Department of Organs Insufficiency and Transplatations

Sant'Orsola-Malpighi Hospital
IRCCS

University Hospital

Bologna - ITALY

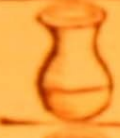
Le novità per la cura della malattia renale cronica dalla prevenzione alla terapia dialitica

Antonio Santoro F.E.R.A.

Albus color vt aqua fontis.

Glaucus color vt cornu lucidū

Lacteꝰ color vt ferum lactis.

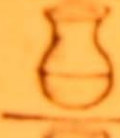


Caropos color vt vellus cameli.

Subpallidus color vt succus carnis semicoctus non remisse.

Remissus pallidus vt succꝰ carnis semicoctꝰ remissi.

Subcrinus vt pomi subacrini non remissus



Citrinꝰ color vt pomi citrini remissi.

Subrussus color vt aurum remissum.

Russus vt aurū parū intensum

Subrubicūdus color vt croꝯ occidentalis.

Rubeus vt croꝯ orientalis.

Subrubicūdus vt flāma ignis remissa.

Rubicundus vt flāma ignis nō remissa.

Inops color vt e pars animalis.

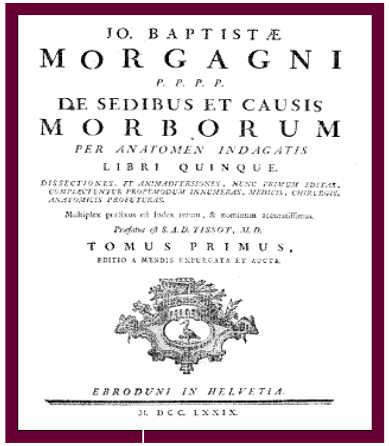
Kyanos color vt vinum bene nigrum.

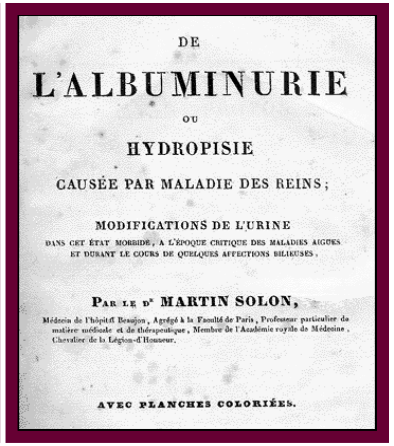
Viridis color vt caulis viridis.

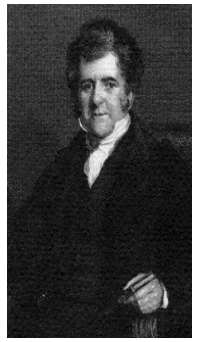
Luteꝰ color vt plumbum.

Niger vt incaustum.

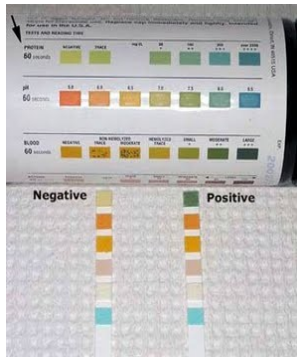
Niger vt cornus bene nigrum.

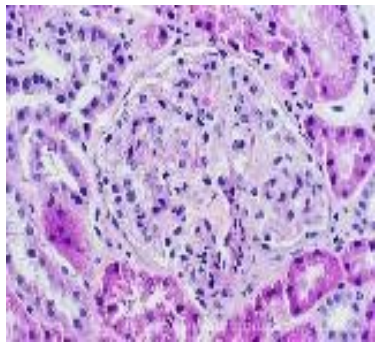

JO. BAPTISTÆ
MORGAGNI
P. P. P. P.
DE SEDIBUS ET CAUSIS
MORBORUM
PER ANATOMEN INDAGATIS
LIBRI QUINQUE.
TOMUS PRIMUS,
EBRODUNI IN HELVETIA.
M. DCC. LXXIX.

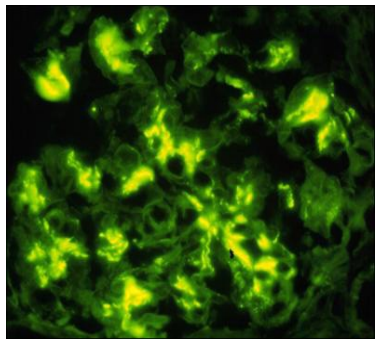

DE
L'ALBUMINURIE
OU
HYDROPISIE
CAUSÉE PAR MALADIE DES REINS;
MODIFICATIONS DE L'URINE
DANS CET ÉTAT MORBIDE, A L'ÉPOQUE CRITIQUE DES MALADIES AIGUES ET DURANT LE COURS DE QUELQUES AFFECTIONS BILIEUSES.
PAR LE Dr MARTIN SOLON,
AVEC PLANCHES COLORIÉES.

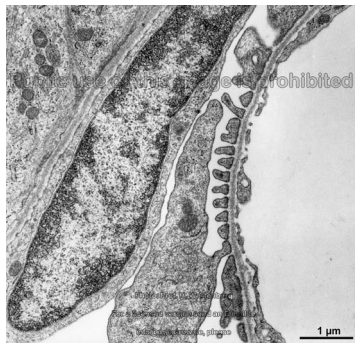

Richard Bright.

RICHARD BRIGHT,
M.D.F.R.S.
Physician Extraordinary
to the Queen

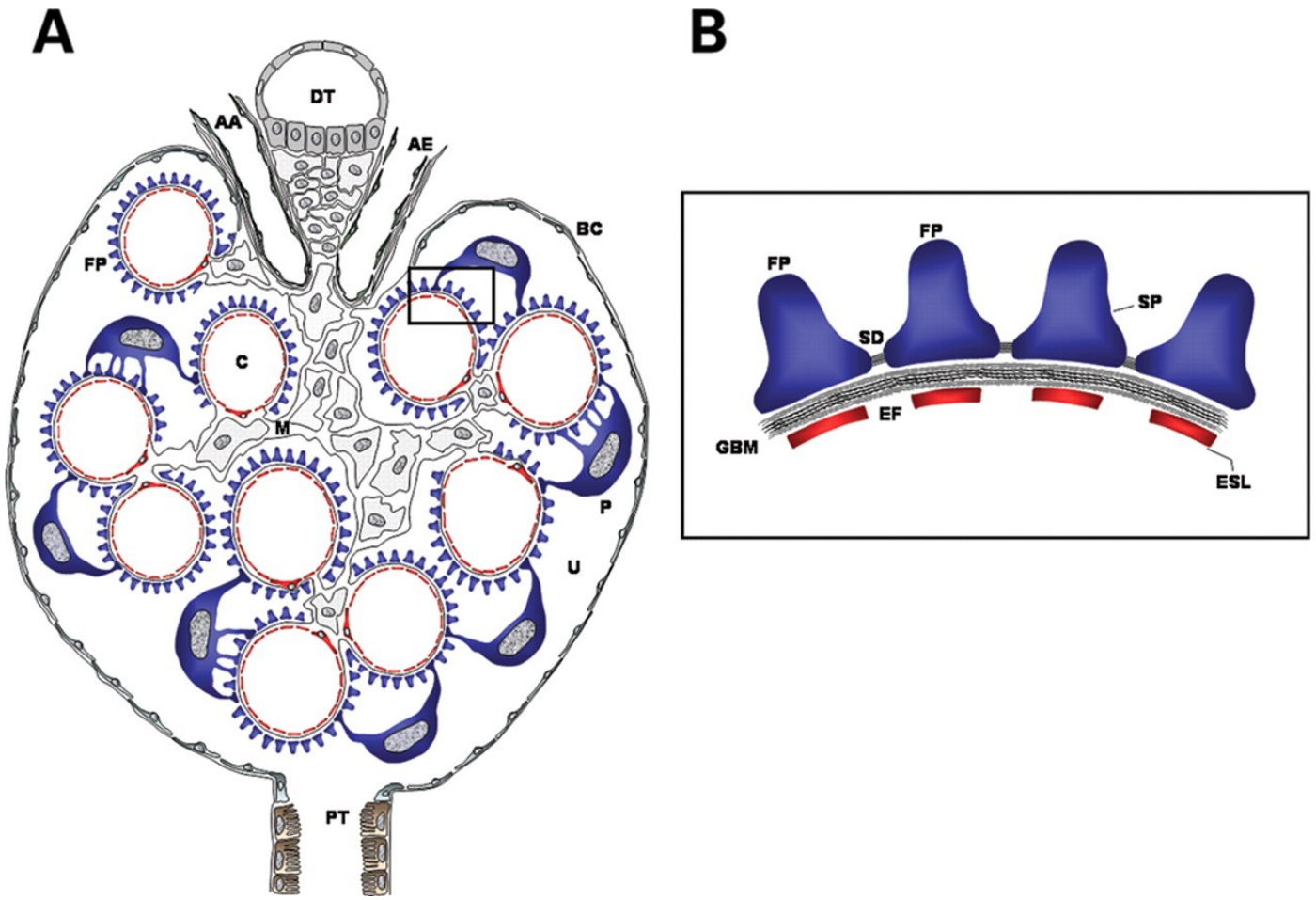






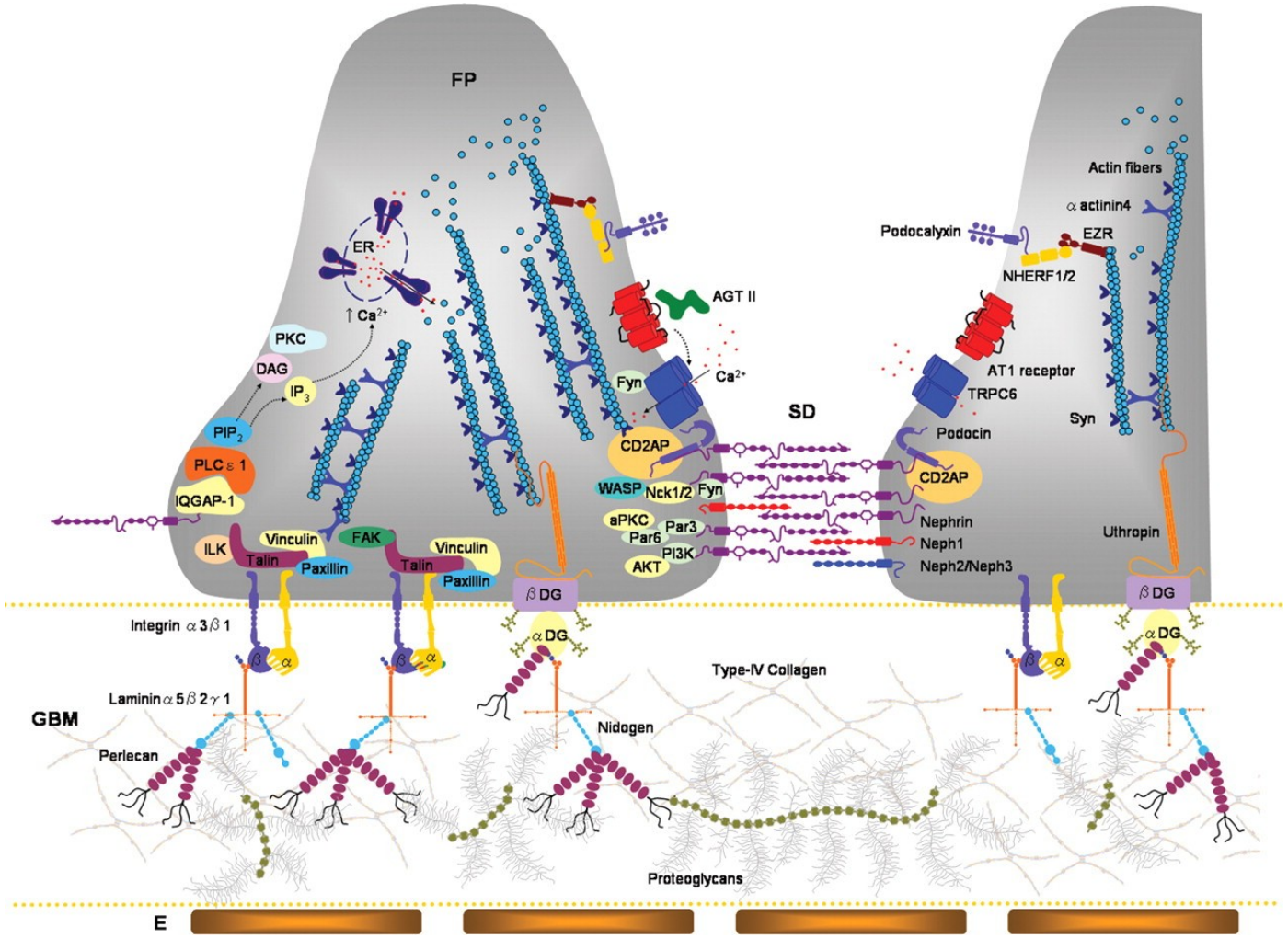


Glomerular filtration barrier structure

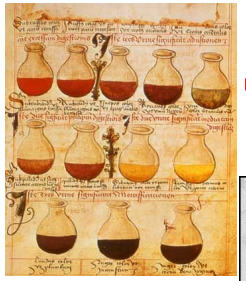


- I podociti sono cellule presenti nel rene, più precisamente nel nefrone a livello del corpuscolo renale (di Malpighi), dove vanno ad abbracciare con numerosi prolungamenti (processi maggiori), al pari dei tentacoli di una piovra, i capillari glomerulari, affiancandosi agli analoghi processi dei podociti adiacenti.
- Diversi meccanismi patogenetici hanno linee convergenti in quanto il riarrangiamento del citoscheletro di actina del podocita è stato identificato come un denominatore comune di una varietà di disturbi glomerulari .
- Il setaccio molecolare formato dalla barriera di filtrazione glomerulare non è una struttura statica. In effetti, lo strato di podociti può essere considerato come una rete particolarmente dinamica di cellule interagenti,che contengono un apparato contrattile a base di actina.
- Sembra probabile che la capacità dei podociti di percepire e adattarsi continuamente ai cambiamenti ambientali sia fondamentale per preservare la permselettività glomerulare. Il danno sul podocita genera riorganizzazione del diaframma a fessura e della struttura del processo peducellare.

Molecular overview of the slit-diaphragm and podocyte cell-matrix interactions



Human
Molecular Genetics



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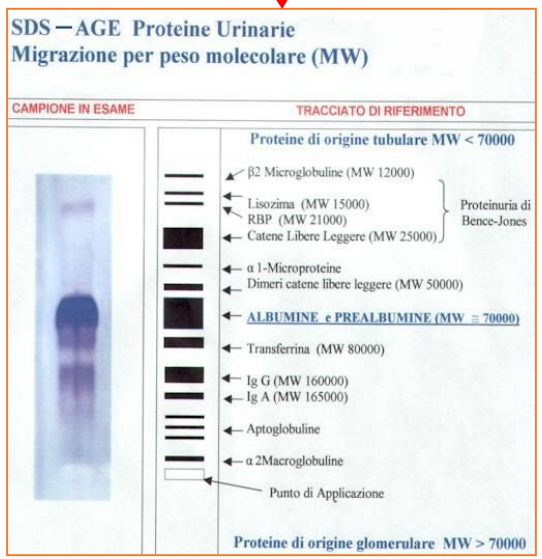
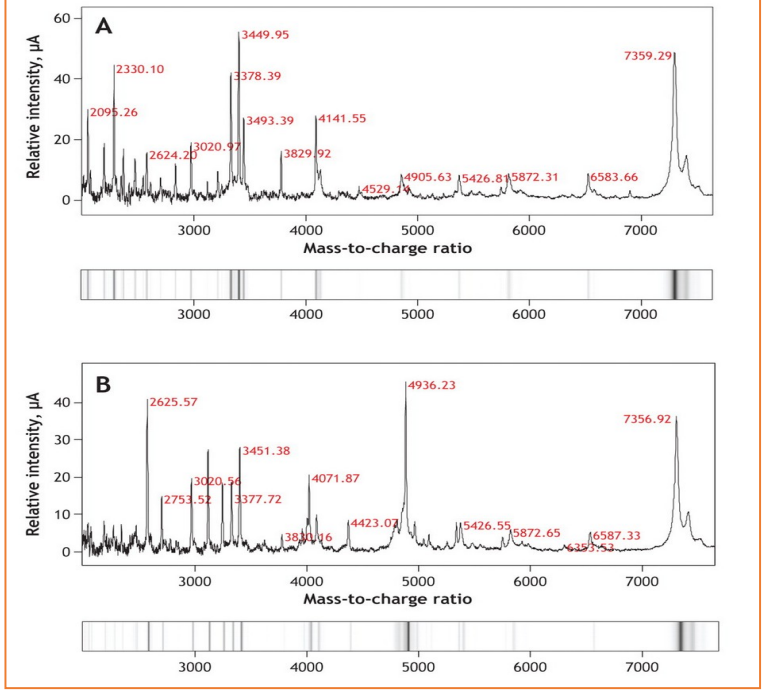


