LA METFORMINA NELLA CKD: UNA TERAPIA DA RICUPERARE?

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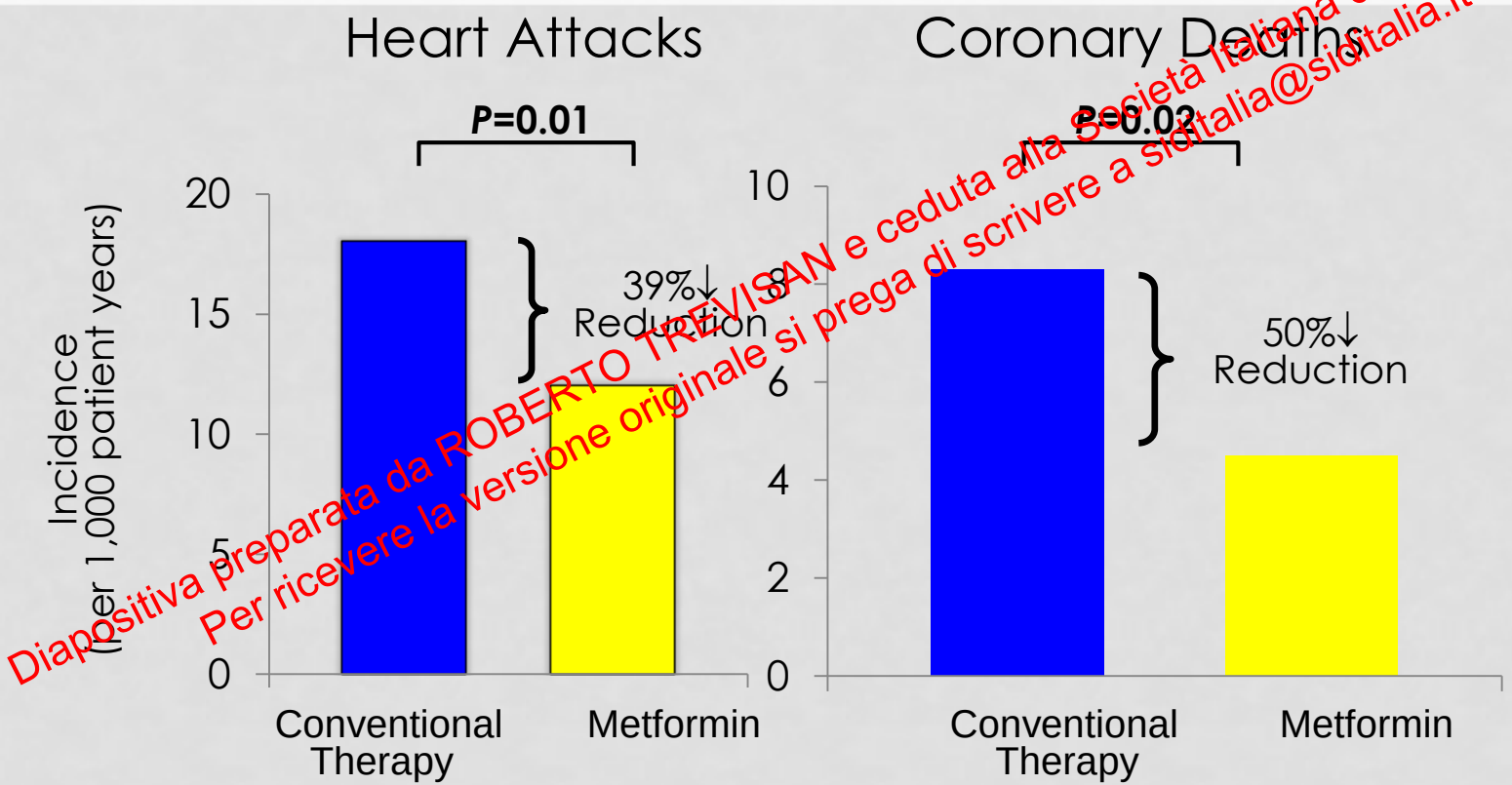
UKPDS 34. *Lancet* 1998; **352**: 854-865

Metformin Prevents Heart Attacks and Reduces Deaths in Type 2 Diabetes



UN PO' DI STORIA….

GALENA OFFICINALIS: FROM BOTANY TO BEDSITE

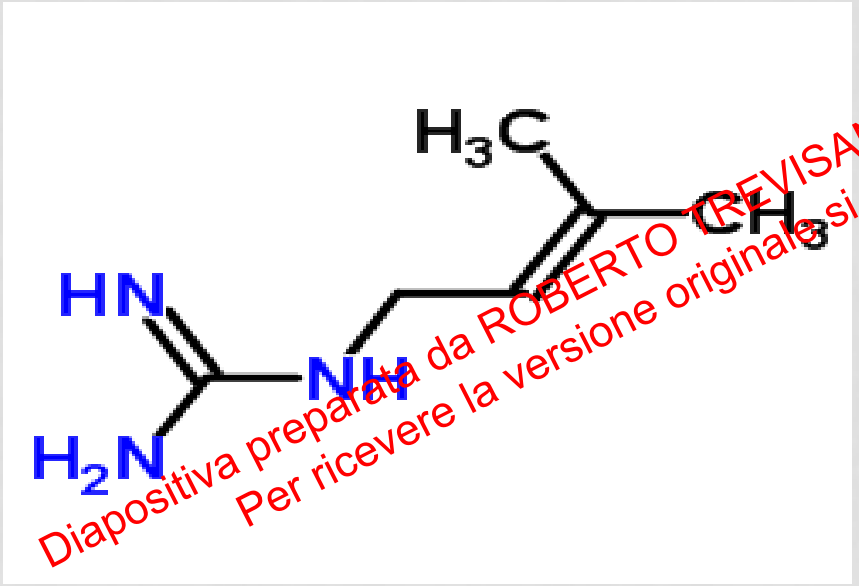
Ganela officinals : Leguminosa

L'uomo e la pianta

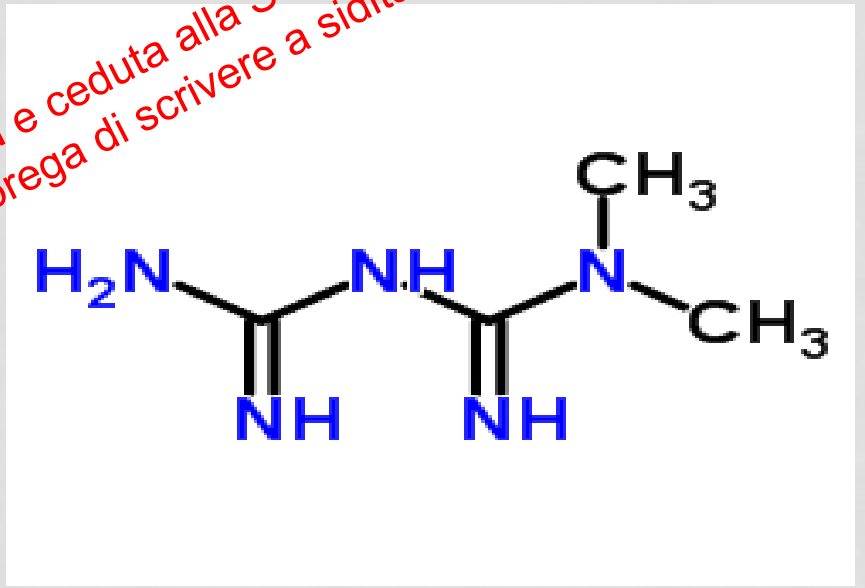
- Nella tradizione popolare veniva impiegato come sudorifero ed antitossico di ordine generale, ma, soprattutto, come stimolatore per aumentare la portata lattea alle nutrici. Il suo potere galattogeno era così apprezzato, che in alcune zone della pianura padana, era consuetudine somministrare decotti alle puerpere.

