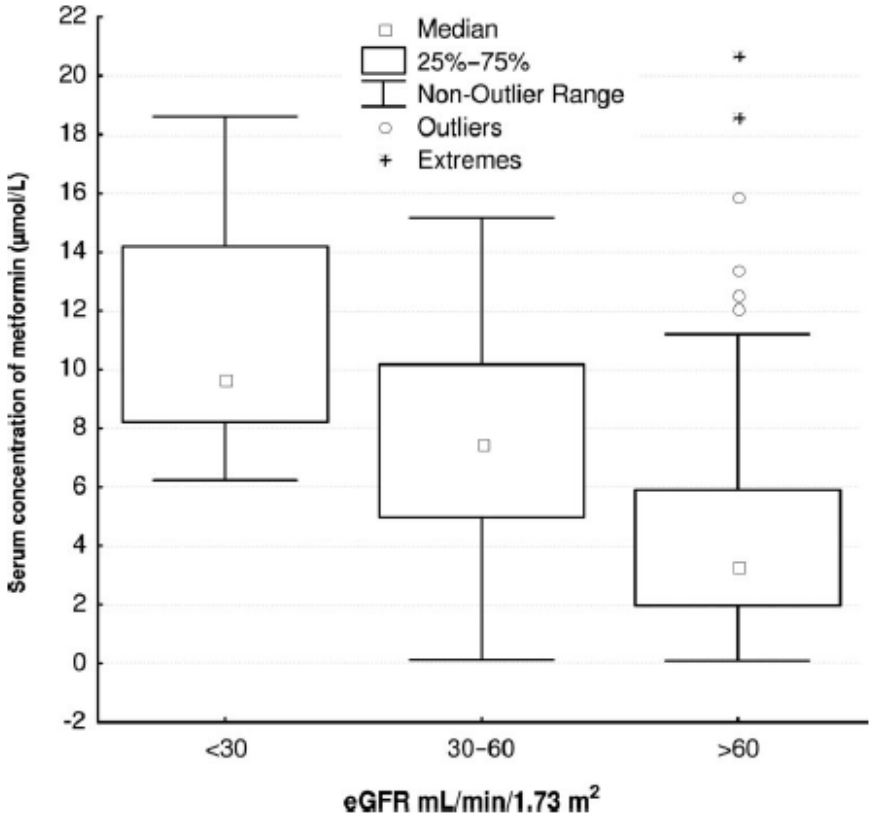


Figure 1—*Box-plot of trough metformin levels in 137 patients grouped in patients with eGFR <30 ml/min/1.73 m² (n = 9), 30–60 ml/min/1.73 m², and >60 ml/min/1.73 m² (n = 107). The outliers marked in the group with eGFR >60 ml/min/1.73 m² are most likely due to patients accidentally taking their medication before the blood test.*

I dati supportano le raccomandazioni che la Metformina possa essere utilizzata nei pazienti con una eGFR ≥ 30ml/min/1.73m^2

Reports of Lactic Acidosis Attributed to Metformin, 2015–2018

James H. Flory,[1] Sean Hennessy,[2] Clifford J. Bailey,[3] and Silvio E. Inzucchi[4]

Diabetes Care Publish Ahead of Print, published online October 9, 2019

https://doi.org/10.2337/dc19-0923

Table 1—Characteristics of LA case reports with metformin present as either primary suspect or incidental drug

	Year			
	2015	2016	2017	2018
All cases				
N	521	717	892	1,939
Country (%)				
Britain	14 (2.7)	27 (3.8)	20 (2.2)	60 (3.1)
France	33 (6.3)	91 (12.7)	65 (7.3)	344 (17.7)
Germany	52 (10.0)	77 (10.7)	26 (2.9)	142 (7.3)
Italy	59 (11.3)	99 (13.8)	245 (27.5)	553 (28.5)
Other non-U.S.	252 (48.4)	252 (35.1)	347 (38.9)	597 (30.8)
Domestic (U.S.) cases only				
N	111	171	189	243
Age (SD)	46.4 (21.9)	60.6 (15.2)	59.5 (15.1)	47.6 (20.3)
Sex				
Not recorded	24 (21.6)	41 (24.0)	21 (11.1)	31 (12.8)
Female	42 (37.8)	28 (16.4)	104 (55.0)	84 (34.6)
Male	45 (40.5)	102 (59.6)	64 (33.9)	128 (52.7)
AKI also reported	30 (27.0)	39 (22.8)	46 (24.3)	104 (42.8)
Sulfonylurea concomitant use	1 (0.9)	3 (1.8)	26 (13.8)	31 (12.8)
DPP-4i concomitant use	3 (2.7)	4 (2.3)	5 (2.6)	4 (1.6)
TZD concomitant use	0 (0.0)	2 (1.2)	1 (0.5)	1 (0.4)
GLP-1RA concomitant use	1 (0.9)	1 (0.6)	3 (1.6)	2 (0.8)
SGLT2i concomitant use	0 (0.0)	1 (0.6)	1 (0.5)	2 (0.8)
Insulin concomitant use	7 (6.3)	12 (7.0)	13 (6.9)	6 (2.5)
LA reports/all reports	0.05	0.06	0.08	0.11
Nonmetformin diabetes drugs				
LA reports	21	26	18	28
LA reports/all reports	0.0004	0.0009	0.0006	0.0007
PRR compared with metformin	144	74	139	145

AKI, acute kidney injury; DPP-4i, DPP-4 inhibitor; GLP-1RA, GLP-1 receptor agonist; PRR, proportional reporting ratio; SGLT2i, SGLT2 inhibitor; TZD, thiazolidinedione.