Urinary proteomics



Le scienze omiche

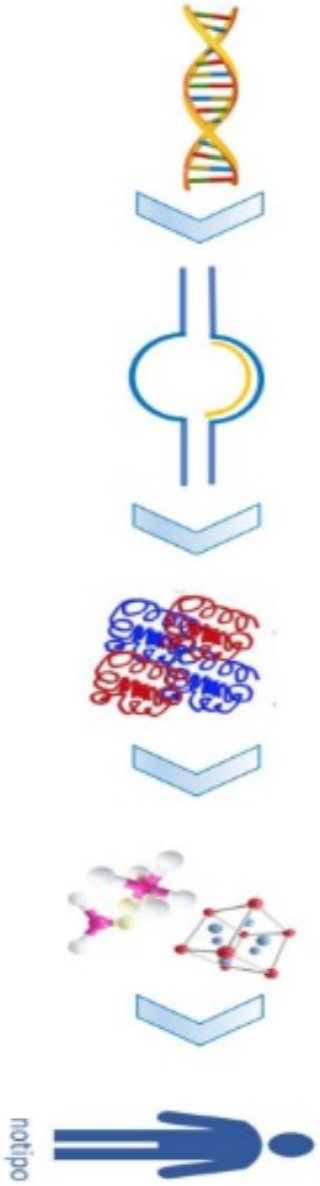
Genomica

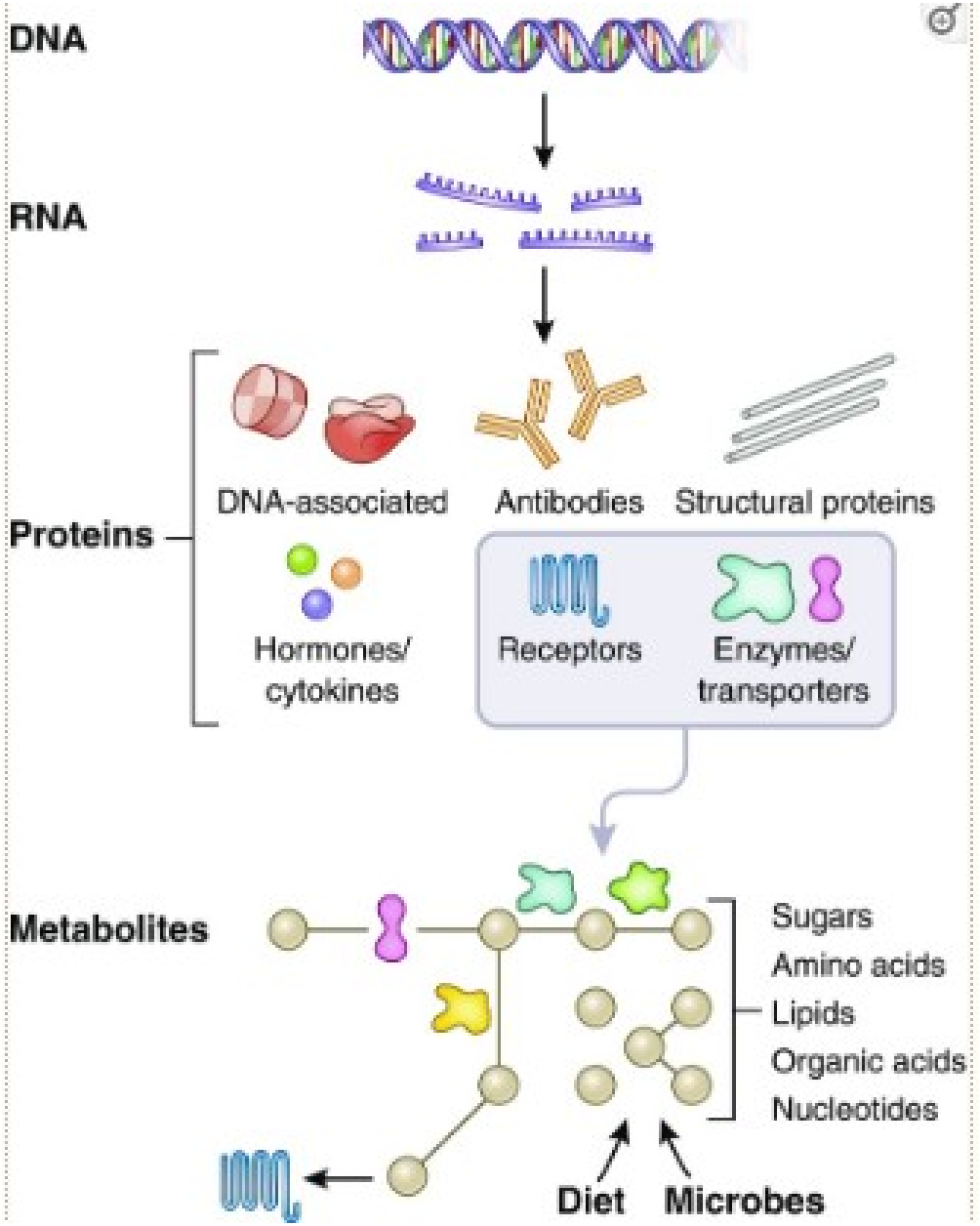
Trascrittomica

Proteomica

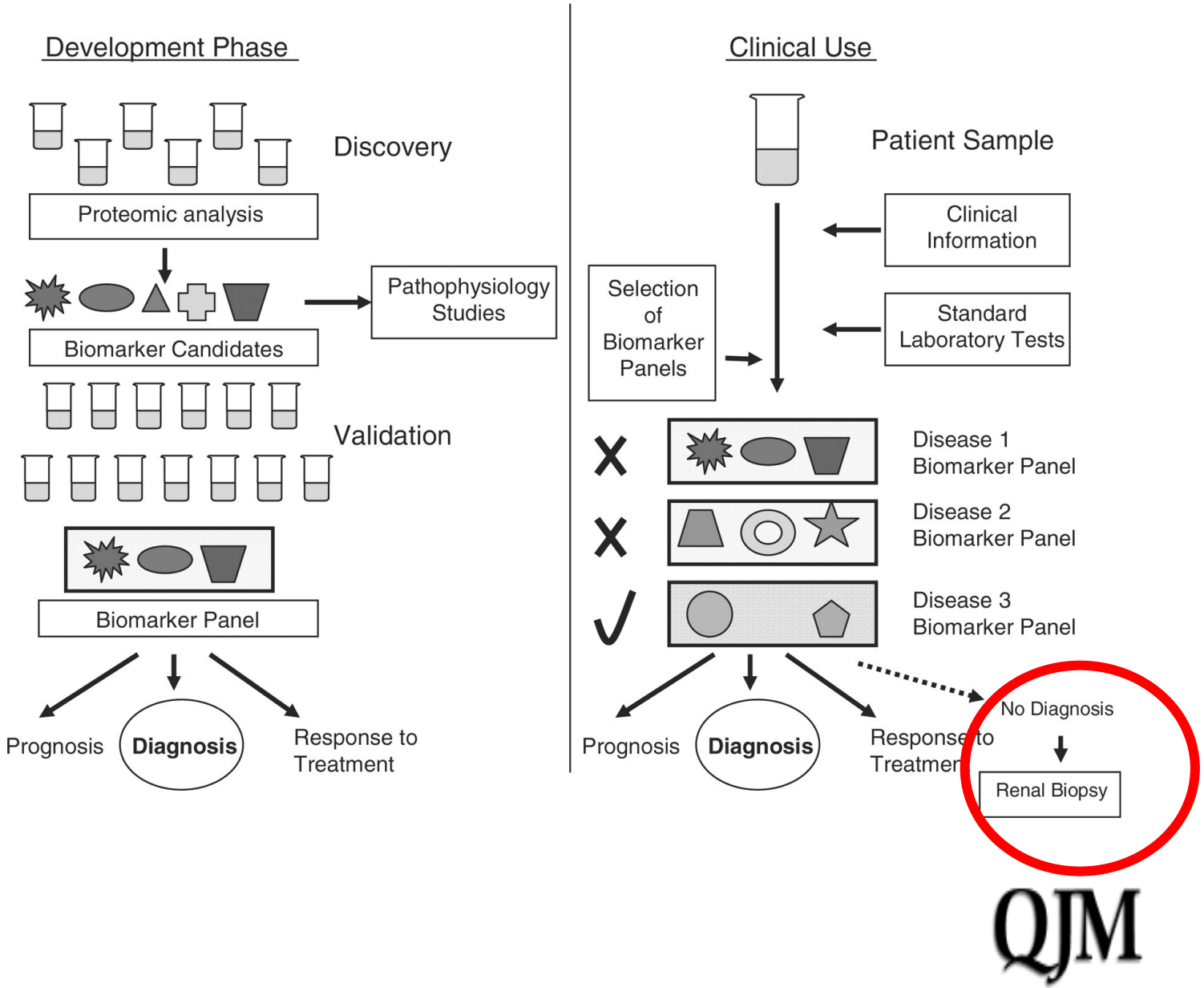
Metabolomica

Fenotipo





Schema of translation of urinary proteomics into clinical practice

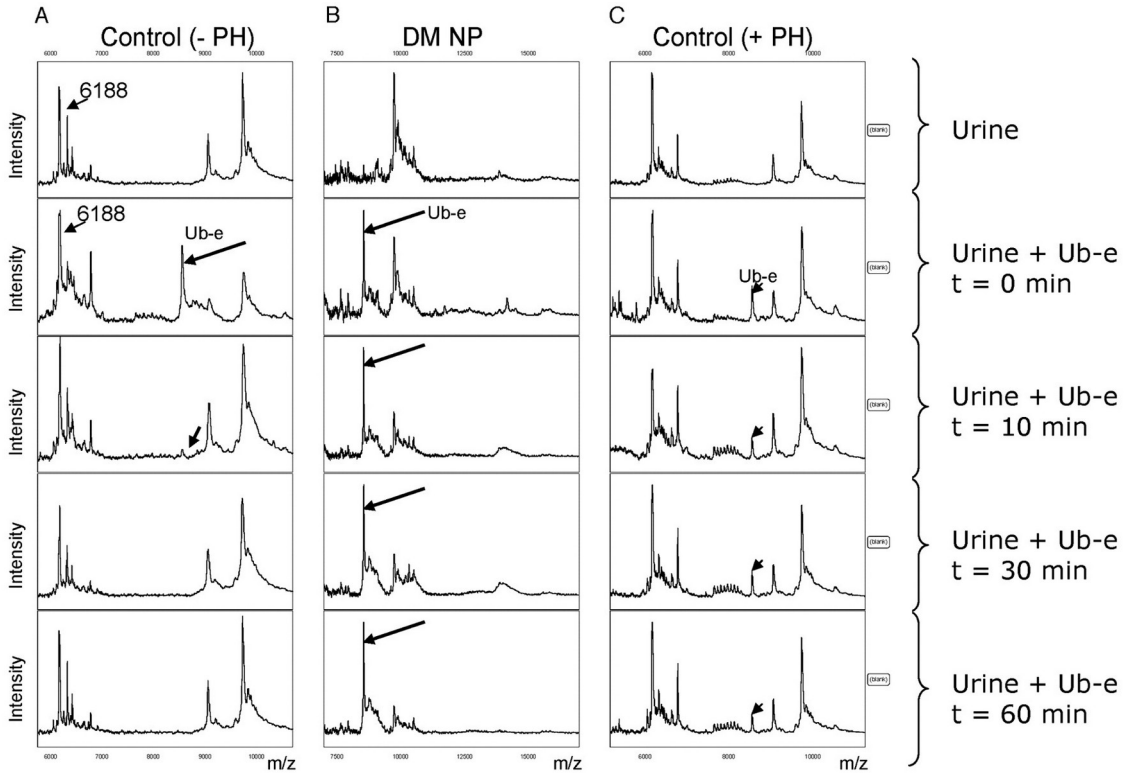


QJM

Characterization of Diabetic Nephropathy by Urinary Proteomic Analysis: Identification of a Processed Ubiquitin Form as a Differentially Excreted Protein in Diabetic Nephropathy Patients

Hassan Dihazi et al. Clinical Chemistry 2007; 53: 1636-1645

Ubiquitin degradation assay



In summary, in this pilot study we identified 3 different proteins that were differentially excreted in the urine of diabetic nephropathy patients compared with the other groups. A processed form of ubiquitin with *m/z* 6188 was missed in the urine of diabetic nephropathy patients.

This ubiquitin form could be used as a prognosis marker for DM-NP. Quantification of this protein during the progressive disease course in the DM-NP patients will give interesting information on the development of the diseases and serve as a good marker for prognosis.

ARIC, Atherosclerosis Risk in Communities; CRIC, Chronic Renal Insufficiency Cohort; CKD, chronic kidney ...

Key Question

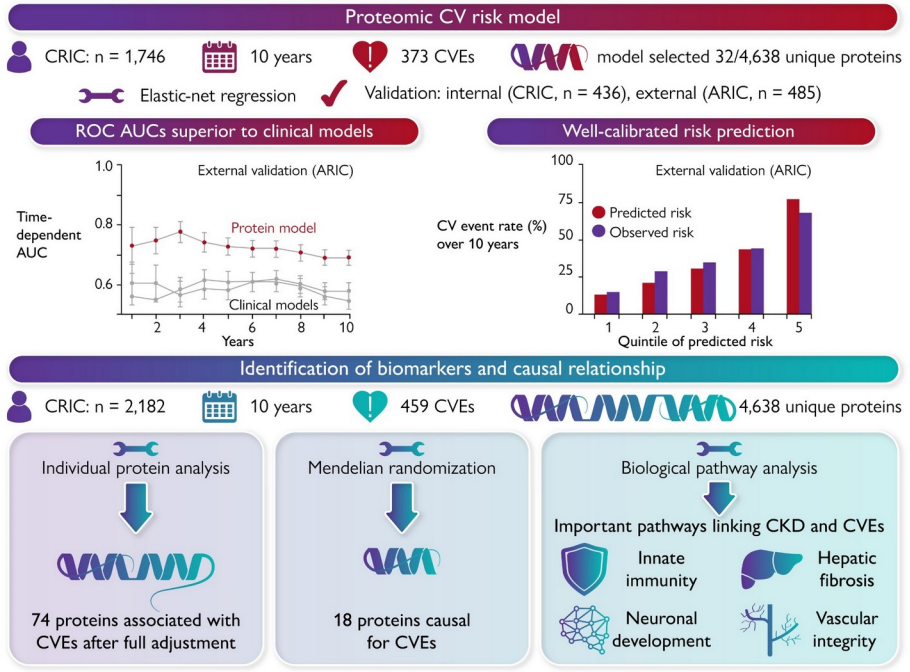
Chronic kidney disease (CKD) is widely prevalent and increases the risk of cardiovascular disease. Risk prediction algorithms have not been developed specifically for CKD patients. Can proteomics identify CKD patients at high risk for cardiovascular disease?

Key Finding

After measuring nearly 5,000 proteins in 2,667 participants with CKD from two different longitudinal cohorts, an elastic-net regression was used to develop a 32-protein risk model. The proteomic risk model surpassed clinical risk models for predicting incident cardiovascular disease.

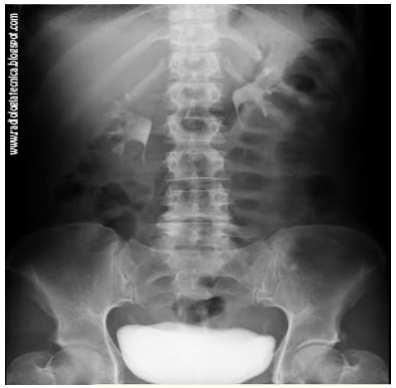
Take Home Message

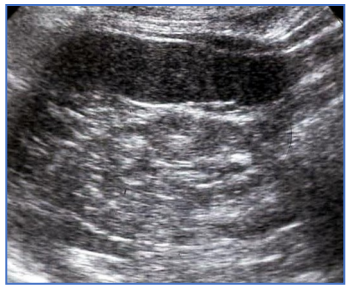
Machine learning and large-scale proteomics can form the foundation for cardiovascular risk models among patients with CKD. Additional biological insights can help to prioritize the development of novel therapeutics.