STRUTTURE CHIMICHE

Galegine



Metformina



La sintesi attribuita a Werner e Bell al Trinity College di Dublino nel 1922

REALIZING THE THERAPEUTIC POTENTIAL OF METFORMIN

Dr Jean Sterne

A french clinician in Paris

- The principal figure in the discovery of metformin as an oral antidiabetic agent in the 1950s

METFORMIN: MODE OF ACTION VERY DIFFICULT TO PINPOINT

In animals and humans, **metformin**

- is absorbed through the upper small intestine,
- is concentrated in enterocytes and hepatocytes,
- circulates essentially unbound,
- **and is eliminated, unchanged, by the kidneys**.

Role of AMP-activated protein kinase in mechanism of metformin action

Rapid Publication

See related Commentary on pages 1105–1107.

Gaochao Zhou,[1] Robert Myers,[1] Ying Li,[1] Yuli Chen,[1] Xiaolan Shen,[1] Judy Fenyk-Melody,[1] Margaret Wu,[1] John Ventre,[1] Thomas Doebber,[1] Nobuharu Fujii,[2] Nicolas Musi,[2] Michael F. Hirshman,[2] Laurie J. Goodyear,[2] and David E. Moller[1]

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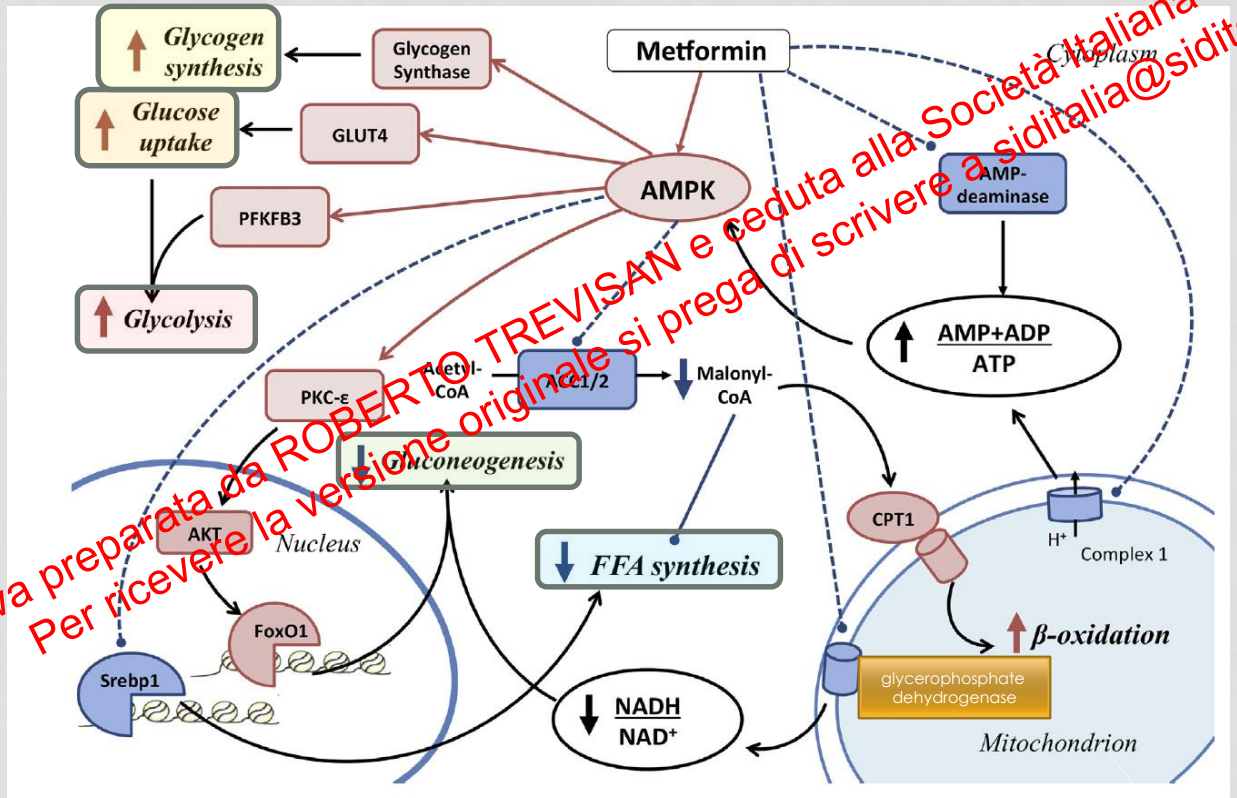
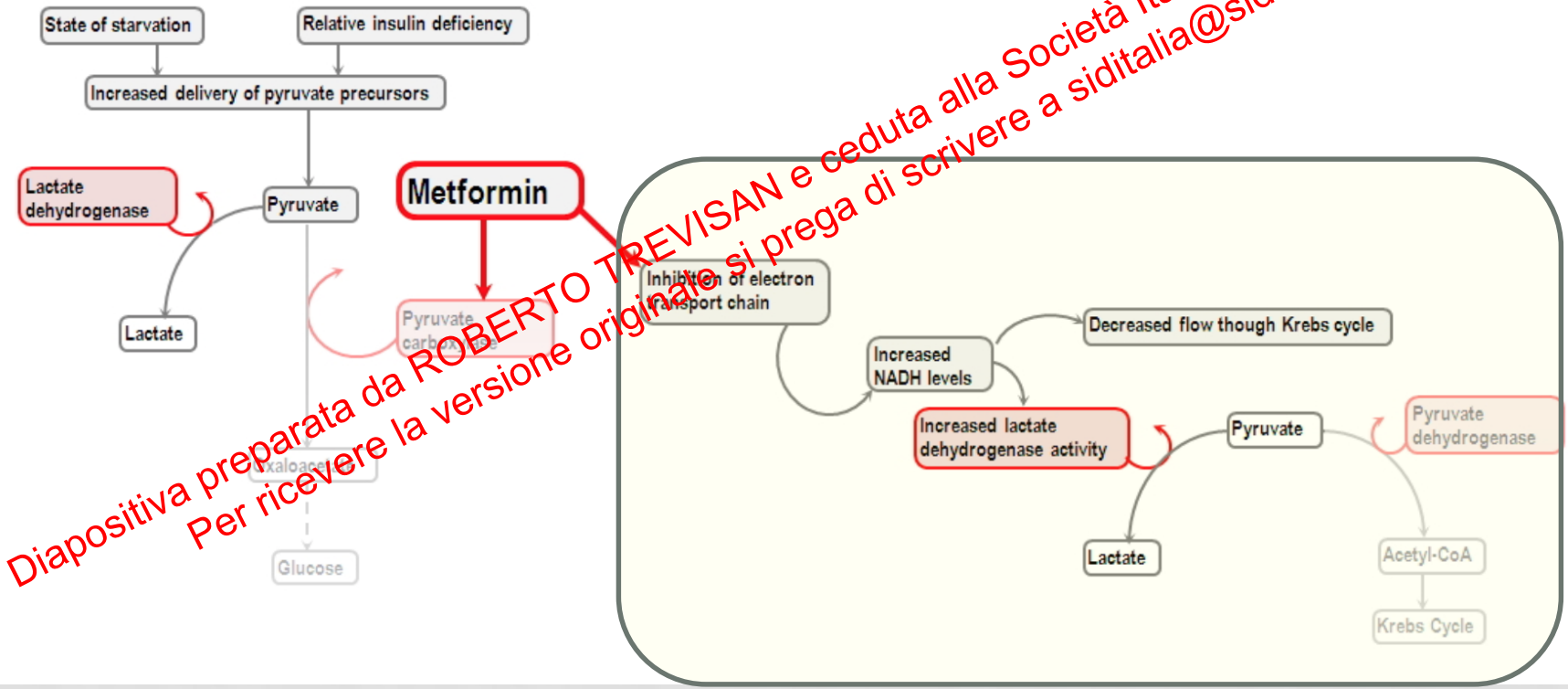
Received for publication June 13, 2001, and accepted in revised form August 28, 2001.