Conclusioni -1

- Acidosi lattica associata alla Metformina «*MALA*» rimane un evento raro
- «*MALA*» è associata alla funzionalità renale soprattutto con eGFR <30ml/min/1,73m^2
- Il più alto dosaggio di Metformina è associato al rischio di «*MALA*» e tale rischio si raddoppia in ridotta funzionalità renale
- Dal 2016 ad oggi sembrerebbe esistere un incremento negli eventi di «*MALA*» a livello globale, ma ulteriori studi sono necessari

Older Adults: *Standards of Medical Care in Diabetes—2019*

American Diabetes Association

Diabetes Care Volume 42, Supplement 1, January 2019

La Metformina rimane il farmaco anti-diabetico di prima scelta

GFR ≥ 30 mL/min/1.73m^2

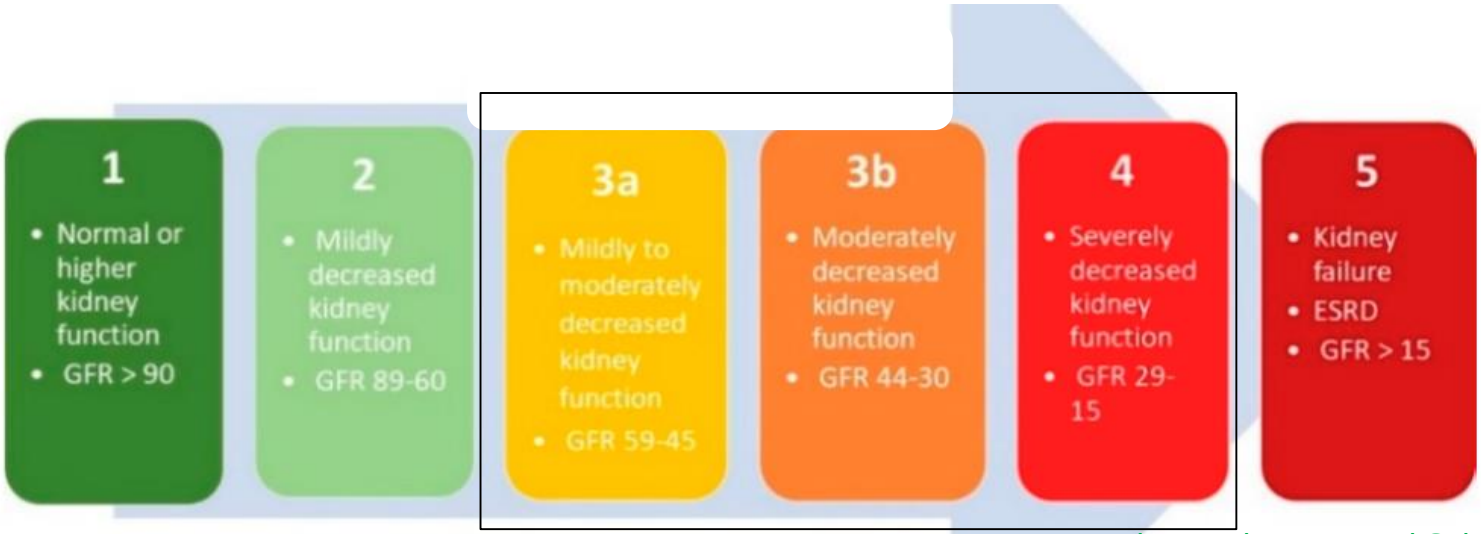
Controindicata in scompenso cardiaco ed insufficienza epatica

Quale dosaggio nell'IR ?

Metformin Treatment in Patients With Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4

Jean-Daniel Lalau,[1,2] Farshad Kajbaf,[1,2] Youssef Bennis,[3] Anne-Sophie Hurtel-Lemaire,[3] Frans Belpaire,[4] and Marc E. De Broe[5]

Diabetes Care 2018;41:547–553 | https://doi.org/10.2337/dc17-2231



Adattato da Int. J. Mol Sci 2018

3 Studi complementari – open label

4 mesi di terapia per evidenziare il dosaggio ottimale di metformina nel IRC

n= 141 pazienti, Età media: 62 anni

Metformin Treatment in Patients With Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4

Jean-Daniel Lalau,[1,2] Farshad Kajbaf,[1,2] Youssef Bennis,[3] Anne-Sophie Hurtel-Lemaire,[3] Frans Belpaire,[4] and Marc E. De Broe[5]