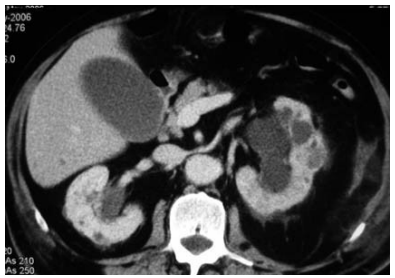


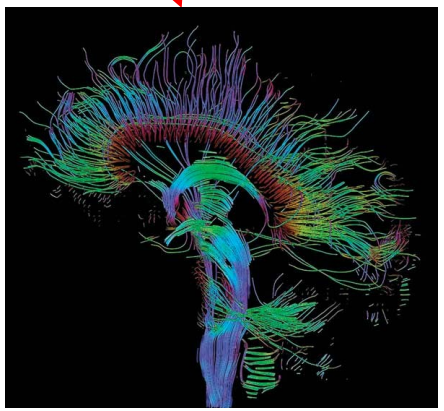
Eur Heart J, ehad115, https://doi.org/10.1093/eurheartj/ehad115

DIAGNOSTICA, passato, presente , futuro

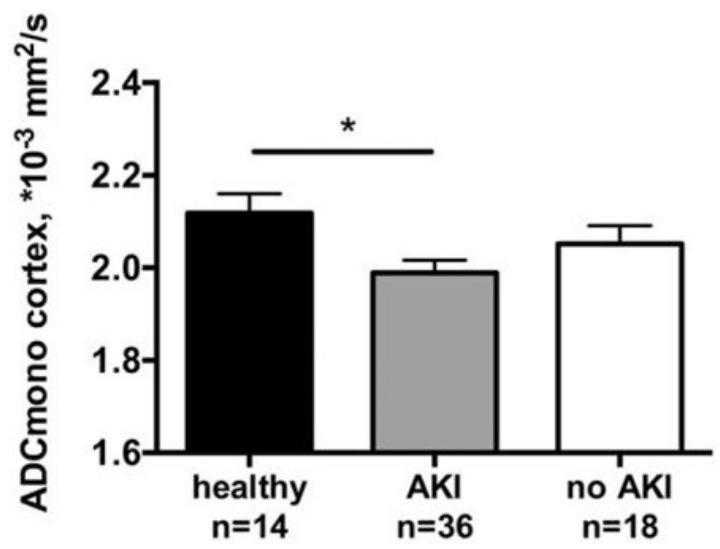




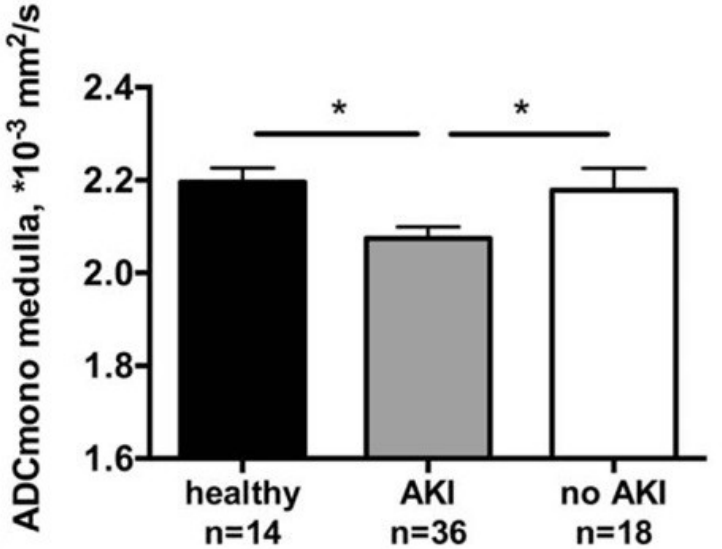




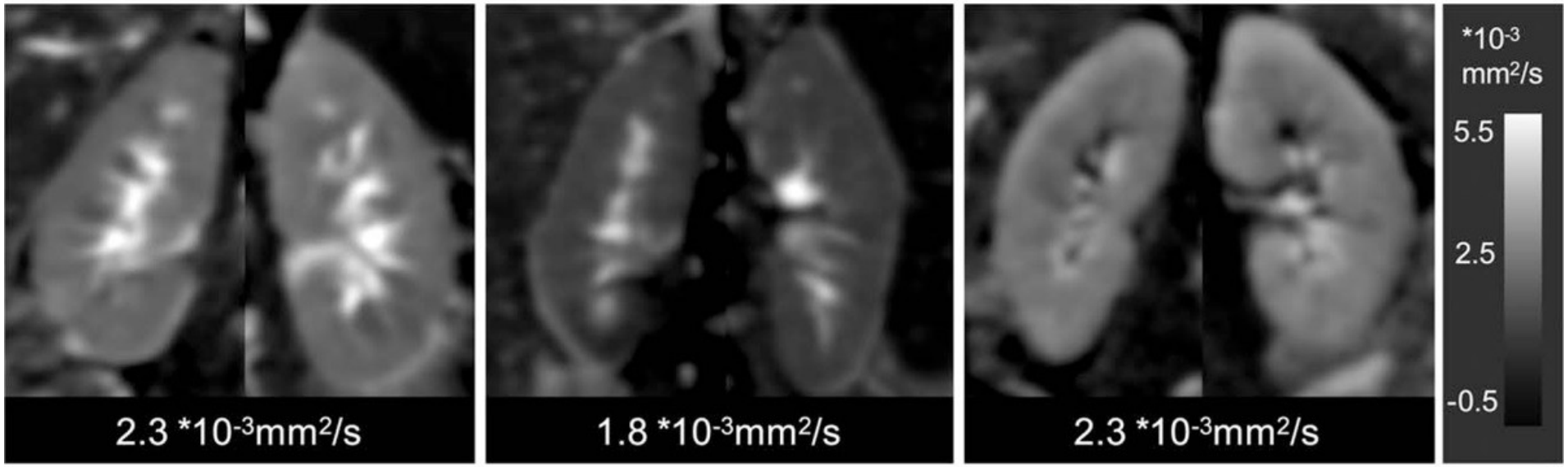
Risonanza magnetica a diffusione



A



B



C healthy AKI no AKI

Diffusion-Magnetic Resonance Imaging predicts decline of kidney function in chronic kidney disease and in patients with a kidney allograft.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Cohort

Is diffusion MRI predictive of renal function decline (>30% eGFR decline or dialysis initiation)?

197 patients

155 kidney allograft patients

42 native kidney patients

Methods

Patients underwent diffusion MRI (ΔADC) on the same week as the biopsy

MRI

+

BIOPSY

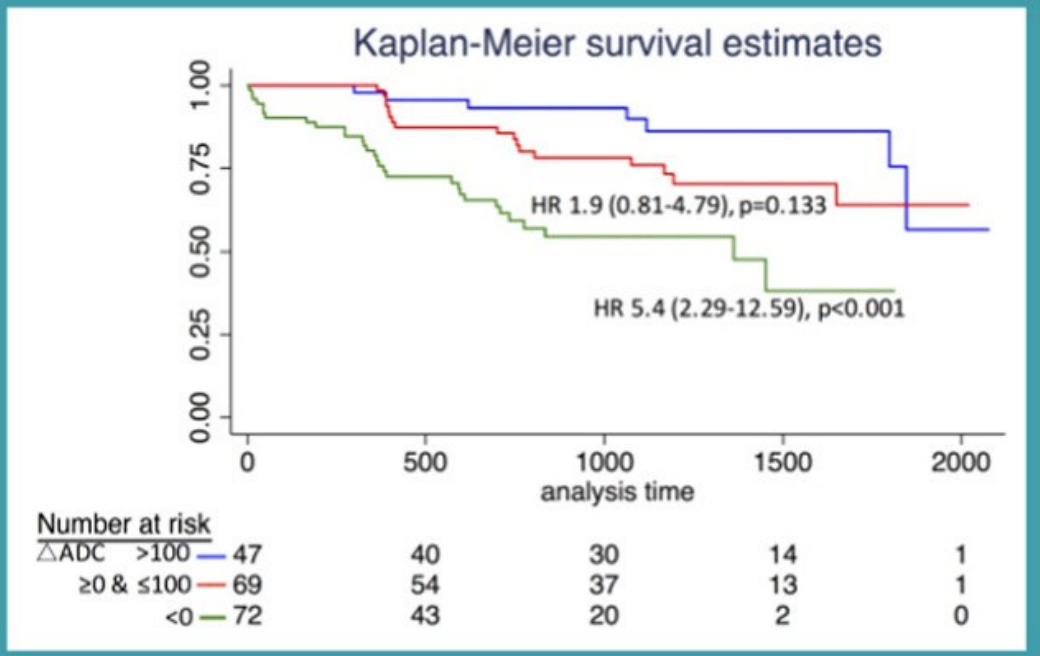
↓

Follow-up of 5 years

Outcomes

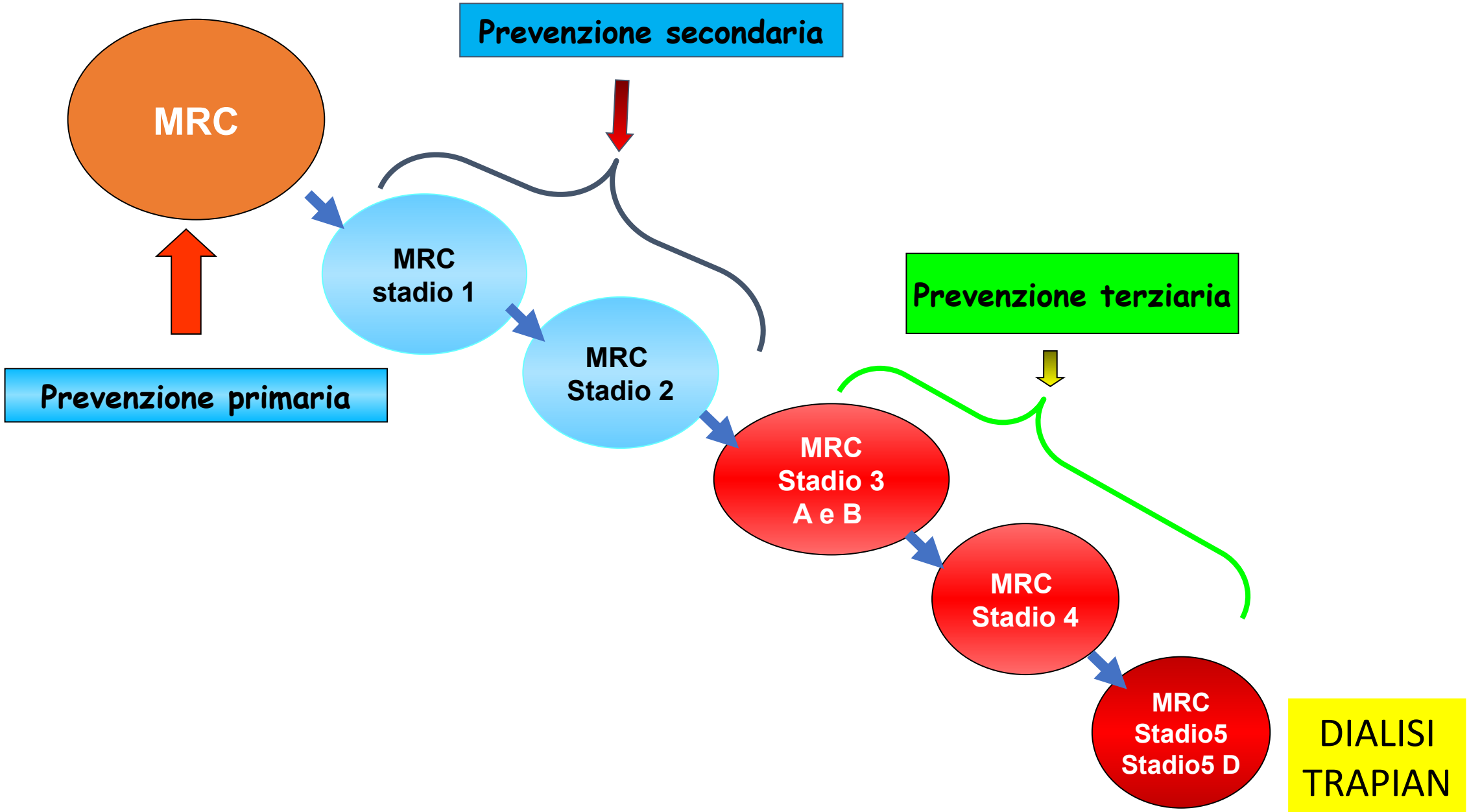
Low ΔADC had 5.4 more risk of rapid decline of renal function or dialysis (95%CI 2.29-12.58; p<0.001).

After correction for renal function at baseline and proteinuria, low ΔADC still predict decline of renal function with an HR of 4.62 (95%CI: 1.56-13.67, p<0.001).

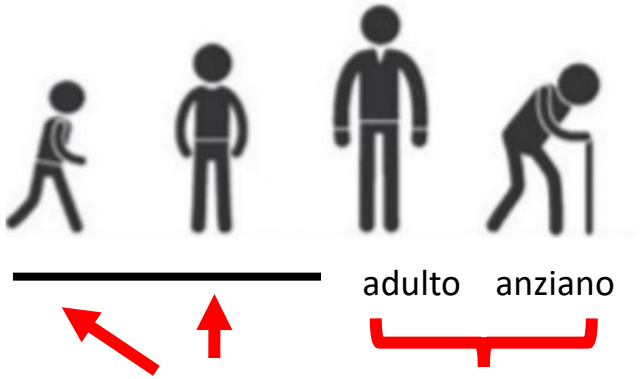


Berchtold et al, 2021

CONCLUSION: Low ΔADC is a predictor of renal function decline and dialysis initiation in CKD and kidney allograft patients, independent of baseline function and proteinuria.


MRC
Prevenzione secondaria
MRC
stadio 1
MRC
Stadio 2
Prevenzione terziaria
Prevenzione primaria
MRC
Stadio 3
A e B
MRC
Stadio 4
MRC
Stadio5
Stadio5 D
DIALISI
TRAPIAN
TO

La prevenzione primaria

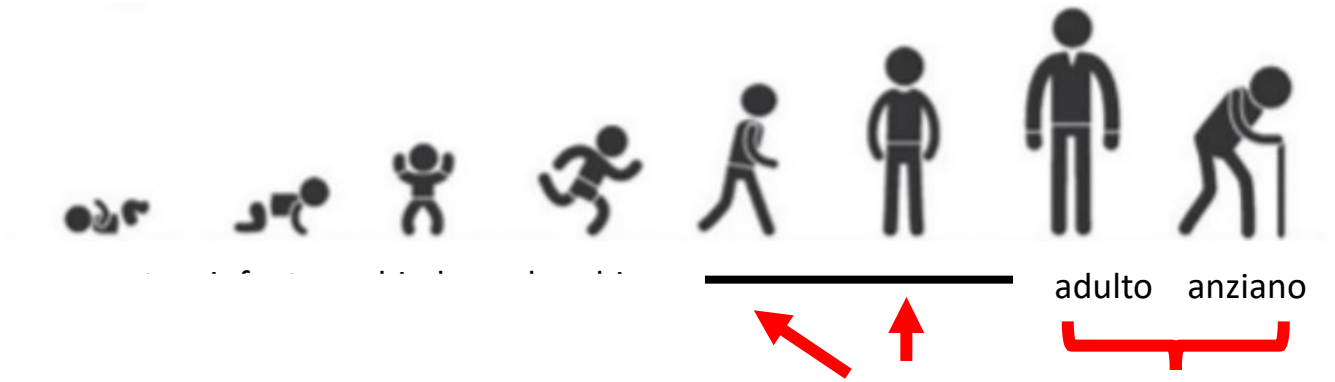


Stile di vita salutare

Corretta nutrizione (poco sale. non diete iperproteiche, preferire vegetali, ecc.)
Evitare obesità
Esercizio fisico regolare
Evitare farmaci nefrotossici e fumo di sigarette
Limitare alcol

Screening per MRC, DM, MCV
Diagnosi precoce

La prevenzione primaria nelle varie epoche della vita



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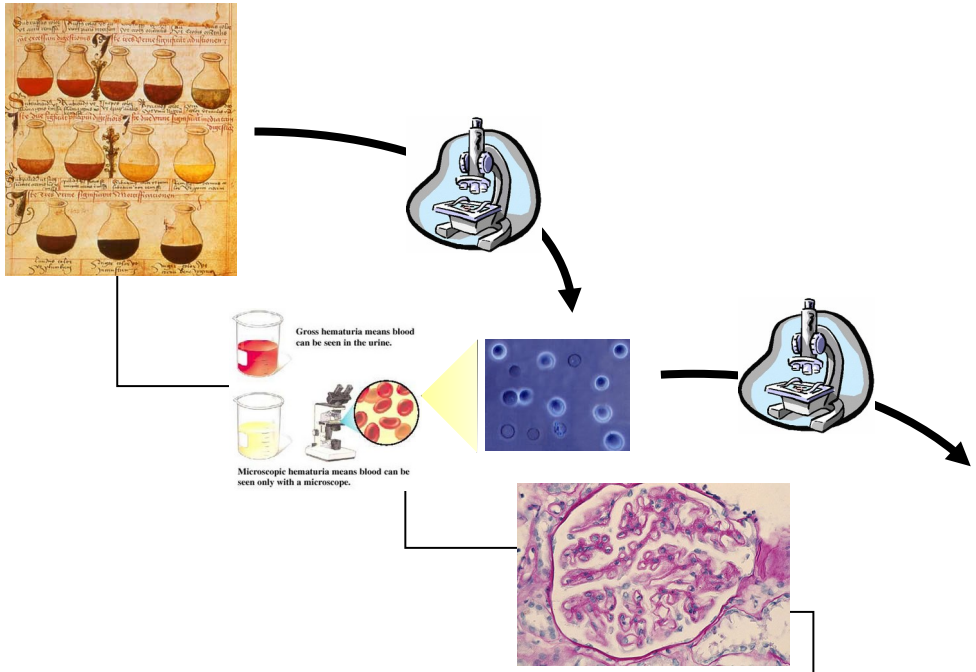
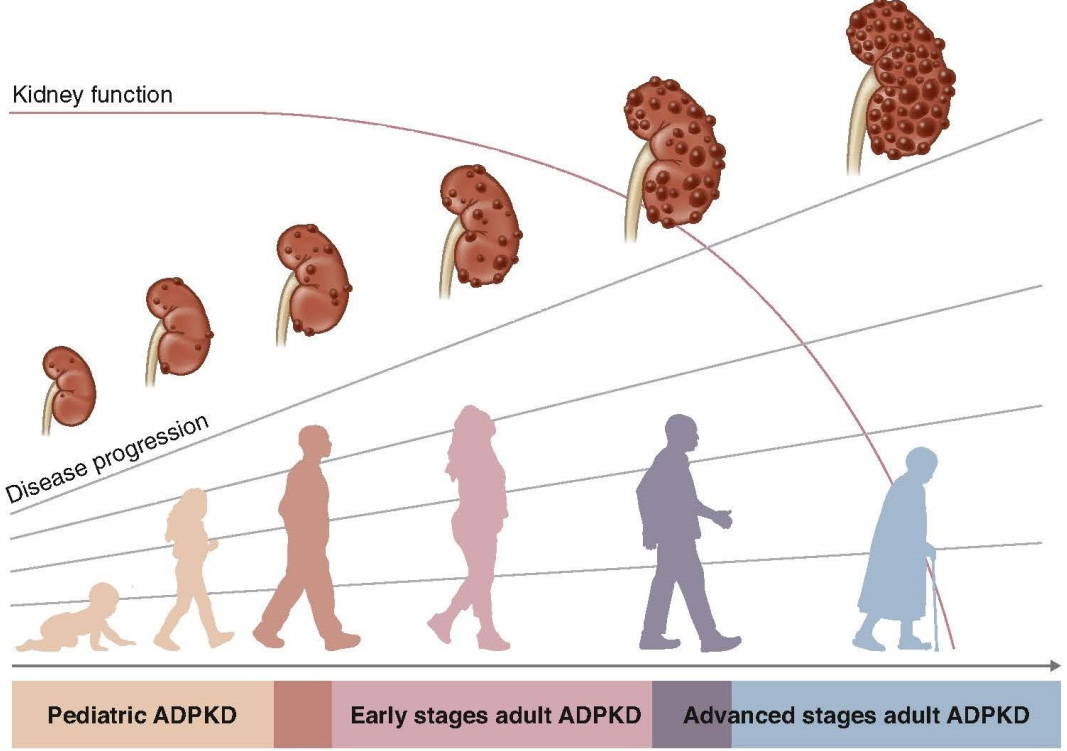