EFFECTS OF METFORMIN ON CELL METABOLISM

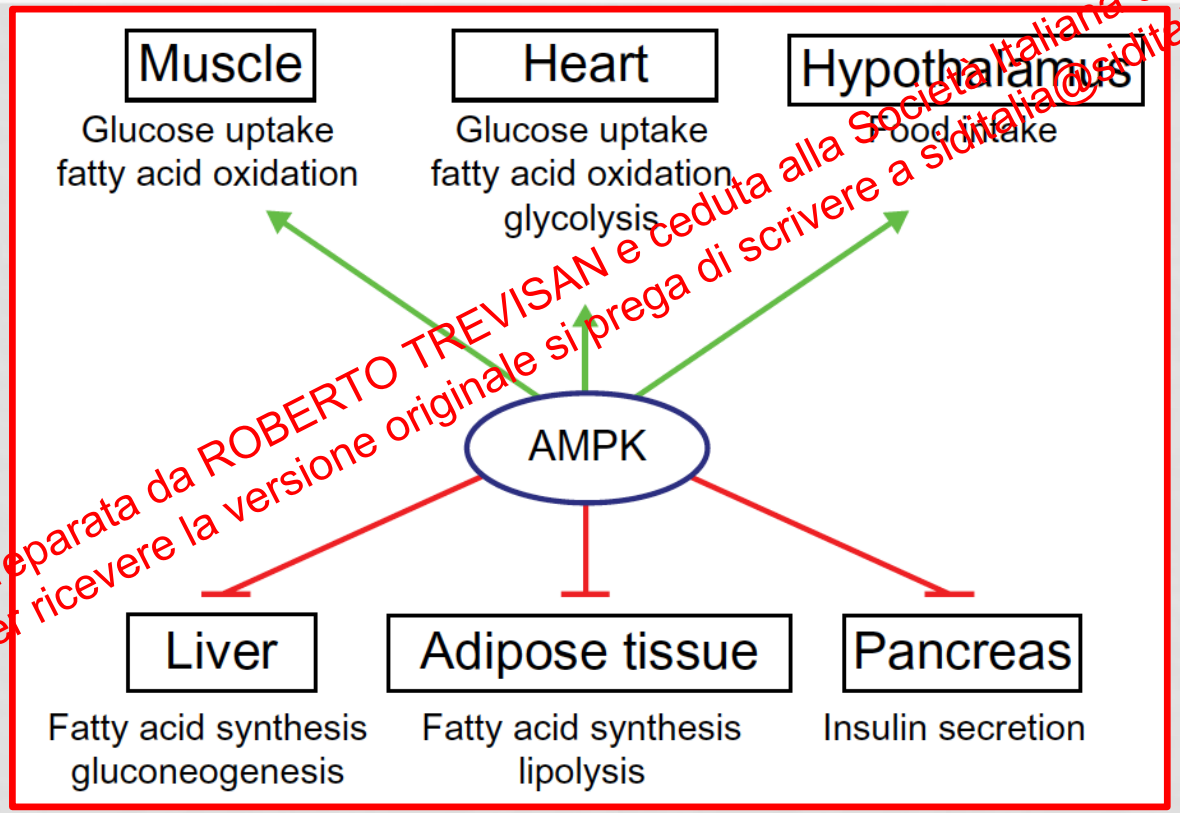


Nutrition, Metabolism & Cardiovascular Diseases (2017) 27, 657e669

METFORMIN AND LACTIC ACIDOSIS



ROLES OF AMPK IN THE CONTROL OF WHOLE-BODY ENERGY METABOLISM

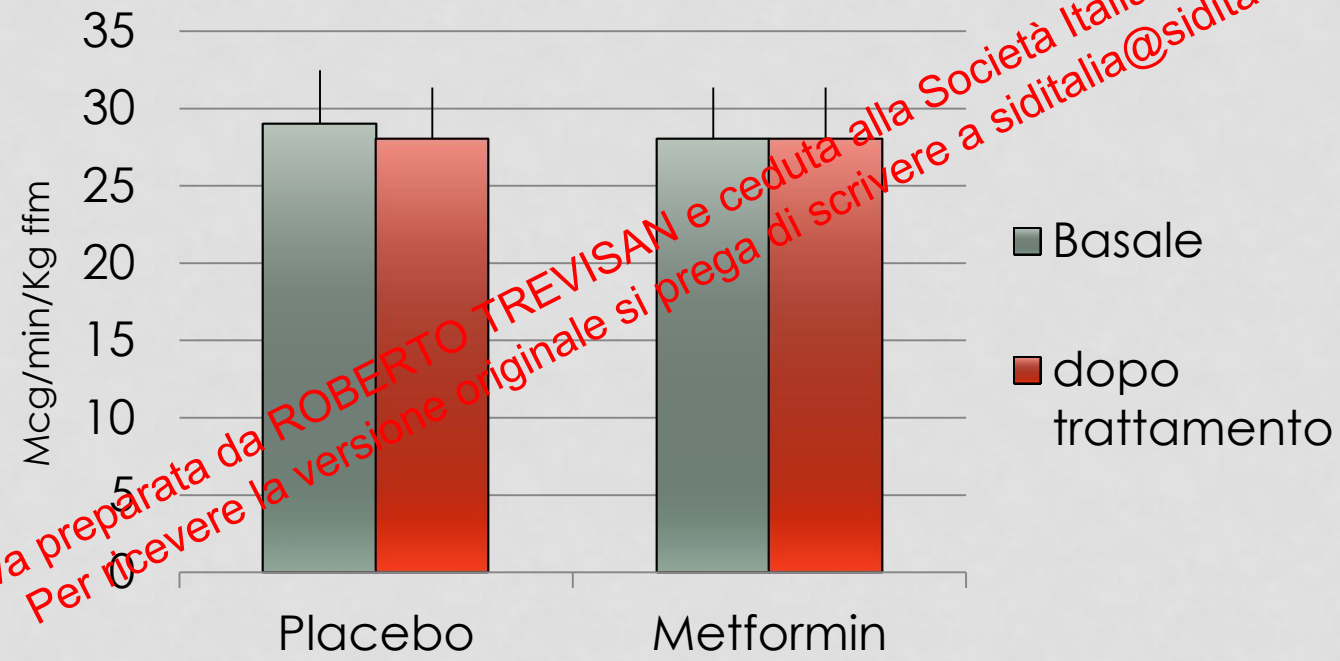


PROPOSED MECHANISMS OF ACTION

- Delayed intestinal glucose absorption,
- Enhanced release of glucagon-like peptide 1
- Augmented lactate production by enterocytes, and activation of **AMPactivated protein kinase** in hepatocytes with consequent decreased glucose production, as well as
- Inhibition of glucagon signaling, glycolytic enzymes, and transcription of gluconeogenic enzymes
- No increase in insulin secretion