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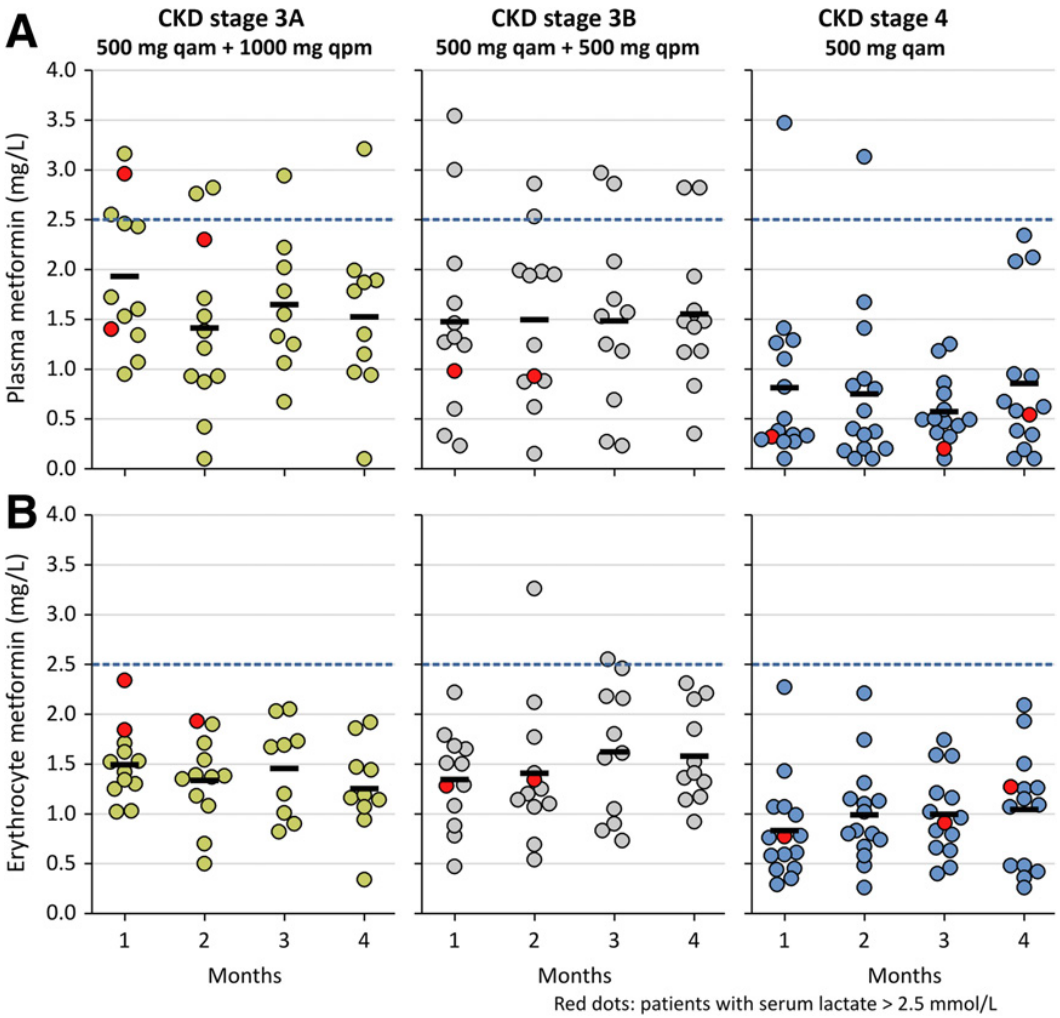

Il livello di Metformina sia negli eritrociti che nel plasma dei pazienti secondo IRC ed il dosaggio/die di Metformina

Metformin Treatment in Patients With Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4

Jean-Daniel Lalau,[1,2] Farshad Kajbaf,[1,2] Youssef Bennis,[3] Anne-Sophie Hurtel-Lemaire,[3] Frans Belpaire,[4] and Marc E. De Broe[5]