Glomerulopatie Genetiche

Sindrome di Alport **Ematuria, sordità, lenticono**	**COL4A5/4/3** **Cr X e Cr 2**	***XL,AR,AD*** **Collageno membrana basale**
Fechtner Syndrome **Trombocitopenia, anomalie piastriniche inclusioni leucocitarie**	**MYH9** **Cr 22**	***AD*** **Collageno membrana basale**
BFH/TBMD **Ematuria**	**COL4A4** **Cr 2**	***AD*** **Collageno membrana basale**
Nail Patella Syndrome **Ipoplasia unghie, rotula, proteinuria, ematuria**	**LMX 1B** **Cr 9**	***AD*** **Fattore di trascrizione**
Sindrome nefrosica congenita (Tipo finlandese)	**NPSH1** **Cr 19**	***Ar*** **Nefrina**
Sindrome nefrosica resistente agli steroidi	**NPHS2** **Cr 1**	***Ar*** **Podocina**
Glomerulosclerosi focale segmentaria familiare FSGS	**ACTN4** **Cr 19**	***AD*** **Alfa Actina 4**

Malattie cistiche renali

Rene Policistico dell'adulto	**PKD1.2** **Cr 16 e Cr 4**	***AD*** **Policistina 1 e 2**
Rene Policistico Infantile	**PKHD1** **Cr 6**	***AR***
Sclerosi Tuberosa **Adenoma sebaceo, epilessia, Ritardo mentale, angiolipomi renali**	**TSC1** **Cr 9**	***AD*** **Amartina**
Von Hippel Lindau **Emangioblastomi, feocromocitoma,** **Carcinoma renale**	**VHL** **Cr 3**	***AD*** **Tumor suppressor**
Malattia Cistica Midollare	**NPHP1** **Cr 2**	***Ar*** **Nefrocistina**
Nefronoftsi giovanile	**NPHP2** **Cr 9**	***AD***
Nefronoftsi adolescenziale	**NPHP3** **Cr 3**	***AD***



Patient stratification	• Very early onset, genetics, hypertension • No available stratification scores	• Age, genetics, urological events, hypertension • Stratification according to Mayo classification/PRO-PKD score	
Current primary end points	• Urine osmolarity	• HtTKV • eGFR	• eGFR • HtTKV
Current secondary end points	• HtTKV • eGFR	• Urine osmolarity • Number of cysts • Copeptin	• Copeptin • Liver cysts
Potential end points	• Texture/segmentation imaging • Number of cysts • Hypertension • uMCP1 • PRO	• Texture/segmentation imaging/ liver cysts • uMCP1/uEGF/suPAR/Kim-1/ β2 microglobulin/NGAL/ FGF23 • Urine-to-plasma urea ratio • PRO/pain	• PRO/pain/QoL • Liver cysts
Future directions	• "Bridging biomarkers": proteomic PKD score, microRNAs, and proteins in urinary extracellular vesicles		• Prediction modeling

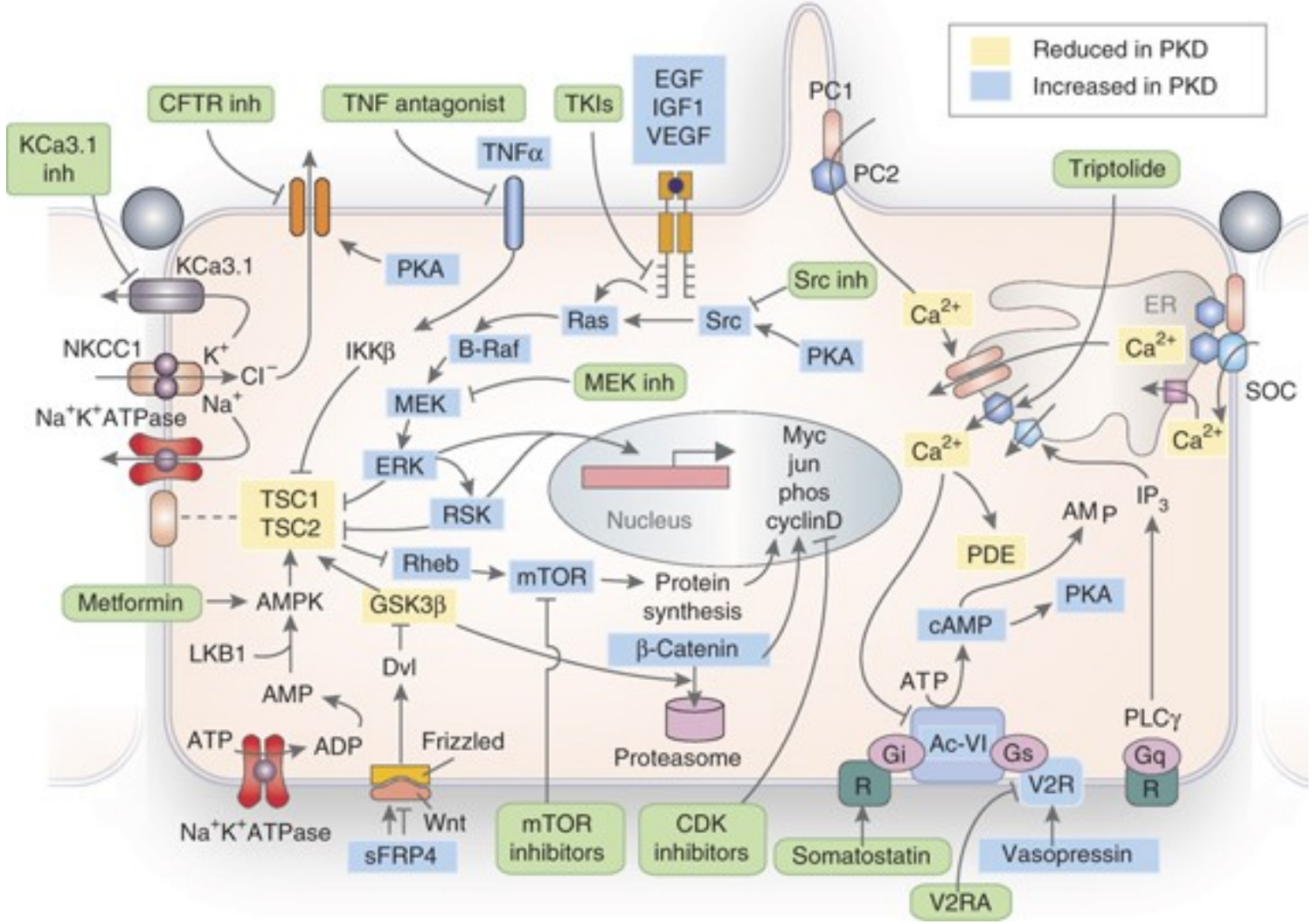


Diagramma raffigurante le vie putative up- o down-regulated nella malattia del rene policistico e il razionale per il trattamento con antagonisti del recettore V2, somatostatina, triptolide; tirosina chinasi, src, MEK, TNF, mTOR o inibitori CDK; metformina e inibitori CFTR o KCa3.1

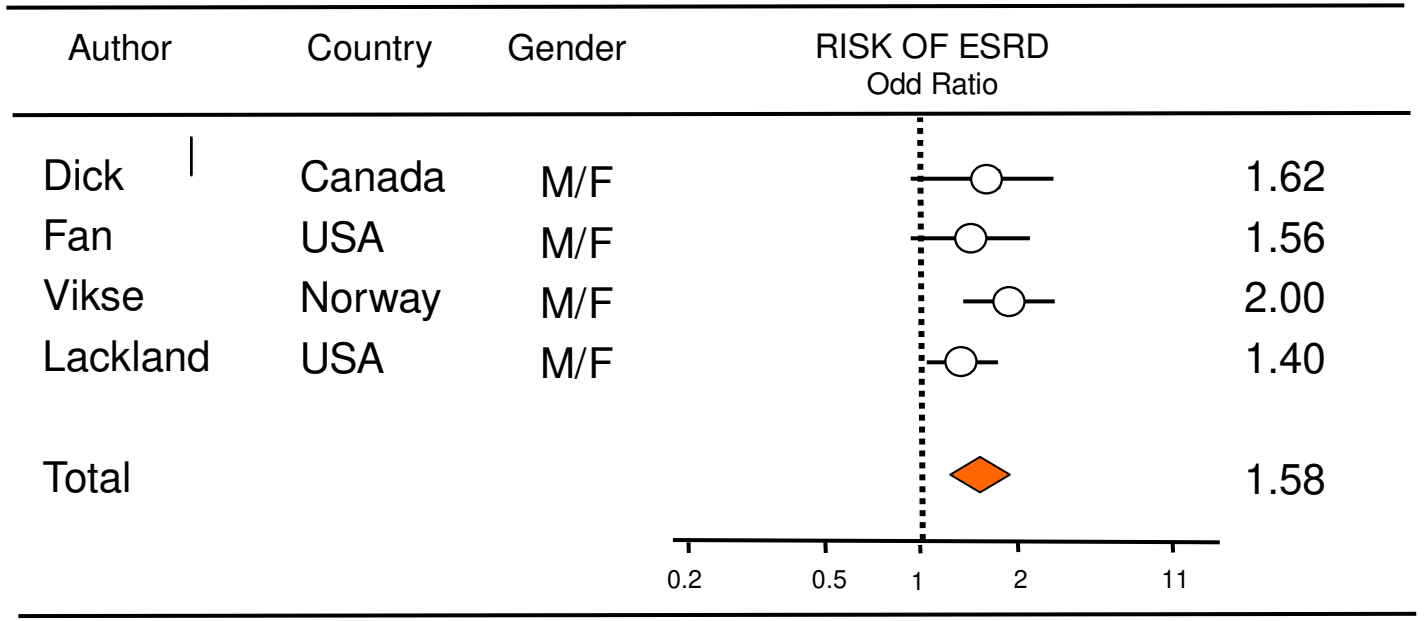
Ma genetica a parte, come mai alcuni di noi sono più propensi a sviluppare una malattia renale o una patologia cardiovascolare ?

THE INFLUENCE OF OUR LIFE AS A FETUS

La prevenzione primaria non inizia in età adulta !!!

LOW BIRTH WEIGHT INCREASES THE RISK OF ESRD

Meta-analysis of 31 cohort or case-control studies including over 2 million individuals



Low Birth Weight (< 2500g) is associated with 70 % greater risk of CKD* in later life compared to normal birth weight

*CKD defined as: albuminuria, eGFR< 60ml/min/1.73m2 or ESRD

White et al, Am J Kidney Dis, 2009

RISK OF ANY RENAL DISEASE ACCORDING TO BIRTH WEIGHT AND GESTATIONAL AGE

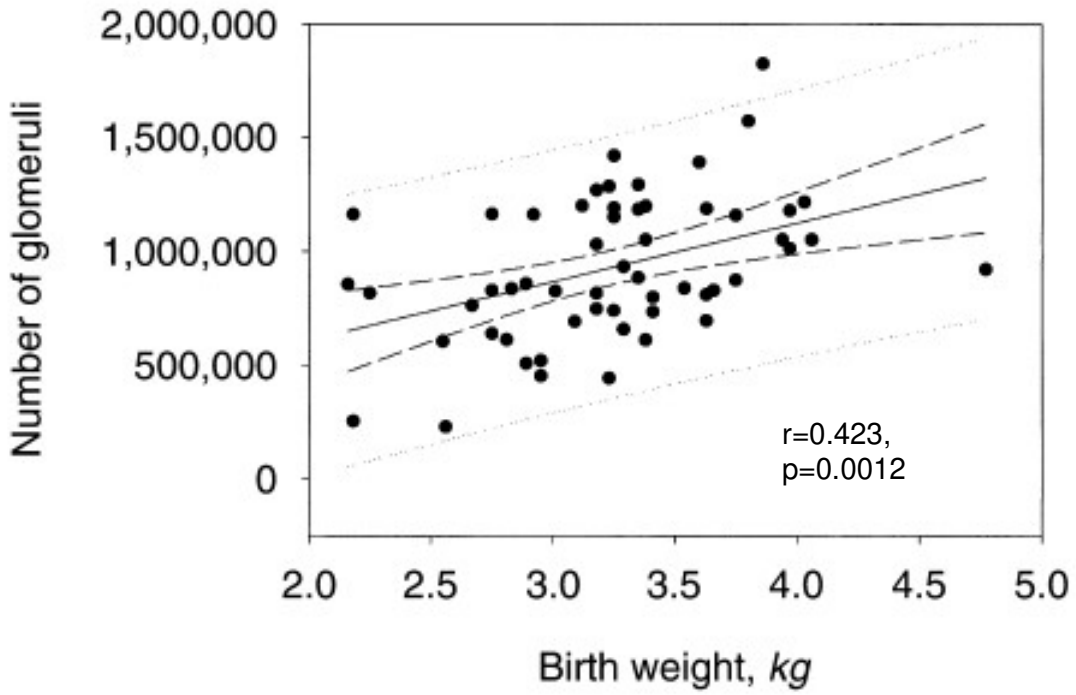
20,431 men and women born during 1924-1944 in the Helsinki Birth Cohort Study

		Hazard Ratio
Birth weight (kg)	≤ 2.0	1.6
	2.5	1.3
	3.0	1.2
	3.5	**1.0**
	4.0	0.9
	4.5	0.7
	> 4.5	0.4
Gestational age at delivery (completed weeks)	≤ 33	2.6
	34-36	1.0
	37-38	0.7
	39-40	**1.0**
	≥ 41	1.0
		1.0

Osmond et al., 2016

NEPHRON NUMBER CORRELATES WITH BIRTH WEIGHT IN HUMANS

Autopsy kidneys from 37 African Americans and 19 Caucasians including infants, children and adults

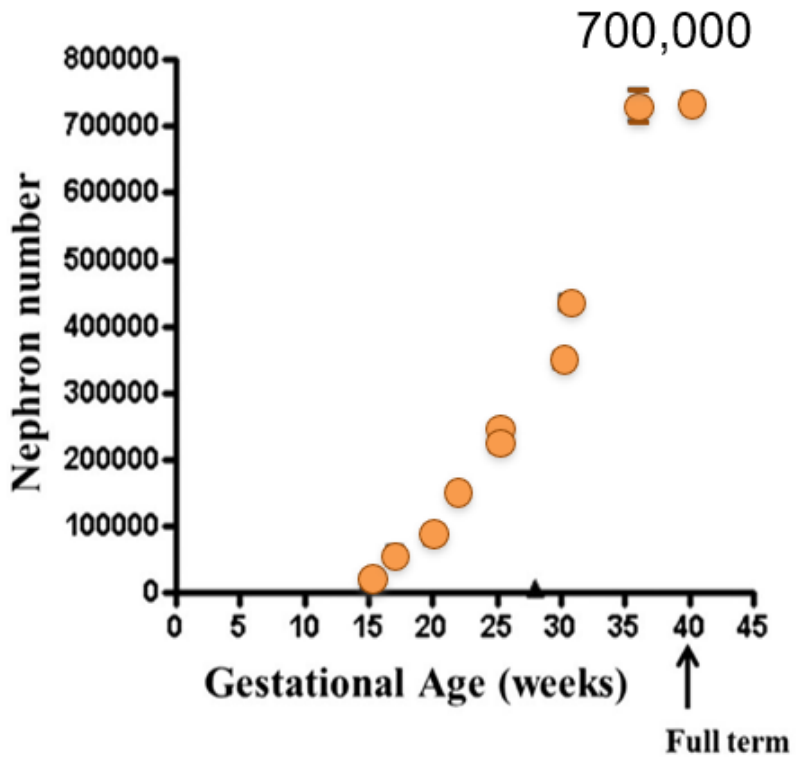


Regression coefficient predicts a gain of 257,426 glomeruli per kg increase in birth weight