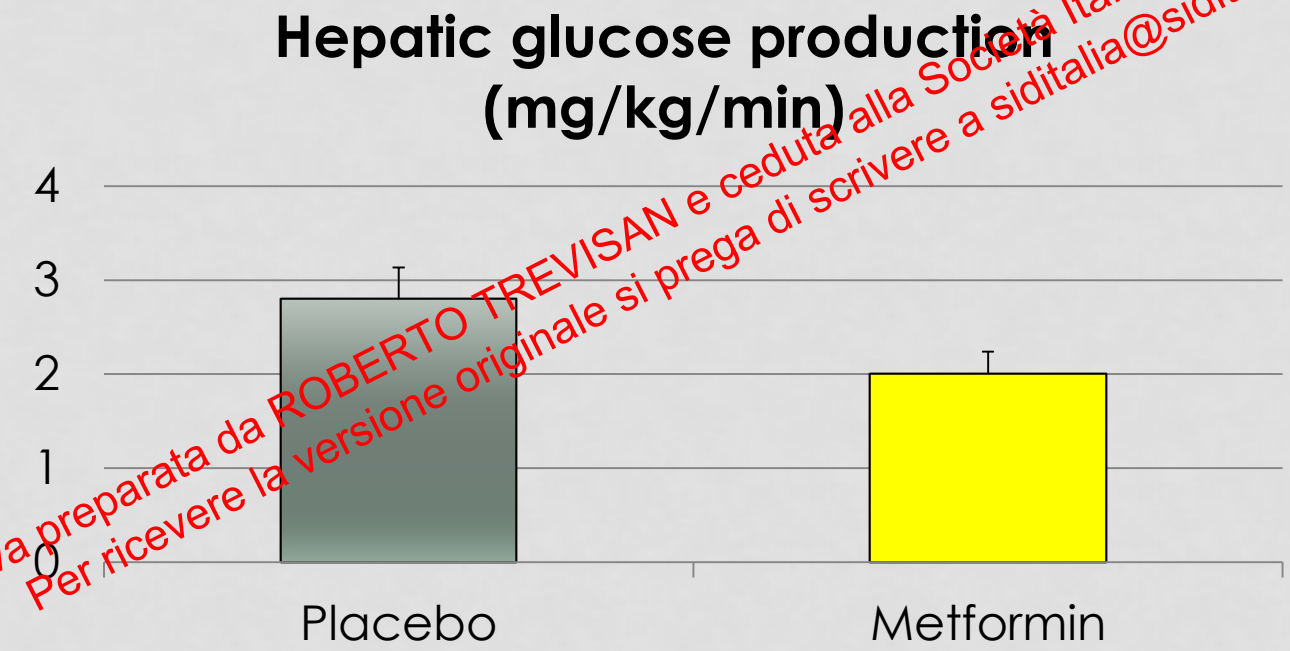
Ferrannini E, NEJM 2014

AT THE WHOLE-BODY LEVEL, METFORMIN ITSELF **DOES NOT AFFECT** INSULIN SENSITIVITY



Diabetes Care 2004;27:1349-57.

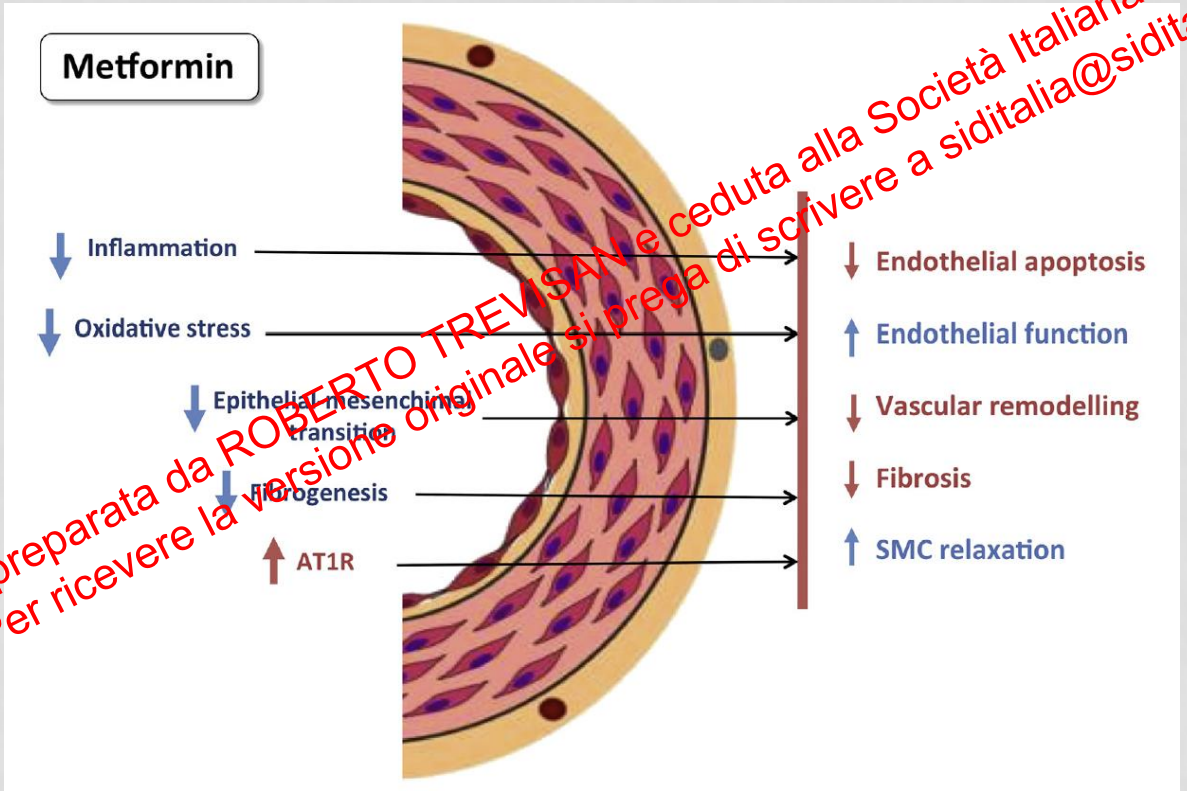
METFORMIN CONSISTENTLY **REDUCES** ENDOGENOUS GLUCOSE PRODUCTION BY **INHIBITING** GLUCONEOGENESIS



Johnson A et al. Metabolism 42; 1217, 1993

EFFECTS OF METFORMIN ON THE VASCULATURE

METFORMIN CAN INDIRECTLY EXERT A PROTECTIVE EFFECT ON THE VASCULATURE MAINLY BY REDUCING INFLAMMATION AND OXIDATIVE STRESS AND PROTECTING FROM FIBROSIS AND REMODELING



Nutrition, Metabolism & Cardiovascular Diseases (2017) 27, 657e669

METFORMIN: THE GOLD STANDARD

In the crowded firmament of antihyperglycemic agents, the biguanide metformin is the brightest star.