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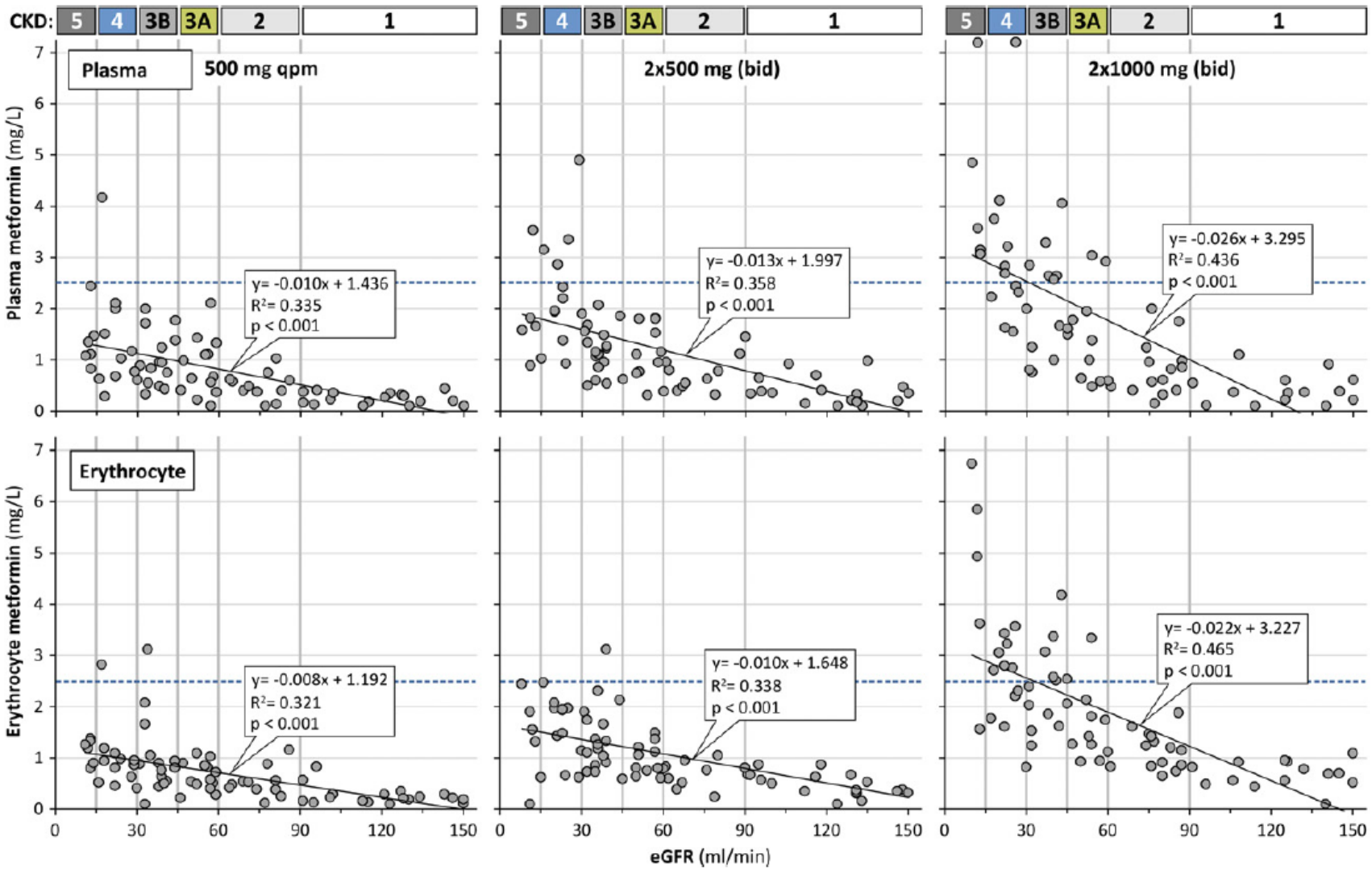

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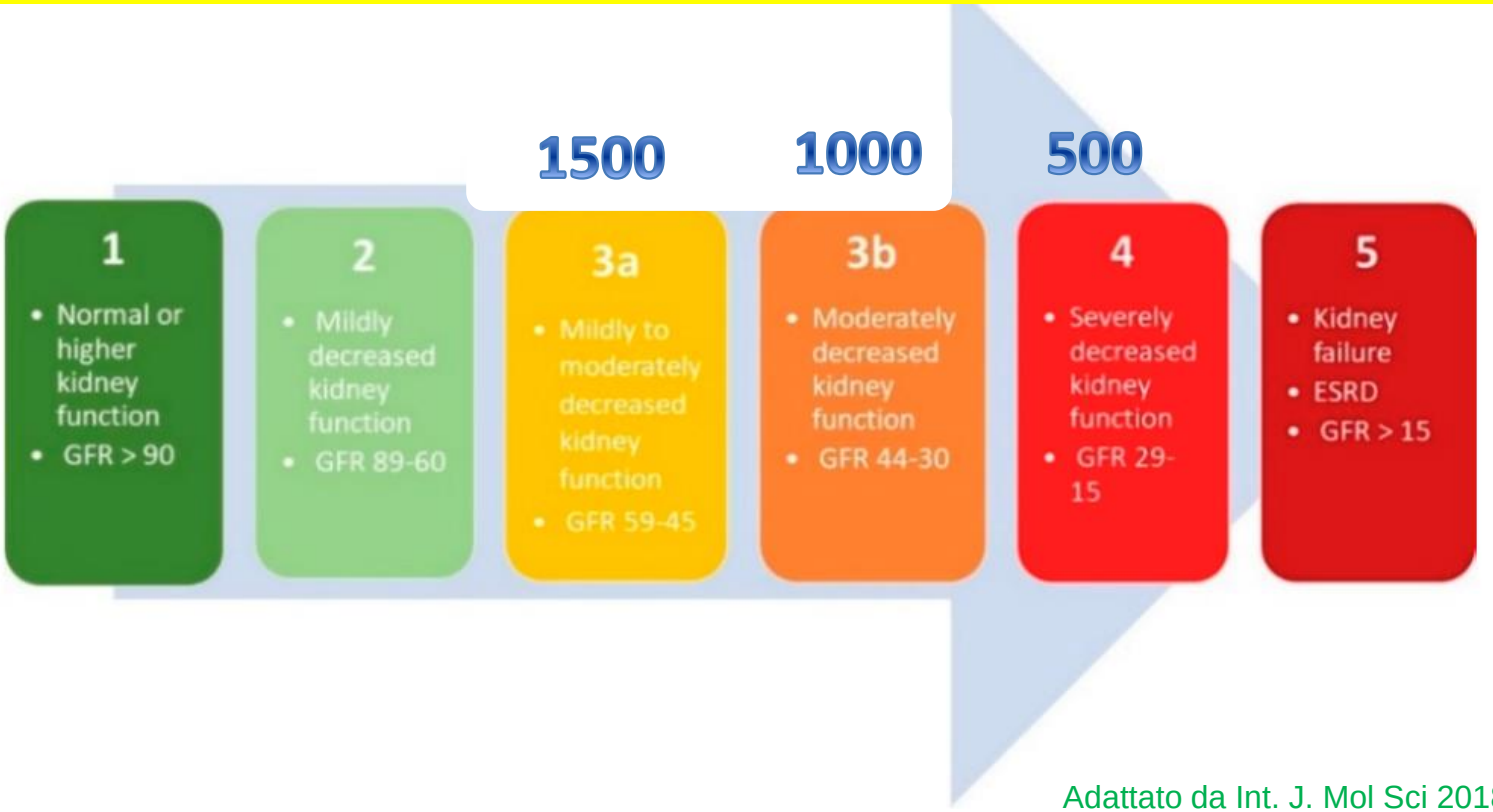
Dosaggi giornalieri appropriati di Metformina (mg)