Hughson et al., Kidney Int, 2003

NEPHROGENESIS IN HUMANS IS COMPLETED BY 36 WEEKS OF GESTATION

Nephron number estimation on pairs of human kidneys from 11 normal spontaneous second trimester abortions and stillbirths (15 to 40 weeks gestation)



Nearly 60 % of nephrons are developed in the third trimester

Hinchliffe et al., Lab Invest, 1991

La prevenzione nelle varie epoche della vita

Vita fetale | neonato | infante | bimbo | bambino | adulto | anziano

- Educazione della madre ad una vita sana (corretta alimentazione)
- Cura pre-concezionale
- Cura pre-natale
- Identificare madri e bambini a rischio di MRC, MCV, Diabete

- Annotare
  - il peso alla nascita,
  - epoca gestazionale,
  - diabete madre, pre-eclampsia
- Ottimizzare la nutrizione
- Allattamento al seno

- Alimentazione
- Evitare sovrappeso/obesità
- Esercizio fisico
- Educazione

Stile di vita salutare

- Corretta nutrizione (poco sale. non diete iperproteiche, preferire vegetali, ecc.)
- Evitare obesità
- Esercizio fisico regolare
- Evitare farmaci nefrotossici e fumo di sigarette
- Limitare alcol

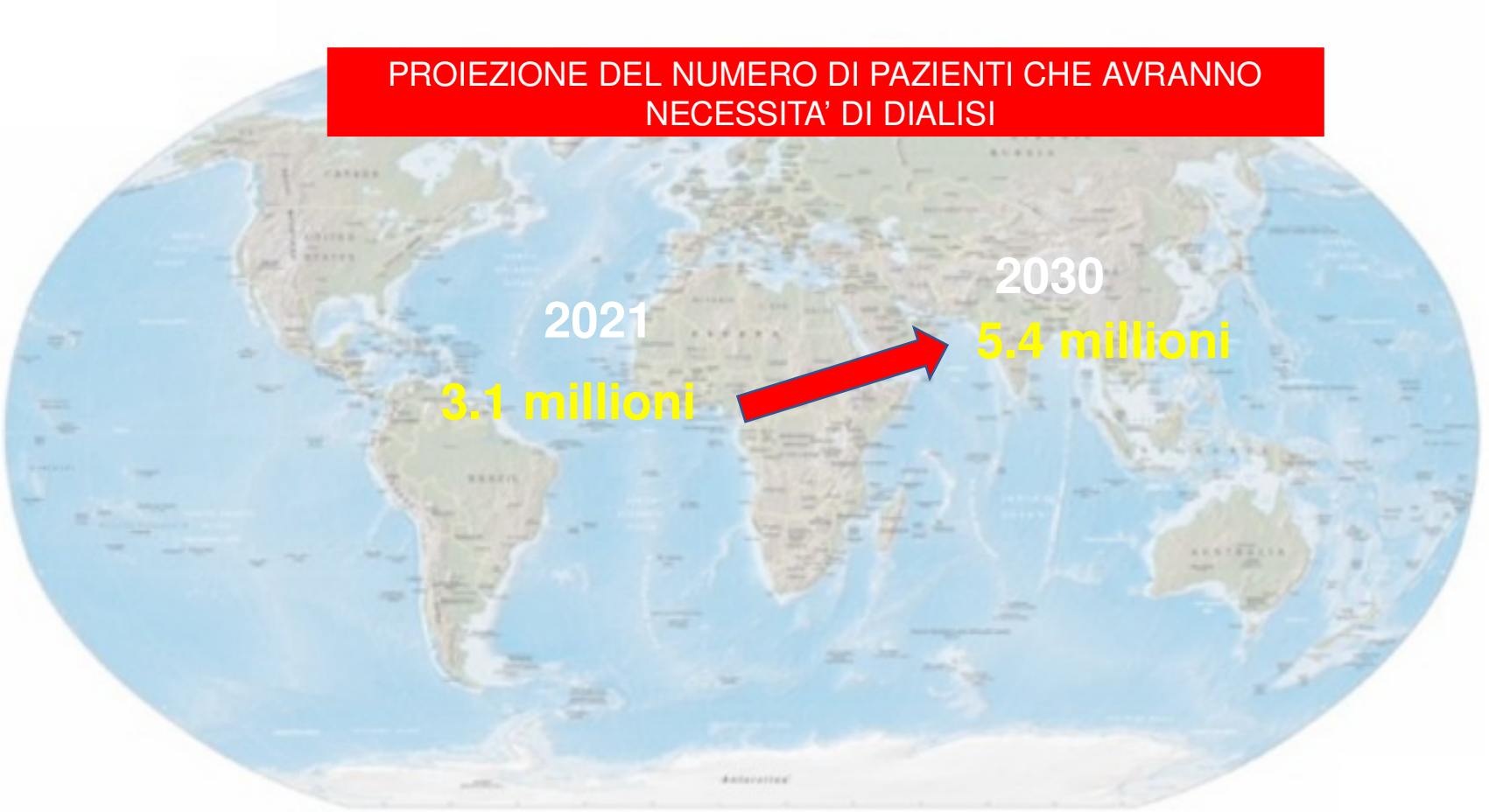
Screening per MRC, DM, MCV
Diagnosi precoce

Prevenzione primaria in tema di Malattia Renale Cronica

Oltre 800 milioni di individui nel mondo hanno una certa forma di Malattia Renale

La Malattia Renale spesso non presenta sintomi sino allo stadio avanzato di malattia

PROIEZIONE DEL NUMERO DI PAZIENTI CHE AVRANNO NECESSITA' DI DIALISI

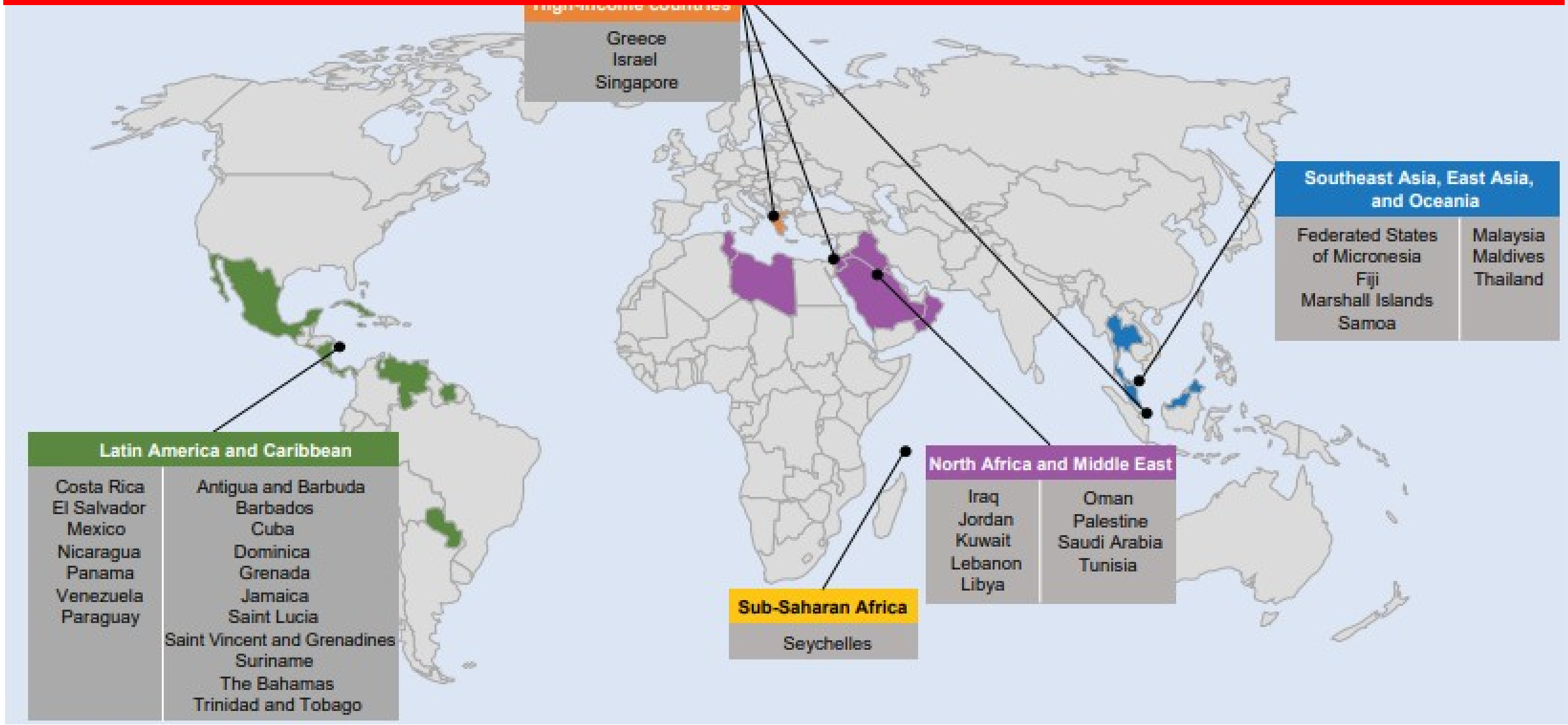


Lancet 2021

Impatto socio-economico delle malattie renali

- 6.5 milioni di europei hanno una MRC
- Spese sostenute per la MRC: € 27 miliardi per anno
- 546,000 pazienti richiedono RRT
- Carenza di organi per il trapianto
- 16-18% di mortalità annua per i pazienti in dialisi cronica

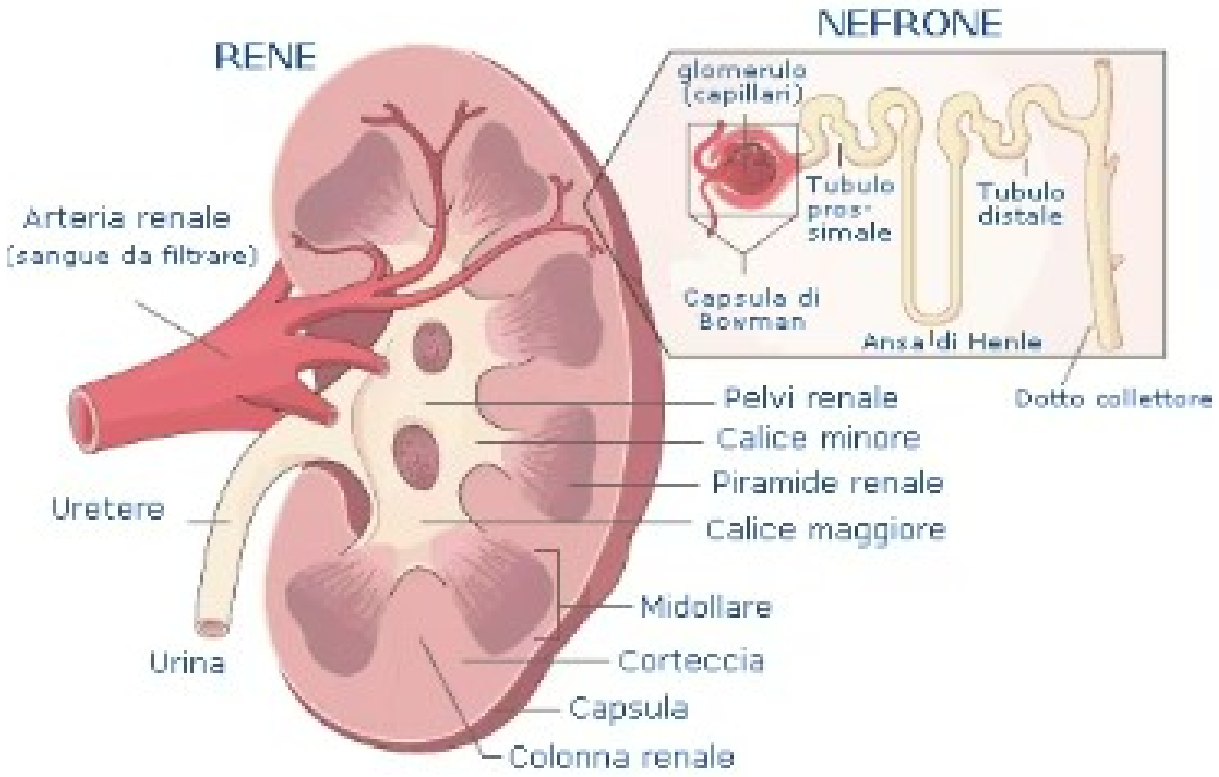
Regions and countries where chronic kidney disease is in the top 10 causes of years of life lost in 2013



Solo attraverso la prevenzione delle malattie renali possiamo sperare in un mondo “senza dialisi”

LE MALATTIE RENALI

- I calcoli renali;
- La pielonefrite;
- La glomerulonefrite;
- La sindrome nefrosica;
- La nefropatia diabetica;
- Il rene policistico;
- L'idronefrosi;
- L'insufficienza renale acuta
- La malattia renale cronica
- Il tumore al rene.



Principali studi con novità nel 2020

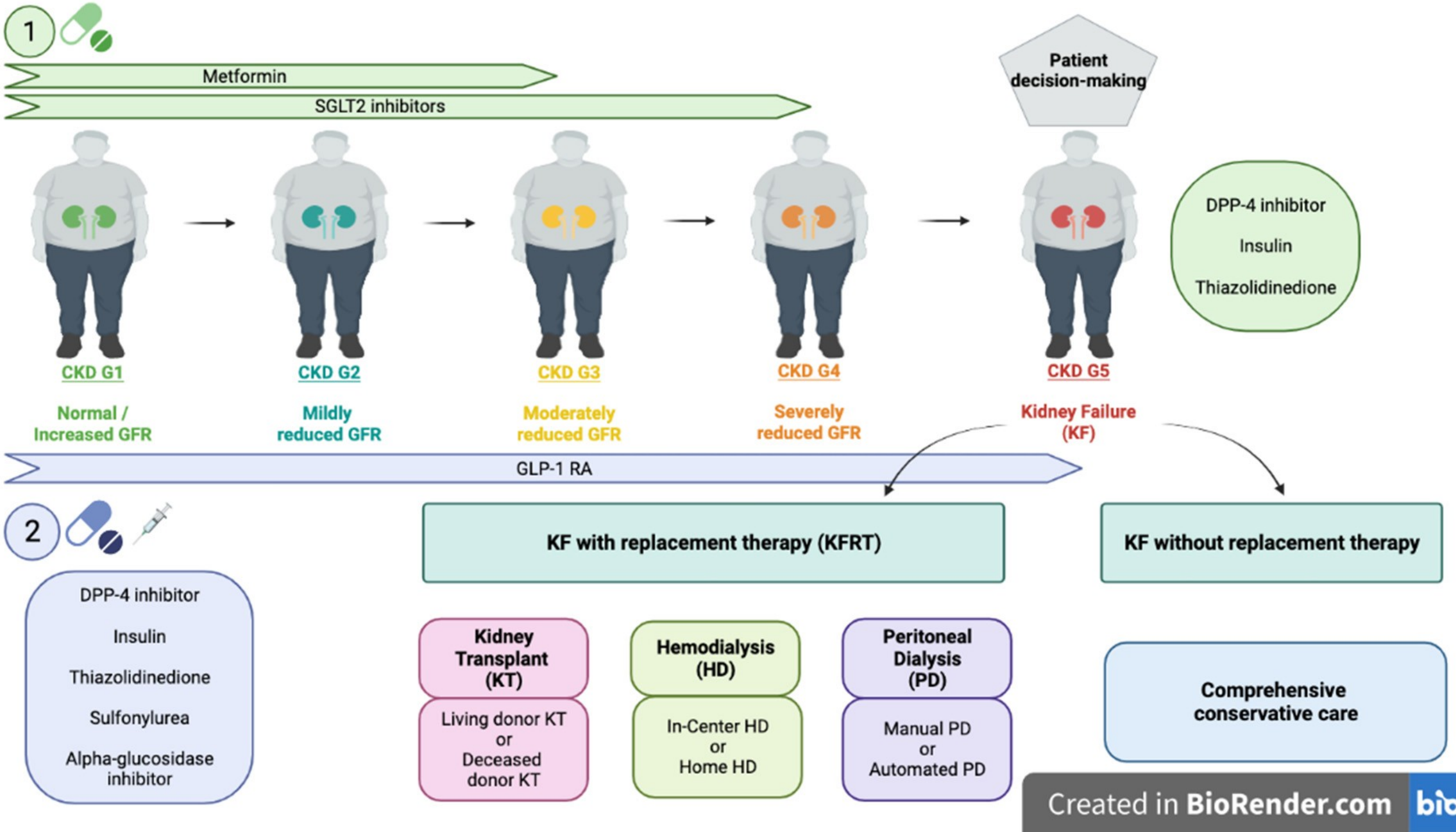
PERL and CKD-FIX Urate lowering in CKD	RACE Correction factor in eGFR equation comes under scrutiny	ISCHEMIA - CKD Optimal medical management is sufficient in CAD	COVID-19 And its impact on the Lidney	FIDELIO Finrenone in DKD
PEXIVAS PLEX and glucorticoids In severe AAV	KIDNEY FIBROSIS Origin of miofibroblasts	STARRT AKI Early versus late dialysis in AKI	SuPAR Predict AKI in Cocid-19	DAPA-CKD Dapaglifozin in diabetic and non diabetic CKD

Principali studi con novità nel 2021

SSaSS trial Potassium salt in HTN reduced stroke and mortality	AUTORA TRIAL Vaclosporin in Lupus Nephritis	FIGARO Cardiovascular otcomes of Finrenone in DKD	SUCCESSFUL PIG KIDNEY TRASPLANTED into humans
CLICK TRIAL Chlortalidone reduces BP In CKD	FLOZIN In IgA subgroups In DAPA-CKD	NEW eGFR EQUATIONS Removal of Race in eCGR	KDIGO UPDATE In Glomerulonephritis