Ferrannini E, NEJM 2014

METFORMINA: CONTROINDICAZIONI?

- **Pazienti con insufficienza renale**
- Pazienti con insufficienza cardiaca
- Pazienti con insufficienza epatica

LA METFORMINA NON HA ALCUN EFFETTO DANNOSO DIRETTO SUL RENE

- Non riduce il flusso renale
- Non ha alcun effetto sul GFR
- Non influenza la escrezione urinaria di albumina
- Non influisce sulla sodiuria

FATTORI DI RISCHIO ASSOCIATI CON MAGGIORE FREQUENZA AD ACIDOSI LATTICA IN PAZIENTI TRATTATI CON METFORMINA

- Shock
- Grave insufficienza epatica
- Disidratazione
- Malattie GI
- IRA
- Sepsi
- Anemia
- IMA
- Neoplasia
- Abuso alcolico
- Mezzo di contrasto

Drug Safety
https://doi.org/10.1007/s40264-019-00854-x
Published online 1 Aug 2019

INCIDENCE OD LACTIC ACIDOSIS IN TYPE 2 DIABETIC PATIENTS

- The overall incidence of lactic acidosis in metformin users with impaired kidney function varies across studies from approximately **3 per 100 000 person-years to 10 per 100 000 person-years** and is generally indistinguishable from the background rate in the overall population with diabetes

Inzucchi et al. JAMA. 2014 December 24; 312(24): 2668–2675

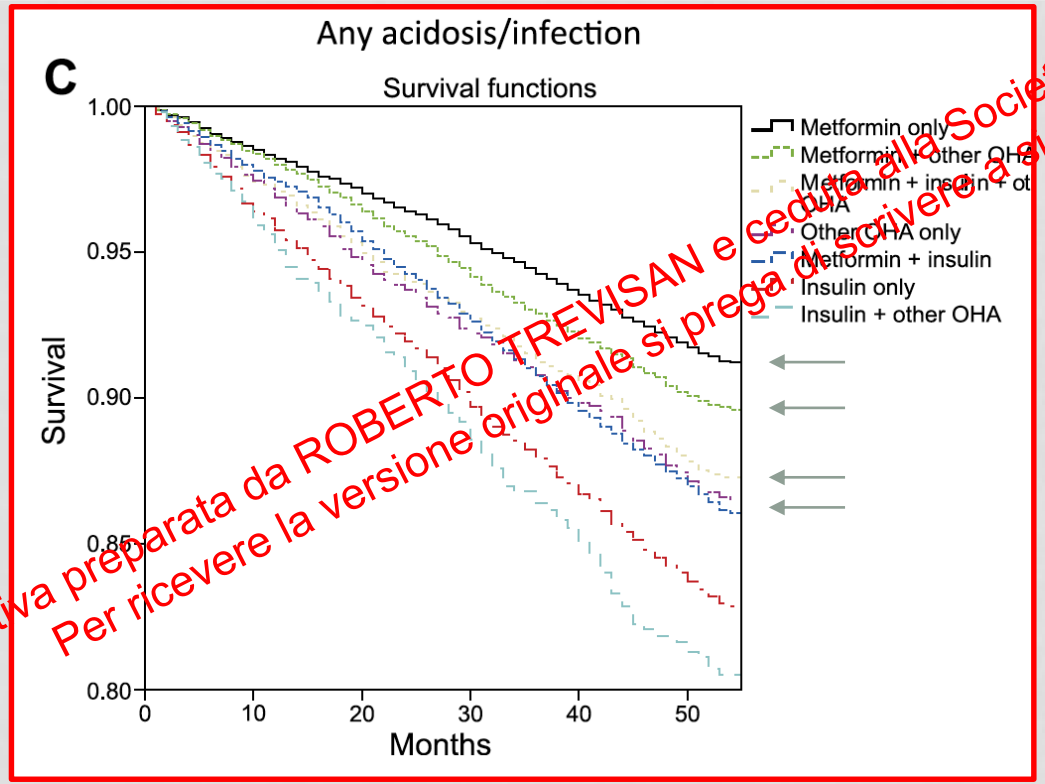
METFORMIN IN PATIENTS WITH TYPE 2 DIABETES AND KIDNEY DISEASE:

A SYSTEMATIC REVIEW

As long as kidney function is stable and the patient is observed closely, metformin is un-likely to measurably increase the risk of lactic acidosis in those with mild to moderate CKD (ie, eGFR 30-60 mL/min per 1.73 m2).

Inzucchi et al. JAMA. 2014 December 24; 312(24): 2668–2675

METFORMIN WAS ASSOCIATED WITH **REDUCED RISK OF CVD, ACIDOSIS/SERIOUS INFECTION AND ALL-CAUSE MORTALITY** COMPARED WITH INSULIN AND A REDUCED RISK OF ALL-CAUSE MORTALITY COMPARED WITH OTHER OHAS



- a cohort study of 51675 type 2 diabetes patients
- 4 yrs follow up
- The effects were consistent in patients with renal impairment (eGFR 45 e 60 ml/min/1.73 m2)
- there were no increased risk of acidosis/serious infection **even in patients with low renal function**

BMJ Open 2012;2:e001076.

RISK OF ACUTE KIDNEY INJURY AND SURVIVAL IN PATIENTS TREATED WITH METFORMIN: AN OBSERVATIONAL COHORT STUDY

25144 patients were included with a total person-time of 126,904 person years. 4944 (19.7%) people had at least one episode of AKI during the study period. There were 32.4 cases of first AKI/1000pyrs on current metformin exposed person-time periods compared to 44.9 cases/1000pyrs in unexposed periods.

Table 5 Hazard ratios (95% CI) for AKI associated with metformin exposure compared to non-exposure by baseline eGFR

eGFR (ml/min/1.73)	<30	30-60	>60
Number of events	88	733	681
HR (95% CI)	0.45 (0.10,1.91)	0.80 (0.66,1.0)	0.76 (0.62,0.95)
p	0.28	0.05	0.01