Adattato da Int. J. Mol Sci 2018

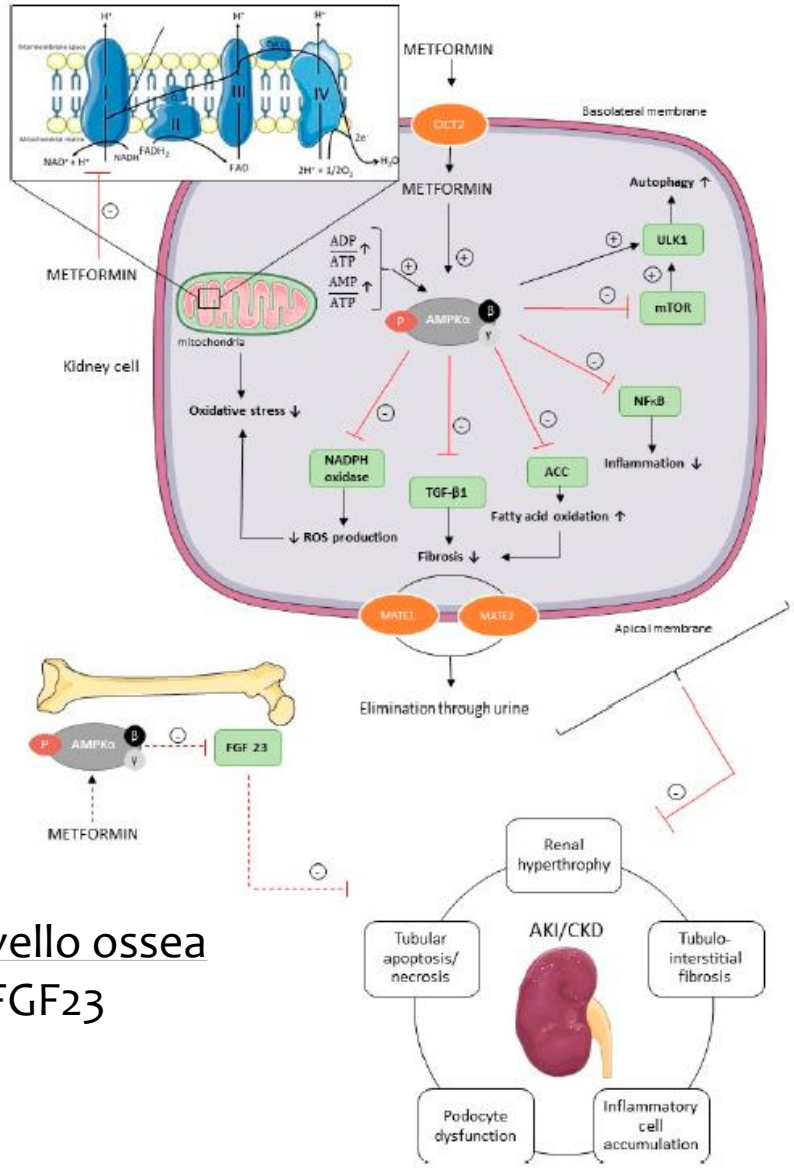
Renoprotezione con Metformina

Review

Metformin: A Candidate Drug for Renal Diseases

International Journal of *Molecular Sciences*

2018



A livello renale migliora:

- Lo stress ossidativo
- Lo stato infiammatorio
- La fibrosi
- ROS

A livello ossea

- FGF23

Risk of acute kidney injury and survival in patients treated with Metformin: an observational cohort study

Bell *et al. BMC Nephrology* (2017) 18:163
DOI 10.1186/s12882-017-0579-5

BMC Nephrology

> 25,000 pazienti con DM2

Studio osservazionale dal 2004-2013 in Tayside, Scozia

Outcome: IRA e Sopravvivenza

IRA = criteria secondo KDIGO
(creatinemia ≥ 26,5 umol/l o creatinemia > 150% dal baseline durante il ricovero)