Principali studi con novità nel 2022

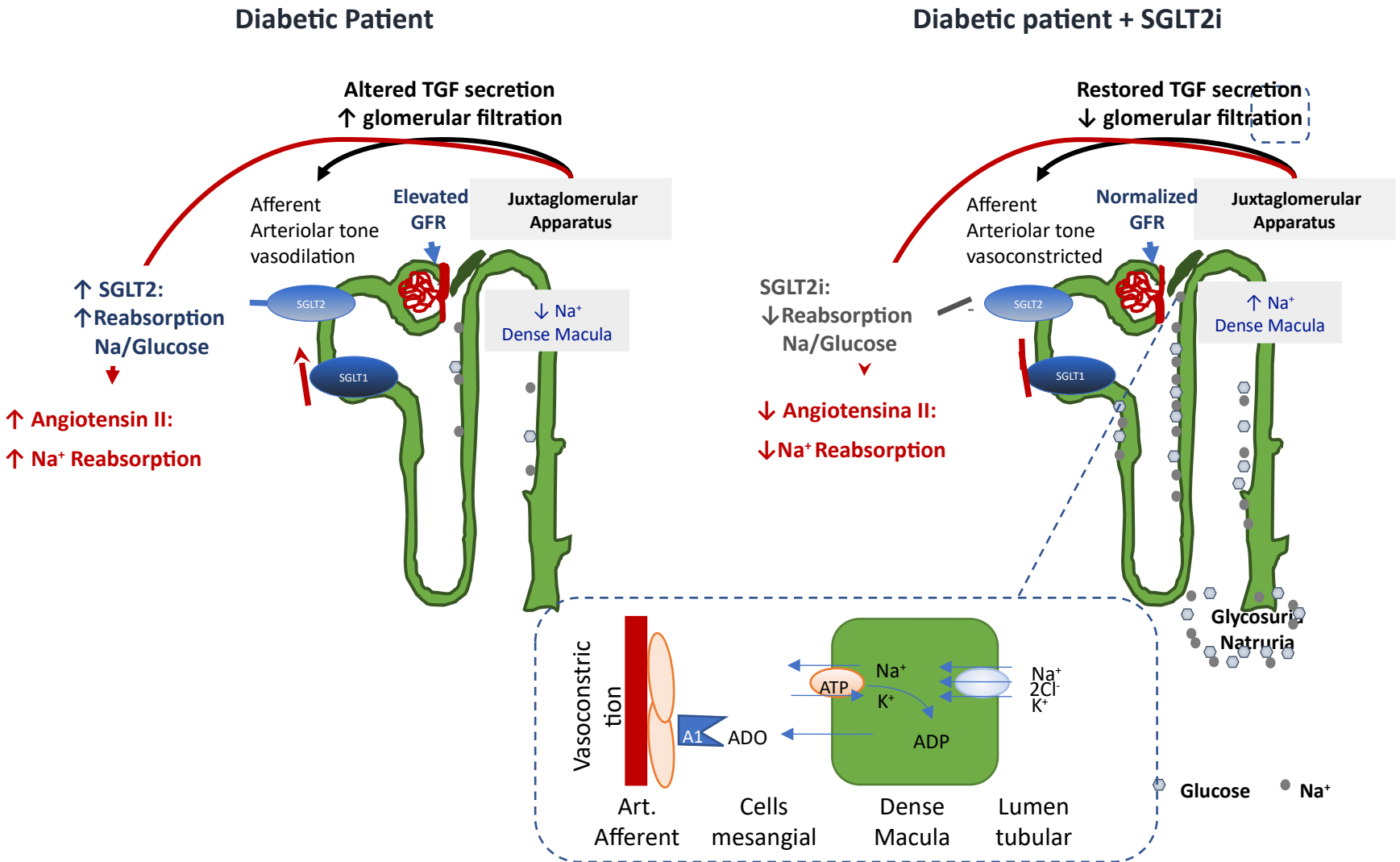
EMPA-KIDNEY Flozins in progressive CKD	ANTI-NEPHRIN ANTIBODIES In MCD	STOP ACEi RAS inhibition in advanced CKD	XENO PIG KIDNEY In decent humans
CAR T In Lupus	Testing 2 Steroids in IgA	DELIVER Flozins in HFpEF	CHAP BP target in Pregnancy

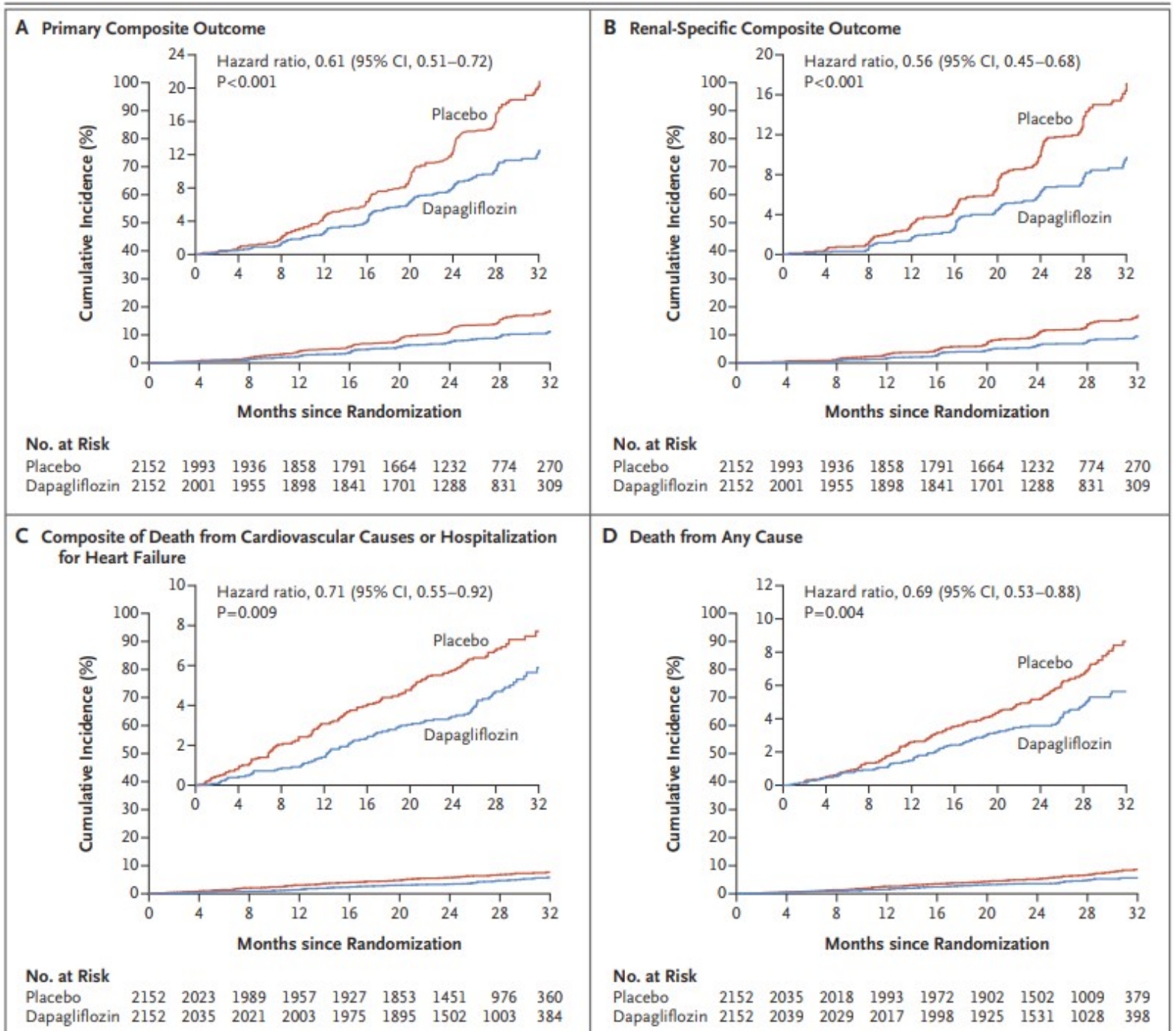

1
Metformin
SGLT2 inhibitors
Patient decision-making
DPP-4 inhibitor
Insulin
Thiazolidinedione
CKD G1
Normal / Increased GFR
CKD G2
Mildly reduced GFR
CKD G3
Moderately reduced GFR
CKD G4
Severely reduced GFR
CKD G5
Kidney Failure (KF)
GLP-1 RA
2
DPP-4 inhibitor
Insulin
Thiazolidinedione
Sulfonylurea
Alpha-glucosidase inhibitor
KF with replacement therapy (KFRT)
KF without replacement therapy
Kidney Transplant (KT)
Living donor KT or Deceased donor KT
Hemodialysis (HD)
In-Center HD or Home HD
Peritoneal Dialysis (PD)
Manual PD or Automated PD
Comprehensive conservative care
Created in BioRender.com
bio

Mechanisms of action of SGLT2 inhibitors and their beneficial effects on the cardiorenal axis

Gronda E , Lopaschuk GD, Arduini A, Santoro A, et al.

Can J Physiol Pharmacol
2022 Feb;100(2):93-106





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D.,

4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m2 of body-surface area and a urinary albumin-to-creatinine ratio of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes

Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo.

Is Empagliflozin Beneficial in Patients With Variable Chronic Kidney Disease and Diabetes Status?

EMPA-KIDNEY Collaborative Group

#NephJC

6609 patients randomized

2-year follow up

eGFR ≥ 20-45 ml/min/1.73 m^2
or
eGFR ≥ 45-90 ml/min/1.73 m^2
and
Urine Albumin to creatinine ratio of > 200 mg/g

	Progressive CKD* or CV death	Hospitalization for CHF or CV death	Hospitalization any cause (per 100 patient yrs)
Placebo n=3305	16.9%	4.6%	29.2
	HR 0.72 (0.64-0.82) p< 0.001	**HR 0.84 (0.67-1.07) p=0.15**	**HR 0.86 (0.78-0.95) p= 0.003**
Empagliflozin 10mg n=3304	13.1%	4.0%	24.8

*sustained 40% eGFR decline / eGFR <10 ml/min / ESKD

or

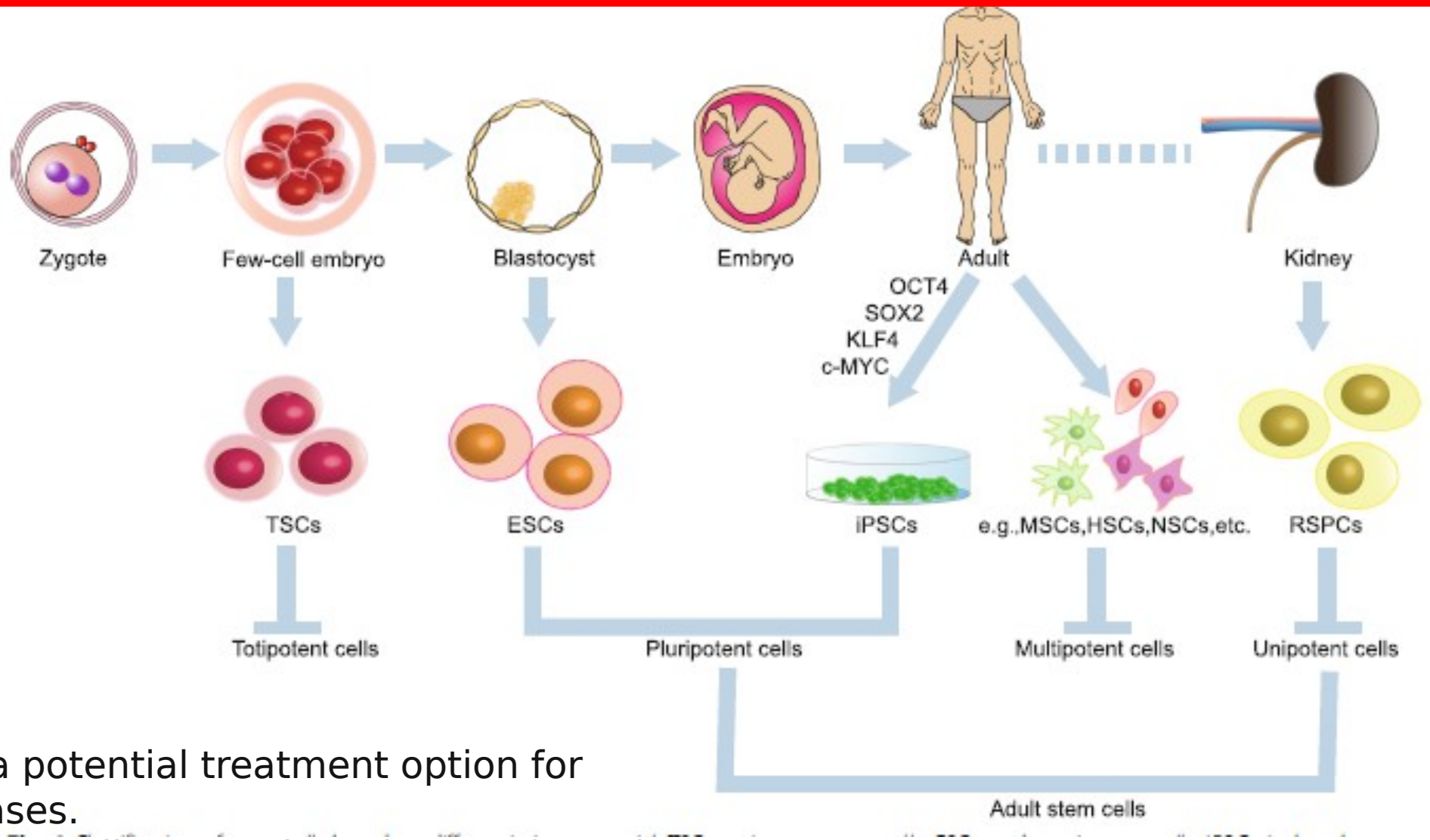
Results were consistent in patients with and without diabetes

Empagliflozin in Patients with Chronic Kidney Disease: The EMPA-KIDNEY Collaborative Group. Herrington WG, Staplin N, Wanner C, et al. N Engl J Med. 2022 Nov 4. doi: 10.1056/NEJMoa2204233

Conclusion: Among a wide range of patients with CKD who were at risk for progression, empagliflozin therapy led to a lower risk of progression of CKD or death from cardiovascular causes than placebo.

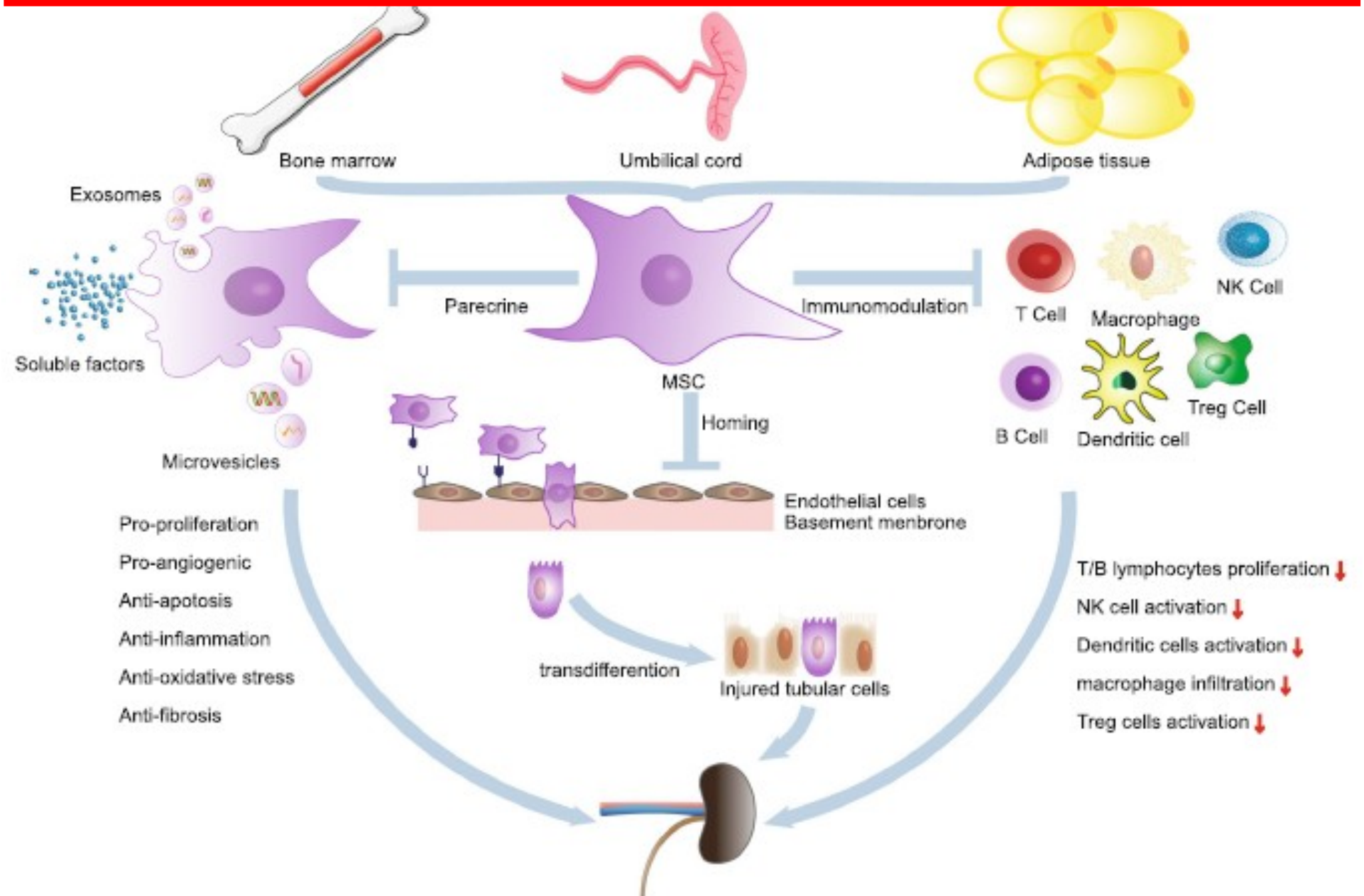
@brian_rifkin

Classification of stem cells based on differentiation potential. TSCs, totipotent stem cells; ESCs, embryonic stem cells; iPSCs, induced pluripotent cells; MSCs, mesenchymal stem cells; HSCs, hematopoietic stem cells; NSCs, neural stem cells; RSPCs, renal stem/progenitor cells



Stem cells: a potential treatment option for kidney diseases.
Liu et al. Stem Cell Research & Therapy (2020)

The diverse mechanism of MSCs in the treatment of kidney diseases



Mineralocorticoid receptor antagonists comparison, structure, chemistry, distribution, and receptors affinity.