Bell et al. BMC Nephrology (2017) 18:163

Annals of Internal Medicine

REVIEW

Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease

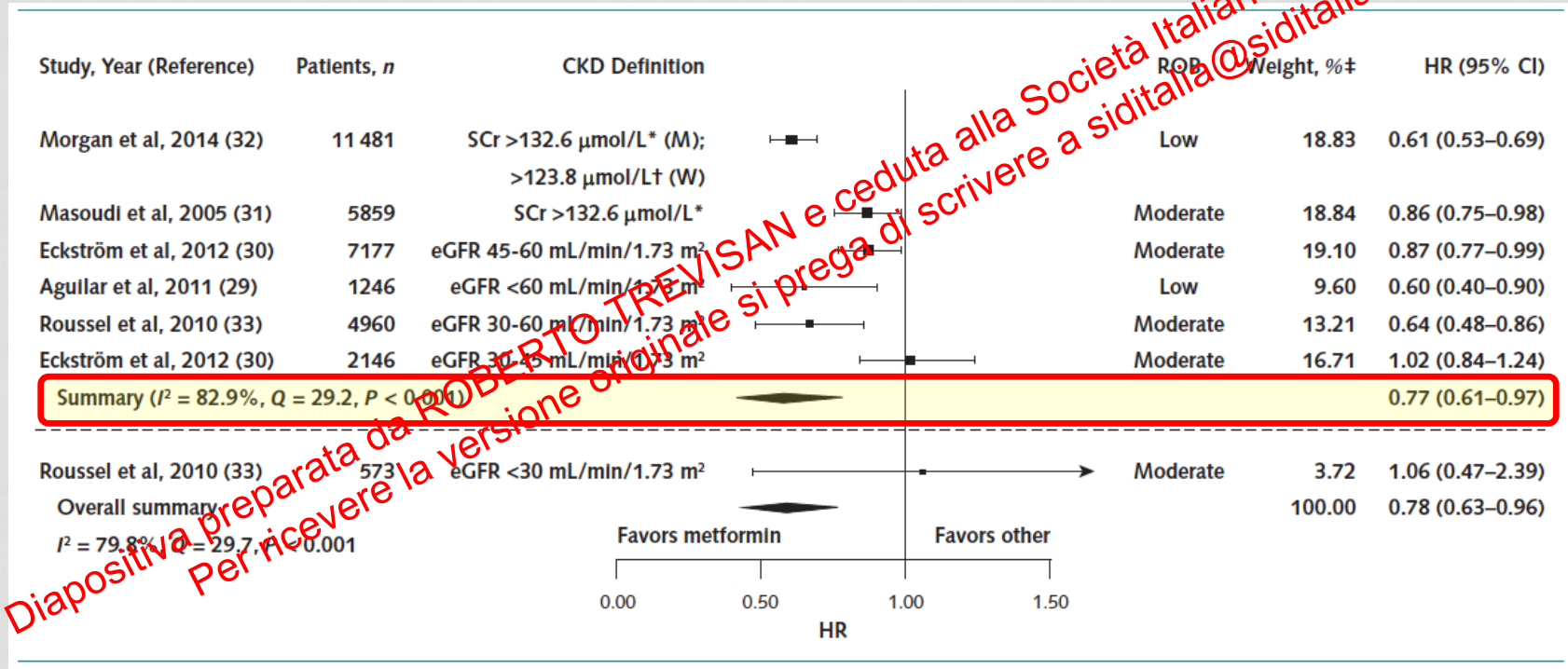
A Systematic Review

Matthew J. Crowley, MD, MHS; Clarissa J. Diamantidis, MD, MHS; Jennifer R. McDuffie, PhD; C. Blake Cameron, MD, MBI; John W. Stanifer, MD, MSc; Clare K. Mock, MD; Xianwei Wang, MD; Shuang Tang, PhD; Avishek Nagi, MS; Andrzej S. Kosinski, PhD; and John W. Williams Jr., MD, MHS

Outcome	Studies, *n*	Patients, *n*
Patients with moderate to severe CKD		
All-cause mortality	5 observational	33 442

Ann Intern Med. 2017;166:191-200.

META-ANALYSIS OF ALL-CAUSE MORTALITY AMONG PATIENTS WITH **MODERATE TO SEVERE CKD** RECEIVING TREATMENT REGIMENS INCLUDING METFORMIN VERSUS THOSE RECEIVING REGIMENS WITHOUT METFORMIN

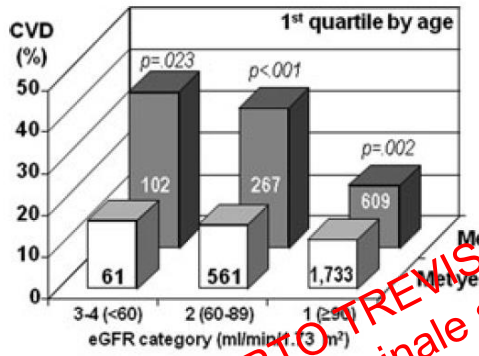


Ann Intern Med. 2017;166:191-200.

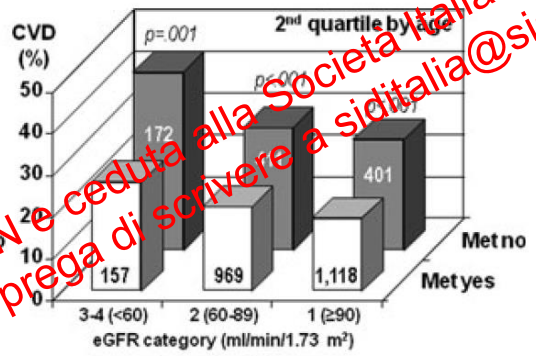
RIACE STUDY

PREVALENCE OF CARDIOVASCULAR DISEASE (CVD) ACCORDING TO QUARTILES OF INCREASING AGE (1–4) ACCORDING TO ESTIMATED GLOMERULAR FILTRATION RATE CATEGORY IN PARTICIPANTS TAKING METFORMIN, ALONE OR IN COMBINATION (MET YES; N = 8,703) VERSUS THOSE TAKING DRUGS OTHER THAN METFORMIN (MET NO; N = 4,944)

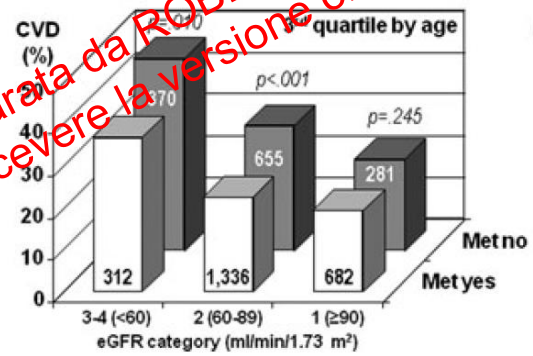
<59 yrs



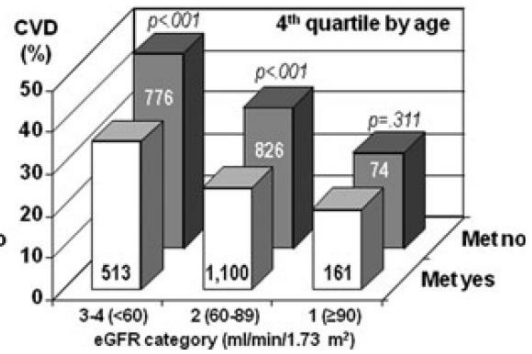
60-66 yrs



67-73 yrs



>74 yrs



J Am Geriatr Soc 61: 1253–1261, 2013.