Risk of acute kidney injury and survival in patients treated with Metformin: an observational cohort study

Bell *et al. BMC Nephrology* (2017) 18:163
DOI 10.1186/s12882-017-0579-5

BMC Nephrology

Table 1 Demographic characteristics of cohort at study midpoint 1st July 2008, n = 12,373

Age in years[a]	68.2 (59.2-75.9)
Sex (M) (%)	6636 (54)
Metformin Use (%)	5975 (48)
Diabetes Duration in years[a]	5.48 (2.50-9.91)
Number of diabetes drug classes prescribed (%)	
0	4187 (33.8)
1	4517 (36.5)
2	2943 (23.8)
3	671 (5.4)
4	53 (0.4)
5	2 (0.02)
eGFR category (%)	
>60	8926 (72.1)
30-59	2574 (20.8)
<29 ml/min/1.73^2	180 (1.5)
Missing	693 (5.6)
HbA_{1c} %	7.0 (6.3 – 7.9)
(mmol/mol)	53 (45- 63)
ACE inhibitor or ARB Use (%)	5074 (41%)
NSAID or Cox-2 inhibitor use (%)	1160 (9.4%)

[a]Median & IQR

Risk of acute kidney injury and survival in patients treated with Metformin: an observational cohort study

Bell *et al. BMC Nephrology* (2017) 18:163
DOI 10.1186/s12882-017-0579-5

BMC Nephrology

L'uso di Metformina era associato ad un rischio minore di IRA (95% CI: 0,70-0,82; p<0,001)

* Aggiustato per età, sesso, durata del diabete, numero di farmaci anti-diabetici

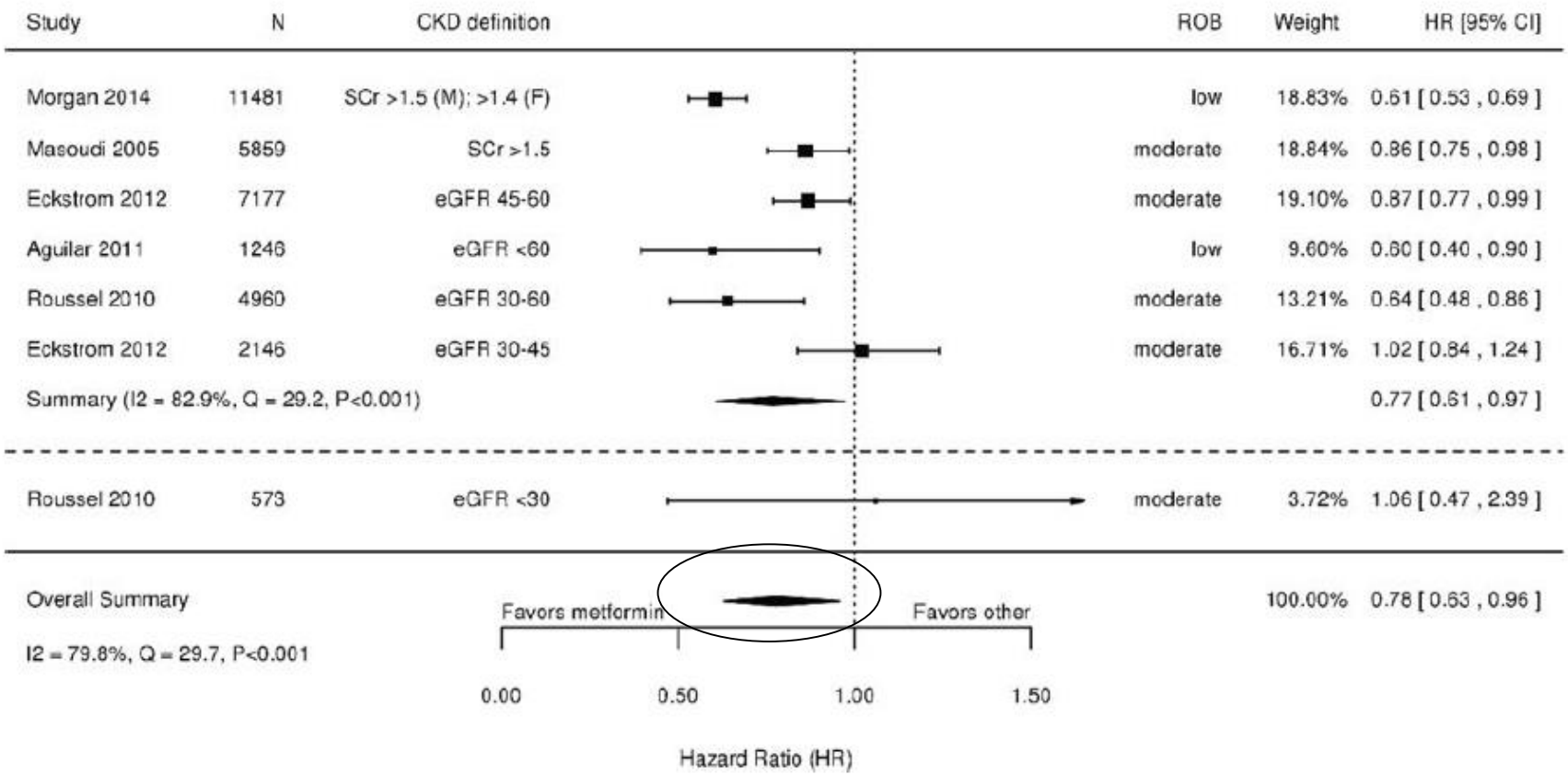
Nei pazienti con un evento di IRA, l'uso di Metformina era associato ad una migliore sopravvivenza (95%CI, 0,69-0,94, p=0,006)