	Spironolactone	Eplerenone	Finerenone
Chemistry	Steroidal		Non – steroidal, Dihydropyridine
Distribution	Higher concentrations in renal tissue in comparison to cardiac tissue.		Distributed relatively equally between the heart and the kidney.
Mineralocorticoid receptor	24	990	18
Glucocorticoid receptor	2400	22,000	>10,000
Androgen receptor	77	21,200	>10,000
Progesterone receptor	740	31,200	>10,000

Finrenone : significant systolic BP reduction at highest dosage; greater protection from cardiac and renal injury and structural remodeling; stronger inhibition of renal expression of pro-inflammatory and pro-fibrotic markers.

Kidney outcomes with finerenone: an analysis from the FIGARO-DKD study

Background

The aim was to evaluate the effects of finerenone on kidney outcomes in patients with CKD and T2D.

Methods

FIGARO-DKD trial (NCT02545049)
7437 patients with T2D and CKD

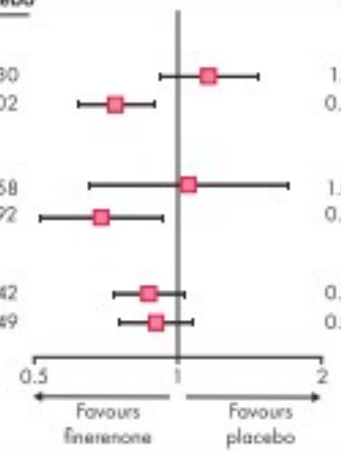
Kidney composite outcomes:
Time to kidney failure, sustained ≥ 40%/≥ 57% decrease from baseline in eGFR over ≥ 4 weeks, or renal death

CV composite outcome:
Time to CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF

Acknowledgments: Funded by Bayer AG; FIDELIO-DKD

Results

Outcome	Finerenone n/N	Placebo n/N	Finerenone n/100 PY	Placebo n/100 PY	Hazard ratio (95% CI)	Pinteraction
eGFR ≥40% kidney composite						
UACR 30–<300 mg/g	145/1726 (8.4)	124/1688 (7.3)	2.63	2.30	1.16 (0.91–1.47)	0.02
UACR ≥300 mg/g	201/1851 (10.9)	268/1878 (14.3)	3.83	5.02	0.74 (0.62–0.90)	
eGFR ≥57% kidney composite						
UACR 30–<300 mg/g	34/1726 (2.0)	32/1688 (1.9)	0.60	0.58	1.05 (0.65–1.71)	0.37
UACR ≥300 mg/g	73/1851 (3.9)	106/1878 (5.6)	1.35	1.92	0.69 (0.51–0.93)	
CV composite						
UACR 30–<300 mg/g	226/1726 (13.1)	251/1688 (14.9)	3.88	4.42	0.87 (0.73–1.04)	0.60
UACR ≥300 mg/g	222/1851 (12.0)	254/1878 (13.5)	3.94	4.49	0.90 (0.75–1.08)	



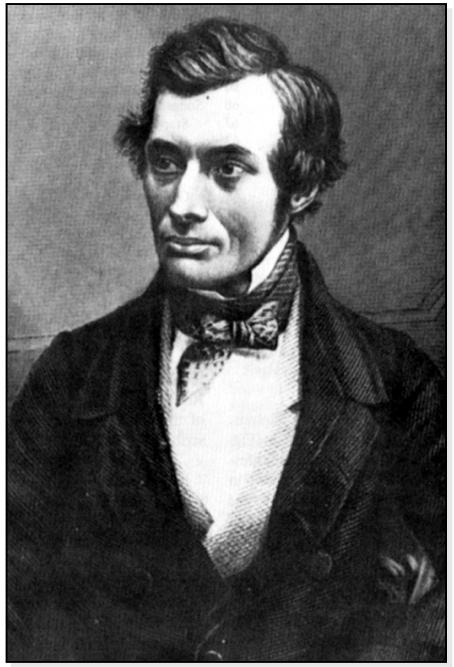
Conclusion

Finerenone protects against CV events and kidney disease progression in patients with T2D and early- or late-stage CKD.

ERA NDT NEPHROLOGY DIALYSIS TRANSPLANTATION

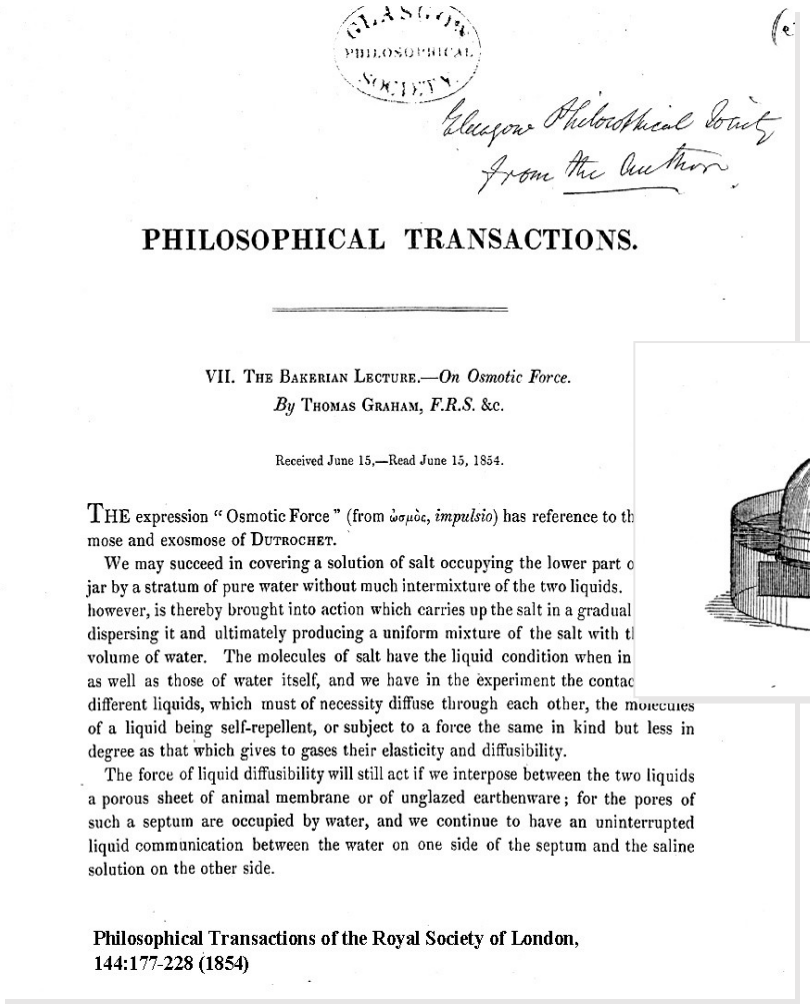
Ruilope et al. NDT (2022)
@NDTSocial

1854: The Scientific Basis for Dialysis



Thomas Graham

1805 - 1869



GLASGOW PHILOSOPHICAL SOCIETY

Glasgow Philosophical Society
From the Author

PHILOSOPHICAL TRANSACTIONS.

VII. The Bakerian Lecture.—*On Osmotic Force.*
By Thomas Graham, *F.R.S.* &c.

Received June 15,—Read June 15, 1854.

THE expression "Osmotic Force" (from ὠσμὸς, *impulsio*) has reference to th
mose and exosmose of Dutrochet.

We may succeed in covering a solution of salt occupying the lower part o
jar by a stratum of pure water without much intermixture of the two liquids.
however, is thereby brought into action which carries up the salt in a gradual
dispersing it and ultimately producing a uniform mixture of the salt with t
volume of water. The molecules of salt have the liquid condition when in
as well as those of water itself, and we have in the experiment the contac
different liquids, which must of necessity diffuse through each other, the molecules
of a liquid being self-repellent, or subject to a force the same in kind but less in
degree as that which gives to gases their elasticity and diffusibility.

The force of liquid diffusibility will still act if we interpose between the two liquids
a porous sheet of animal membrane or of unglazed earthenware; for the pores of
such a septum are occupied by water, and we continue to have an uninterrupted
liquid communication between the water on one side of the septum and the saline
solution on the other side.

Philosophical Transactions of the Royal Society of London,
144:177-228 (1854)

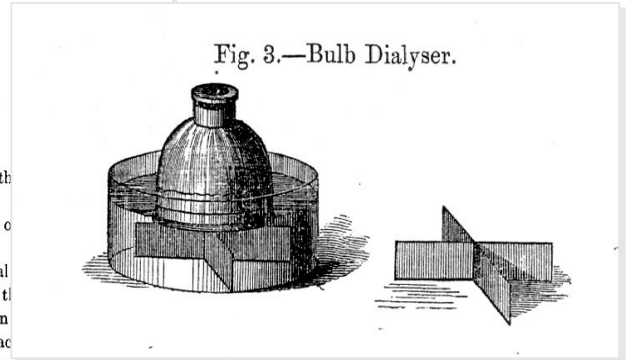
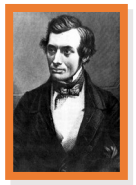


Fig. 3.—Bulb Dialyser.

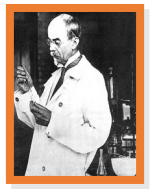
"... might be applied to medicine ..."

Script of Graham´s Bakerian Lecture, 1854

I Progressi in dialisi



Trasporto diffusivo



Prima dialisi nell'animale

Primo paziente in dialisi cronica

Primo programma di Dialisi cronica

Macchina a sinsle pass dialyzers

Monitoring &Biofedback

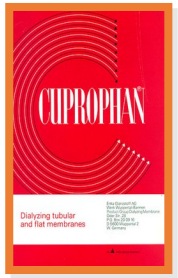
Polysulfone

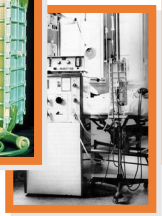
1850 1860 1870 1880 1890 1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000

Primo anticoagulante (Irudina)

Prima Dialisi , uomo

Eparina come prodotto di estrazione animale



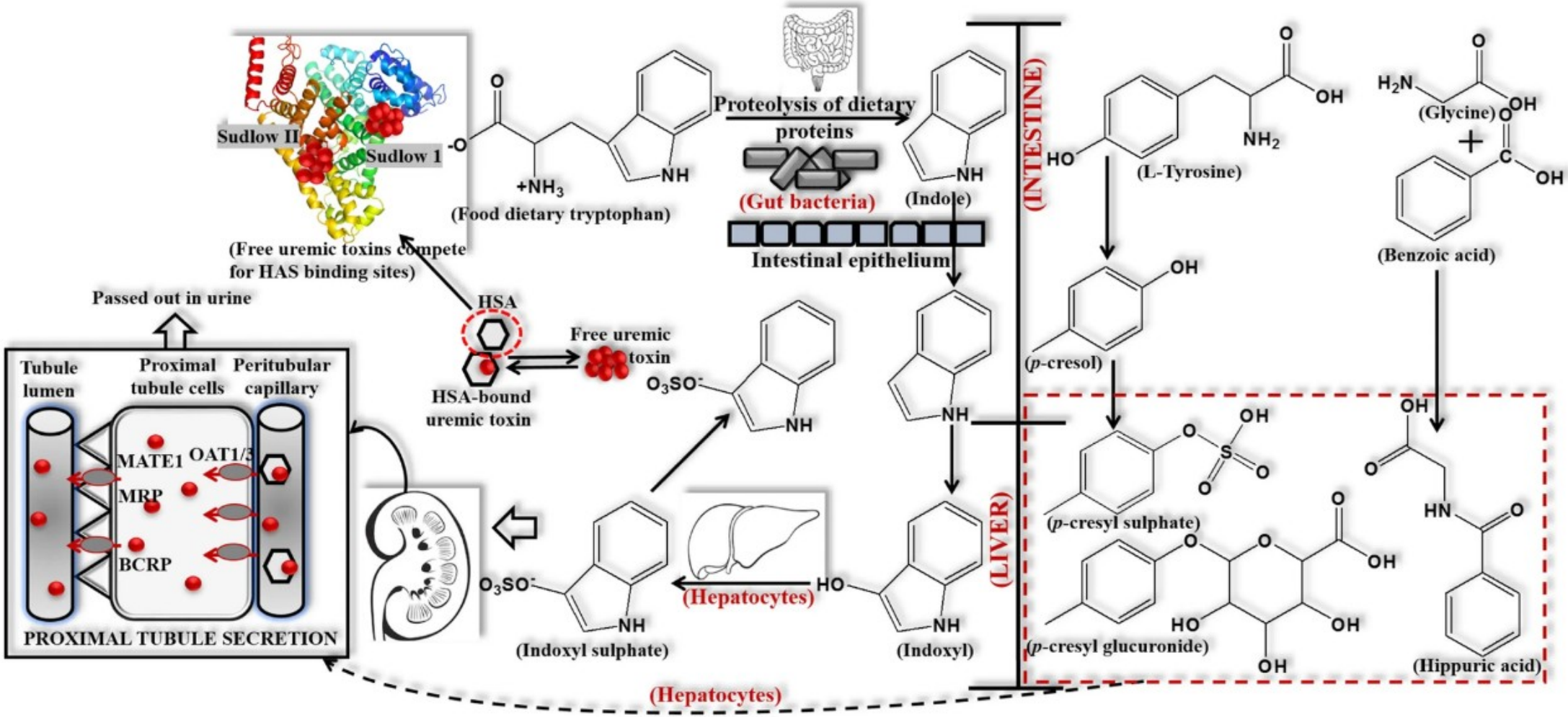


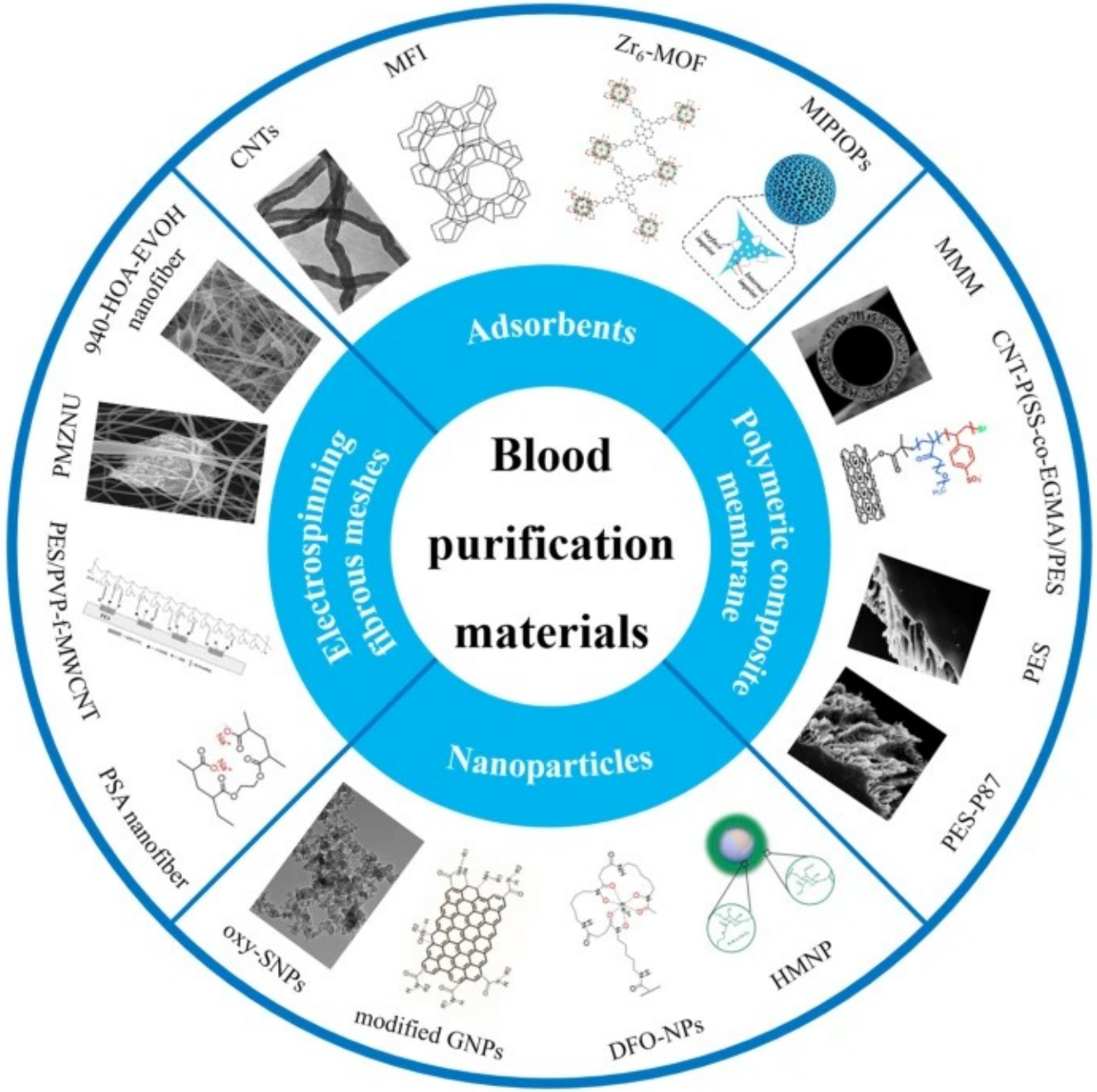
Primo dializzatore

High flux e macchina relativa

EPO

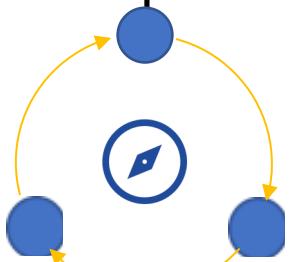
Pathway for production and clearance of protein-bound indoxyl sulfate (IS), p-cresyl sulphate (PCS), p-cresyl glucuronide (pCG) and hippuric acid (HA) toxins from the body.