Original Investigation

September 19, 2019

Association of Treatment With Metformin vs Sulfonylurea With Major Adverse Cardiovascular Events Among Patients With Diabetes and Reduced Kidney Function

Christianne L. Roumie, MD, MPH[1,2]; Jonathan Chipman, PhD[3]; Lea Young Min, PharmD, MPH, PhD[1,4]; et al

» Author Affiliations

67 749 metformin and 28 976 sulfonylurea persistent monotherapy users

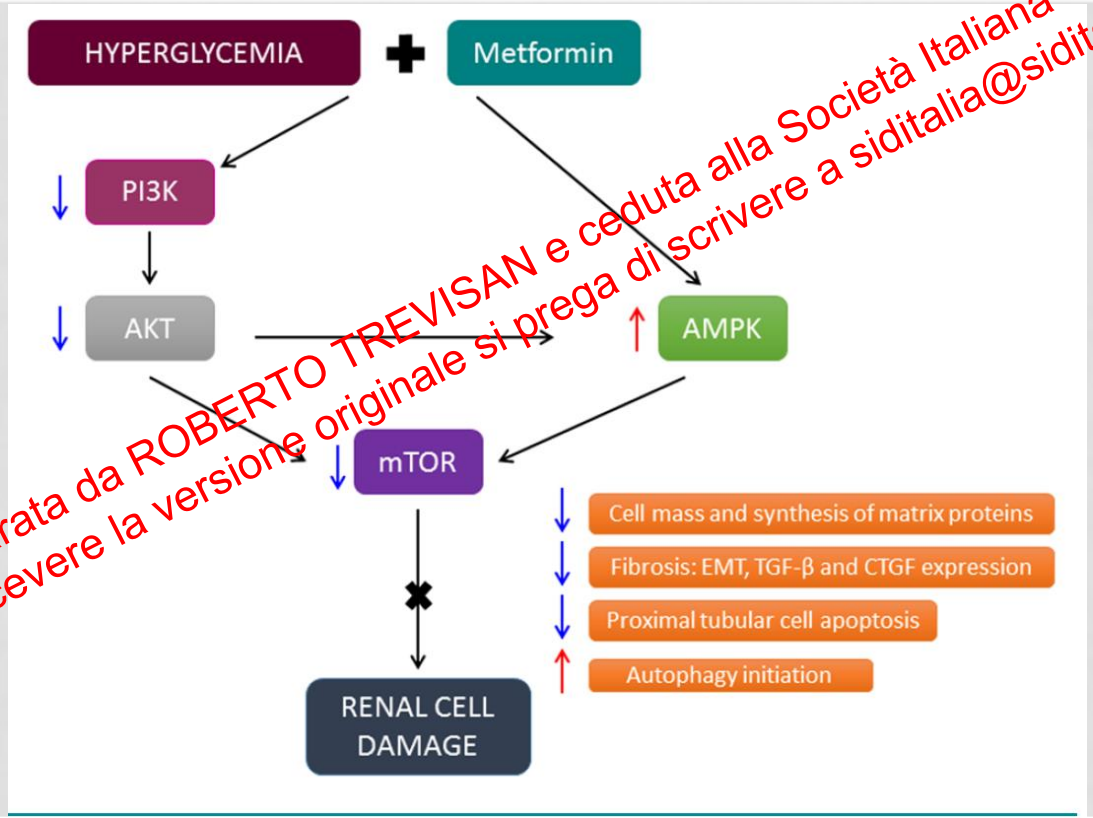
Conclusions and Relevance Among patients with diabetes and reduced kidney function persisting with monotherapy, treatment with metformin, compared with a sulfonylurea, was associated with a lower risk of MACE.

Metformin in T2DM patients with renal impairment

eGFR	Metformin
> 60 ml/min	No problem with metformin Check renal function yearly
45 ÷ 60 ml/min	Keep meformin Check renal function (every 3 -6 months)
30 ÷ 45 ml/min	Be careful in prescribing metformin Use a lower dose Check frequently renal function (every 3 months)
< 30 ml/min	Stop metformin

METFORMIN: NEPHROPROTECTION?

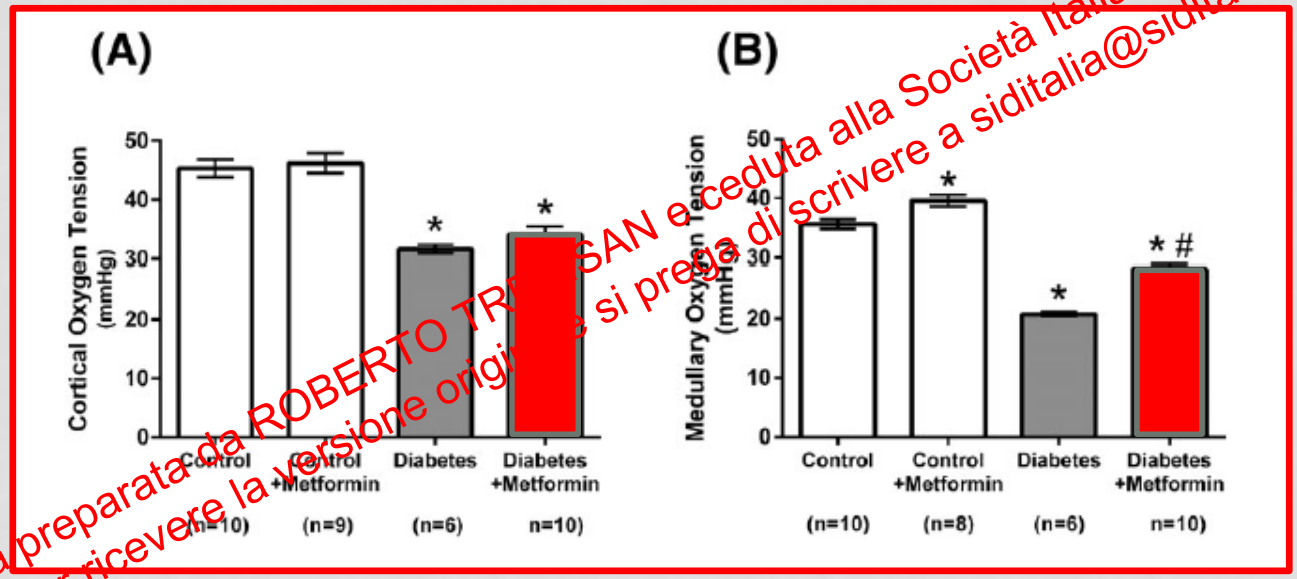
NEPHROPROTECTIVE EFFECTS OF METFORMIN IN DIABETIC NEPHROPATHY



J. Cell. Physiol. 232: 731–742, 2017.

Int. J. Mol. Sci. 2019, 20, 42;

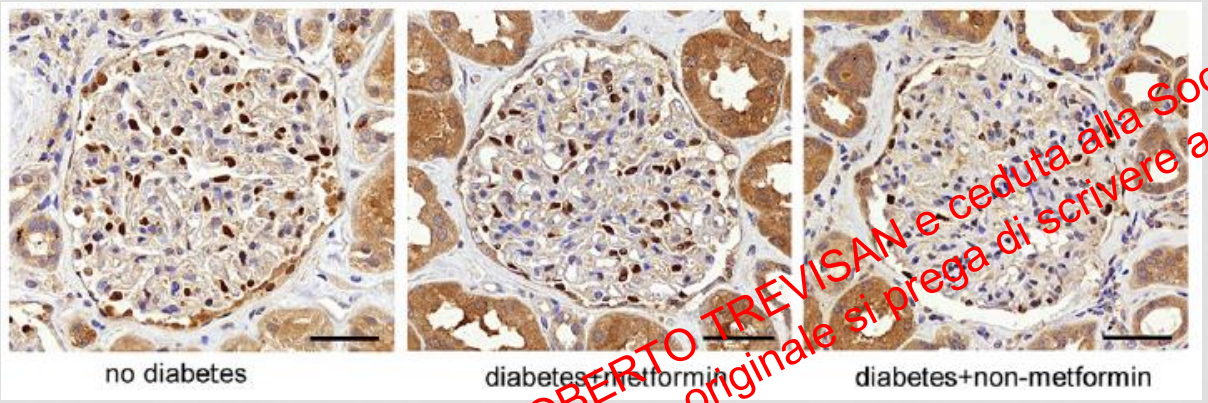
METFORMIN ATTENUATES RENAL MEDULLARY HYPOXIA IN DIABETIC NEPHROPATHY THROUGH INHIBITION UNCOUPLING PROTEIN 2