Aggiustato per età, sesso, durata del diabete, baseline eGFR, HbA1c

Clinical Outcomes of Metformin Use in Populations with Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review

Ann Intern Med. 2017 February 07; 166(3): 191–200. doi:10.7326/M16-1901.

Meta-analysis of all-cause mortality among patients with moderate-to-severe CKD using treatment regimens including metformin versus regimens not including metformin



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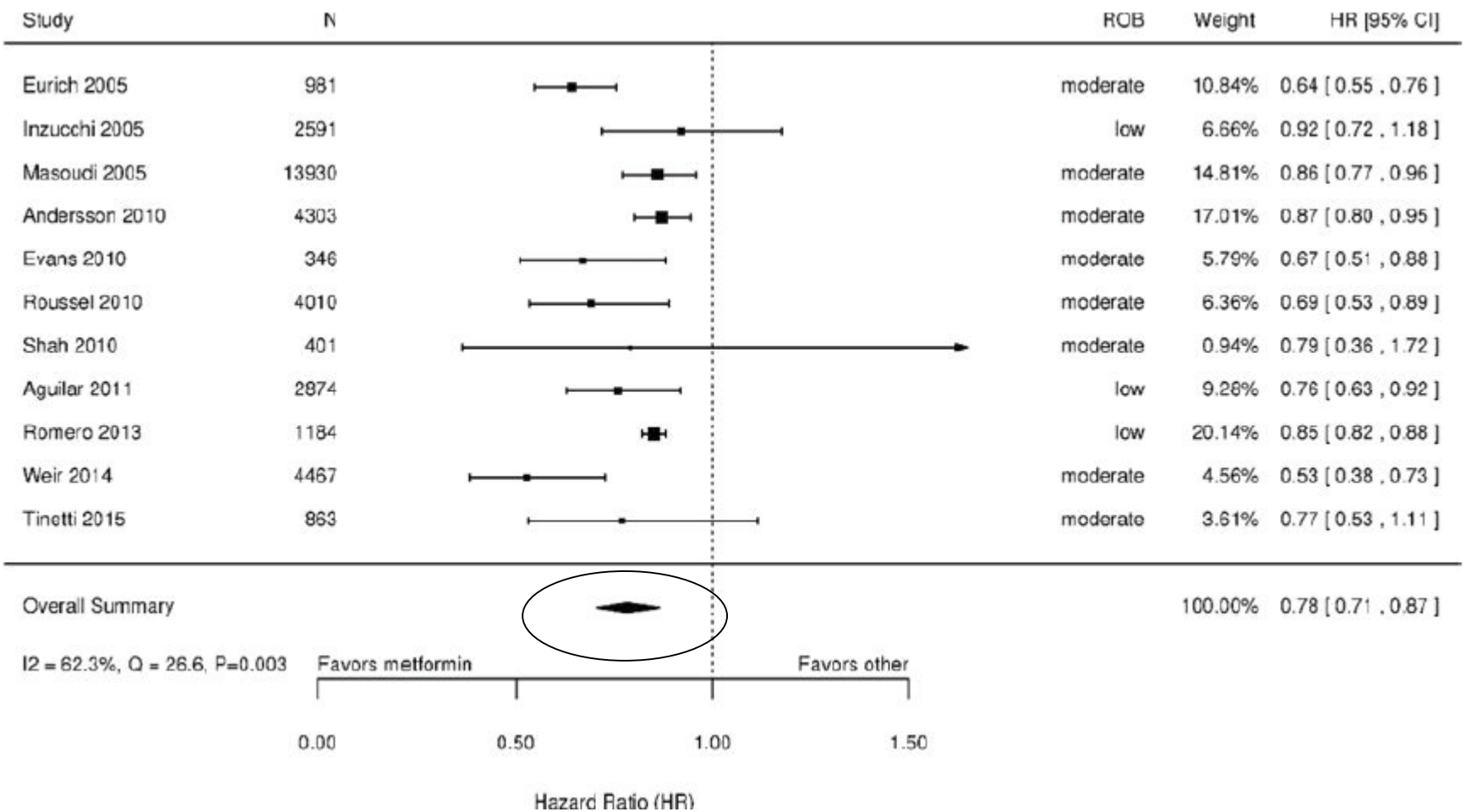
Meta-analysis of all-cause mortality among patients with CHF using treatment regimens including metformin versus regimens not including metformin



Clinical Outcomes of Metformin Use in Populations with Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review *Ann Intern Med.* 2017 February 07; 166(3): 191–200. doi:10.7326/M16-1901.