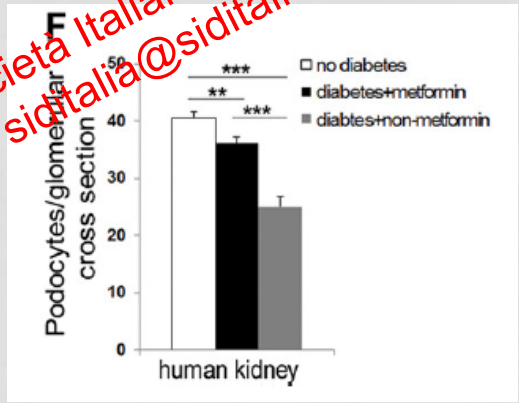


The effect of metformin on diabetes induced medullary hypoxia is independent of blood glucose homeostasis

Diabetes Metab Res Rev. 2019;35:e3091.

METFORMIN INCREASES GLUCOSE UPTAKE AND ACTS **RENOPROTECTIVELY** BY REDUCING **SHIP2** ACTIVITY



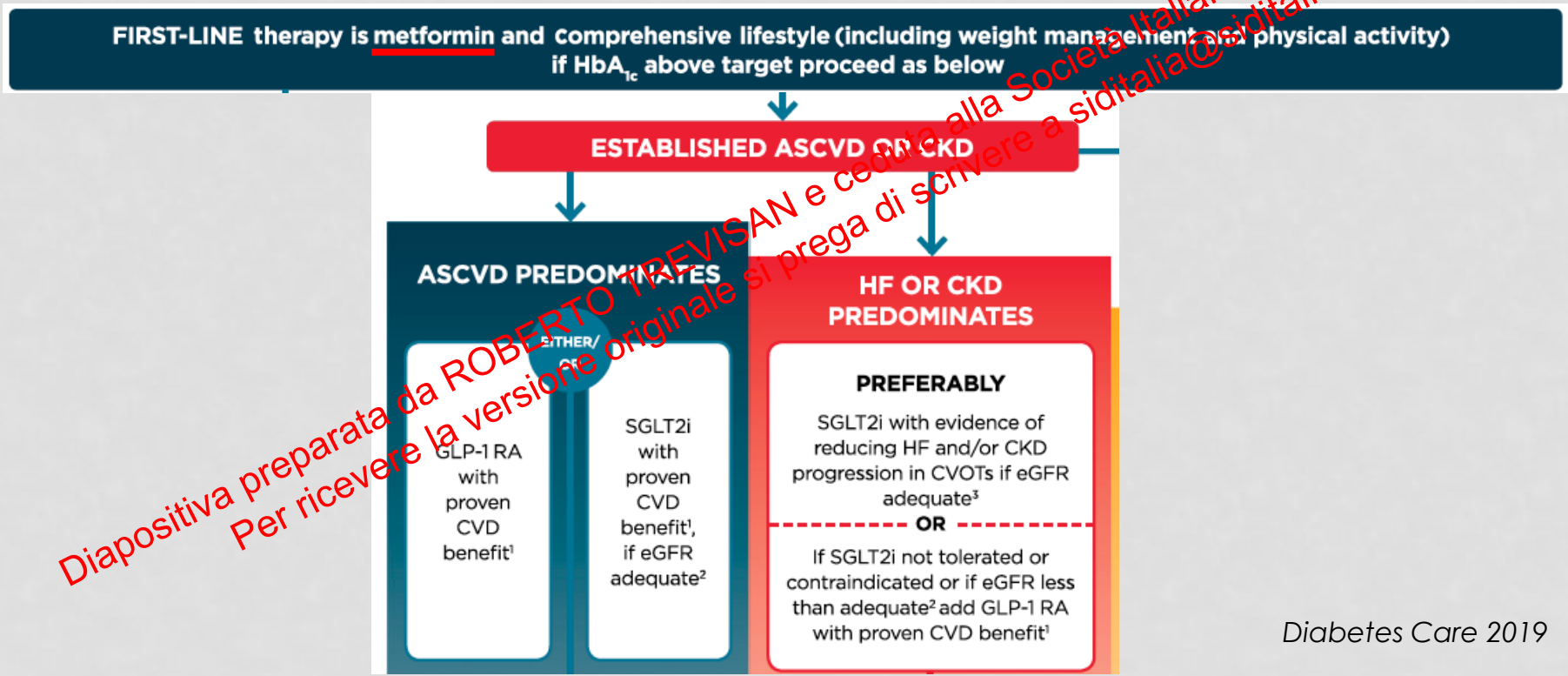


Lipid phosphatase Src homology 2 domain-containing inositol-5-phosphatase 2 (SHIP2) is upregulated in diabetic rodent models and suppresses insulin signaling by reducing Akt activation, leading to insulin resistance and diminished glucose uptake.

SHIP2 activity is elevated in glomeruli of patients with T2D, but not in patients receiving metformin, compared with people without diabetes. Furthermore, podocyte loss in kidneys of metformin-treated T2D patients is reduced compared with patients receiving nonmetformin medication.

FASEB J. 33, 2858–2869 (2019).

STANDARDS OF MEDICAL CARE IN DIABETES
ADA – EASD 2019



Diabetes Care 2019

IL CARDINE DELLA TERAPIA DEL DIABETE DI TIPO 2

Metformina

Statine

ACEi/ARBs

METFORMIN
DO WE FINALLY HAVE AN ANTI-AGING DRUG?

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
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Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results > Study Record Detail Text Size

Trial record **1 of 10** for: metformin ageing
Previous Study | Return to List | Next Study

Metformin in Longevity Study (MILES)

This study is currently recruiting participants. (see Contacts and Locations)
Verified April 2015 by Albert Einstein College of Medicine of Yeshiva University

Sponsor:
Albert Einstein College of Medicine of Yeshiva University

Information provided by (Responsible Party):
Albert Einstein College of Medicine of Yeshiva University

ClinicalTrials.gov Identifier:
NCT02432287

First received: February 24, 2015
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Last verified: April 2015
History of Changes

Received: 11 May 2019 | Revised: 16 July 2019 | Accepted: 4 August 2019
DOI: 10.1111/acel.13028

ORIGINAL ARTICLE

Aging Cell WILEY

Reversal of epigenetic aging and immunosenescent trends in humans

Gregory M. Fahy[1] | Robert T. Brooke[1] | James P. Watson[2] | Zinaida Good[3] | Shreyas S. Vasanawala[4] | Holden Maecker[5] | Michael D. Leipold[5] | David T. S. Lin[6] | Michael S. Kobor[6] | Steve Horvath[7]