Non è stato possibile creare una meta-analisi

Uno studio con pochi bias è stato calcolato una migliore sopravvivenza nei pazienti in terapia con la metformina (HR:0,43, CI 95% 0,24-0,78) indipendentemente dalla severità della cirrosi

Conclusioni

Acidosi lattica è associata all'IRA nel paziente in terapia con Metformina

FDA & EMA guidelines:

- ✓ eGFR ≥60 mL/min/1.73 m² – monitoraggio funzionalità renale annuale

E' necessario individuare il dosaggio ottimale per uso di Metformina nell'IR nel paziente anziano

nuova terapia con metformina, ma pazienti già in terapia possono continuare con controlli ogni 3 mesi

No Metformina in pazienti con eGFR < 30 mL/min/1.73 m²

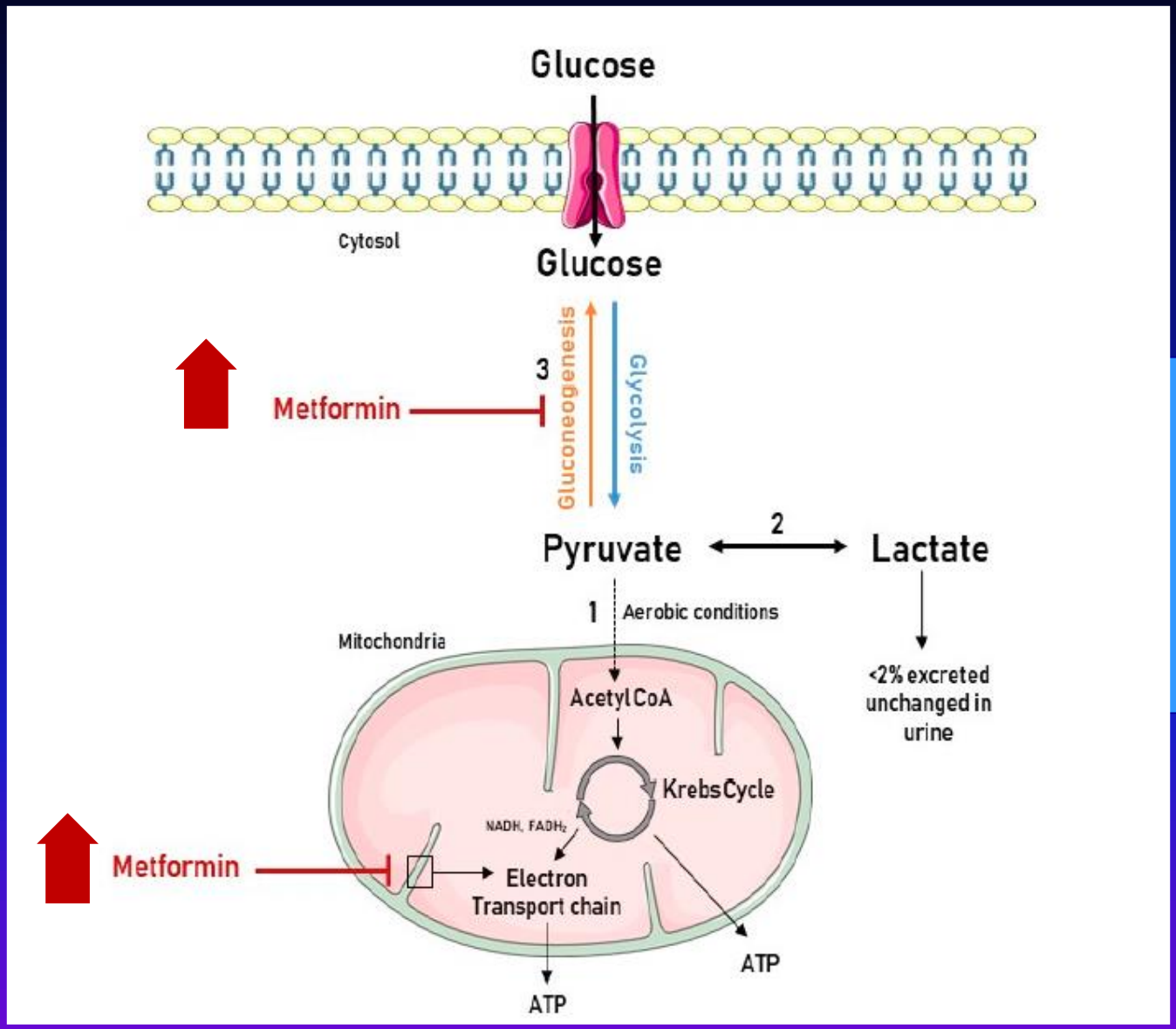
Conclusioni

Nuovi studi indicano un potenziale ruolo di Renoprotezione con la Metformina nel paziente anziano

IRA/IRC ? **Metformina**

Sono necessari studi randomizzati per determinare il ruolo del Metformina nell'IR

Acidosi Lattica Associata alla Metformina– MALA



pH < 7,35

Lattato
> 45 mg/dl,
> 5 mmol/L

Adattato da Int. J. Mol Sci 2018