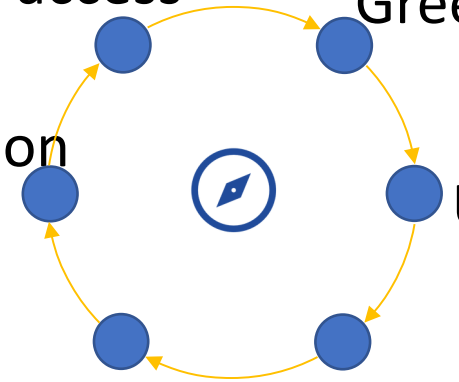

Blood purification materials
Adsorbents
Electrospinning fibrous meshes
Polymeric composite membrane
Nanoparticles
MFI
Zr6-MOF
MIPIOPs
CNTs
940-HOA-EVOH nanofiber
PMZNU
PES/PVP-f-MWCNT
PSA nanofiber
MMM
CNT-P(SS-co-EGMA)/PES
PES
PES-P87
oxy-SNPs
modified GNPs
DFO-NPs
HMNP

Major topics still debated

Organisation

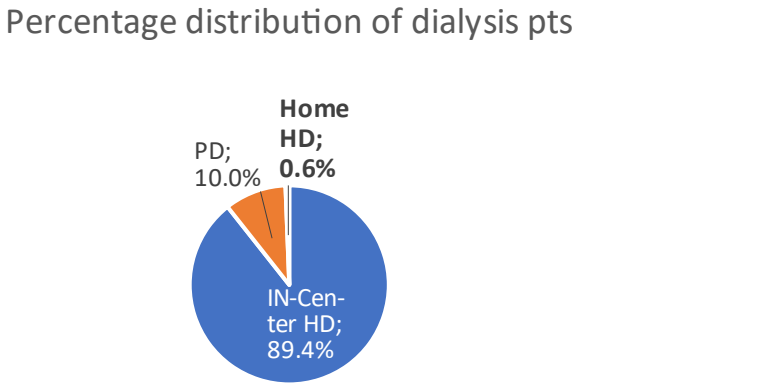


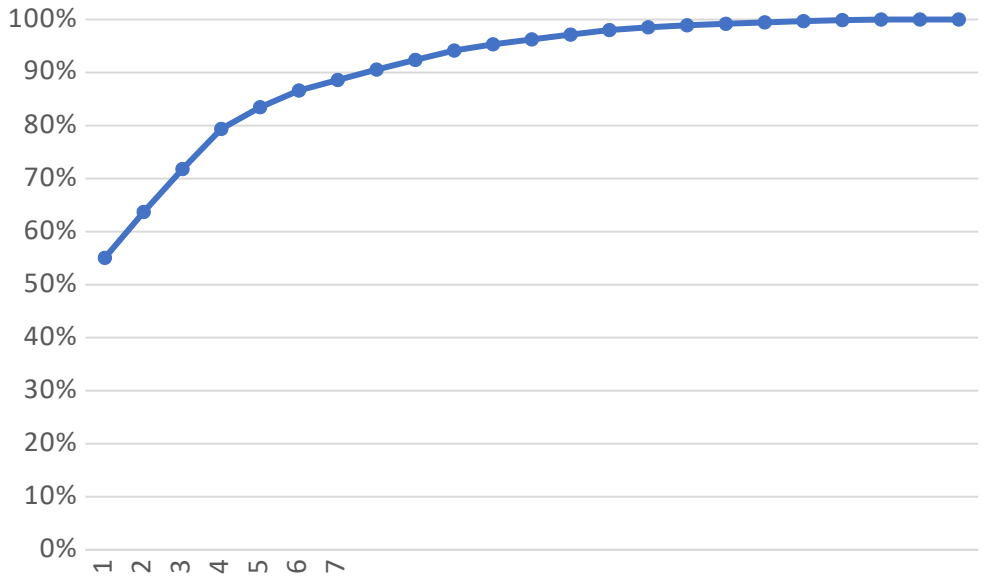
Technology



Computer Assisted Renal Care
(Artificial Intelligence)

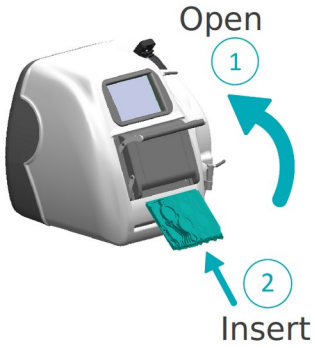
Home Hemodialysis





Source: USRDS 2018/2017/2016/2015

DIMI - Infomed



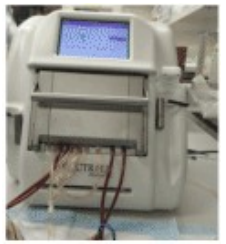
System One - Nxstage

Dharma - Duomedica

Physidia

Quanta SC+

SAM - Spectral



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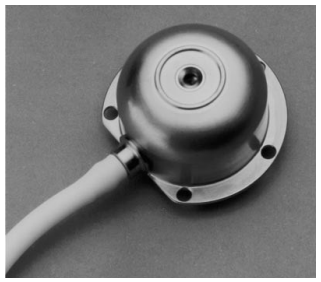
TABLO – Outset Medical

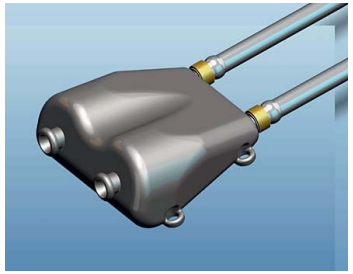
Vascular access

Vascular access ports

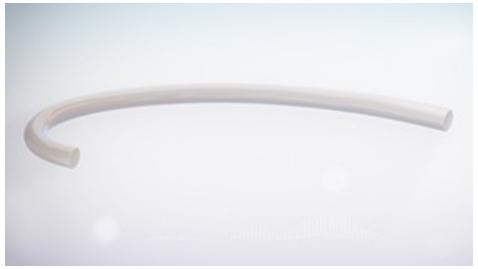
Dialock (1)



LifeSite (2)



Biolink (3)



Humacyl by Humacyte

The Human Acellular Vessels is a tissue engineered vessel replacing the traditional grafts in HD patients.

Is the buttonhole techniques still a valid alternatives?

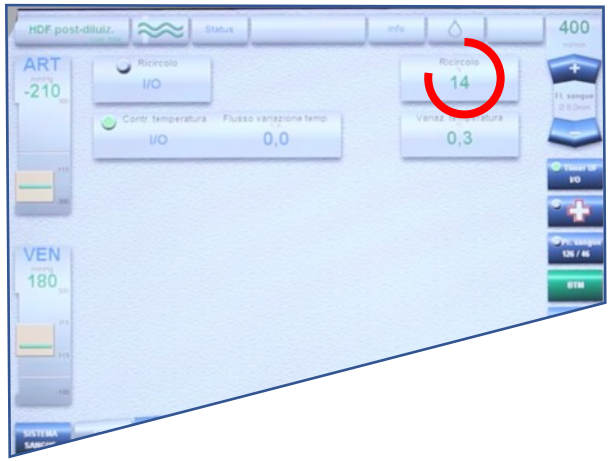
Canaud B. et al, Nephrol Dial Transplant, 1999, 14: 692–698
Beathard G.A. et al, Kidney International, 2000, 58: 2221–2227
Prosl F. et al, Blood Purif 2013; 35: 72–76

Vascular Access Care

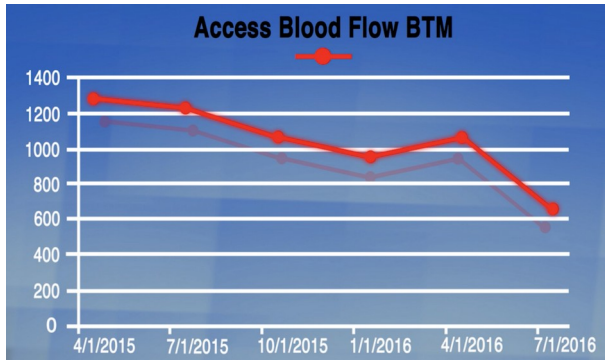
Vascular access surveillance

Parametri	Methods
Physical examination	• Inspection • Finger palpation • Sound
Pressurre Surveillance	• Intra Access pressure • Static Venous Pressure • Dynamic Venous Pressure
Recirculation	• Ultrasound dilution • Thermodilution
Flows Methods	• Duplex Doppler Ultrasound • Variable Flow Doppler Ultrasound • Ultrasound Dilution Transonic • Opto-dilution • Urea Dilution • Magnetic Resonance Angiography • Glucose Pump Infusion Technique • Differential Conductivity • In-line Dialysance • In-line Termodilution

Real time assessment



Time series analysis



Am J Kidney Dis, 2006, 48 (S1) :S1-S322

Anticoagulation: is zero-heparin hemodialysis still a goal?

Kidney International, Vol. 31 (1987), pp. 1351–1355

Heparin free dialysis: Comparative data and results in high risk patients

RALPH J. CARUANA, RASIB M. RAJA, JASMINE V. BUSH, MARK S. KRAMER, and STEPHEN J. GOLDSTEIN

The Kraftsow Division of Nephrology, Albert Einstein Medical Center, Philadelphia, Pennsylvania, USA

Heparin free dialysis: comparative data and results in high risk patients. Heparin free hemodialysis was compared to systemic heparinization, intermittent saline flushes and constant saline infusions in eight, stable chronic patients dialyzing on hollow–fiber artificial kidneys (HFAK) at blood flows of 250 to 300 ml/min. No significant differences in small molecule clearance, fluid removal or dialyzer clotting were noted. Since this data showed that heparin free hemodialysis without supplemental saline was feasible in a group of stable, chronic dialysis patients, we then prospectively studied twenty–nine patients judged to be at increased risk of hemorrhage from heparinization during 100 heparin–free dialyses. The incidences of severe and moderate dialyzer clotting were 7% and 20%, respectively. Seventeen of 27 treatments in which moderate or severe clotting occurred had identifiable factors thought to predispose to dialyzer clotting such as low blood flows, poor vascular–access function, severe hypotension and intradialytic blood transfusions. Although higher hematocrit values were associated with greater degrees of dialyser clotting, stepwise discriminant analysis employing blood flow, blood pressure, hematocrit and transfusion administration could not develop an accurate predictor or combination of predictors of clotting. No patient experienced de novo or increased bleeding and problems with inadequate dialysis were not observed. Since this method of heparin free dialysis is as safe and effective as previously reported strategies and requires no specialized equipment or procedures, it is a reasonable initial strategy for dialyzing high risk patients.

Strategies for hemodialyzing patients judged to be at increased risk of bleeding during systemic anticoagulation include low–dose systemic heparinization [1, 2], regional heparinization [1, 3], regional citrate anticoagulation [4], systemic epoprostenol administration [5], development of membrane materials of low thrombogenicity [6], and anticoagulant free hemodialysis with [7–12] or without [13, 14] intermittent saline flushes. In this study we compare four different anticoagulation strategies in a controlled fashion in eight, stable chronic–hemodialysis patients and report the results of 100 consecutive dialysis–treatments without systemic heparinization or saline flushes, performed on 29 patients judged to be at increased risk of bleeding complications.

Methods

For the controlled study of four different anticoagulation strategies, eight volunteers were solicited from a group of 18 patients receiving chronic hemodialysis at Albert Einstein Medical Center. Patients receiving anti-platelet or anti-coagulant drugs were excluded. Each patient was dialyzed once with each of four anticoagulation strategies on four consecutive–midweek dialyses.

The first anticoagulation strategy utilized intermittent boluses of heparin at doses previously determined in each patient to be adequate to sustain a full treatment with negligible fiber clotting. Total heparin doses ranged from 4000 to 5000 units per treatment. In the second strategy no supplemental heparin or saline were given during dialysis. In the third strategy a bolus of 200 cc of 0.9% saline was infused into the arterial line every 30 minutes. In the fourth strategy a constant infusion of 0.9% saline was run into the arterial line at a rate of 400 cc/hr throughout the entire treatment. The heparinized saline solution used to prime the extracorporeal circuit prior to dialysis was infused into the patients at the start of dialysis. This resulted in patients receiving up to 500 units of heparin at the beginning of dialysis.

Prior to each dialysis, 10 minutes into dialysis and at the end of the treatment the activated clotting time (ACT) was determined with an ACTester (TRI Med, Inc., Huntington Beach, California, USA). Other determinations made at the start of dialysis included patient weight, BUN and serum creatinine. When peak blood flow was reached (usually 15 to 20 minutes after initiation of dialysis) and at the end of the treatment dialyzer urea and creatinine clearances were measured. The rinse back procedure was effected with 150 to 200 cc of 0.9% saline. The arterial and venous lines were then clamped and cut at the blood ports of the artificial kidney. Residual fiber–bundle volume was then measured by a manual method using a hand–squeezed air pump to express fluid from the kidney and a graduated cylinder to measure the fluid volume evacuated. The percent fiber loss was calculated using the manufacturer's specifications for the fiber bundle volume of a fresh kidney.

In the prospective study of patients judged at increased risk of bleeding, 100 consecutive heparin–free dialyses in 29 patients were performed over a three month period. Data reviewed included the reason for heparin free dialysis, artificial kidney type, hematocrit, peak blood flow, intra-dialytic blood transfusions and pre- and post-dialyzer pressures.

A severe clotting episode was defined as clotting necessitating termination of the treatment or replacement of the artificial kidney. Mild clotting was defined as up to 25% fiber loss and

Received for publication June 6, 1986
and in revised form October 27, 1986

Dialysis technique:
1. Citrate, Predilution
2. Oral anticoagulation

Membrane biocompatibility
1. Coating
2. New Polymers

Tubing Systems:
1. Geometry
2. Volumes
3. Fluid-dynamics
4. Coating
5. Polymers

Caruana et al, Kidney Int, 1987, 31, 1351-1355

Anticoagulation: dialysis techniques

Citrate Intermittent Dialysis:

PRO

- No new technique translated from CRRT
- Encouraging preliminary results of safety and effectiveness

CONS

- Perceived as more complex
- Lack of dedicated surveillance software into haemodialysis machines
- Few concentrate formulations Ca^{2+}-free
- Lack of large, long term clinical trials on safety
- Recently some concerns about Citrate containing dialysate safety (France, Dec 2018)

Prospective, observational trial in 75 HD patients

Table 5 Efficacy and safety of regional citrate anticoagulation

	Original regional citrate protocol ($n = 357$)	Modified regional citrate protocol ($n = 694$)	p value
Dialyzer clotting	1 (0.3 %) severe	2 (0.3 %) moderate streakiness	1
Systemic $[Ca_{ion}]$ <0.81 mmol/L	2 (0.6 %)	1 (0.1 %)	0.27
Systemic $[Ca_{ion}]$ <0.96 mmol/L	35 (9.8 %)	26 (3.7 %)	<0.0005
Systemic $[Ca_{ion}]$ >1.32 mmol/L	2 (0.6 %)	12 (1.7 %)	0.16

Singer et al, Can J of Kidney Health and Dis, 2016, 3, 22

Anticoagulation: dialysis techniques

Oral anticoagulation

PRO
- Heparin-free dialysis
- No anticoagulation at all

CONS
- No clinical evidence
- Only a suggestive hypothesis

Prospective, observational trial in 8 HD patients
Warfarin or Apixaban

- 2 / 47 session complicated by dialyzer clotting
- Post HD hemostasis:
- 9.51 min in Hep-free vs 9.91 min standard HD

Abra G et al, Hemodialysis Int, 2018, 22, A27

Anticoagulation: membrane biocompatibility

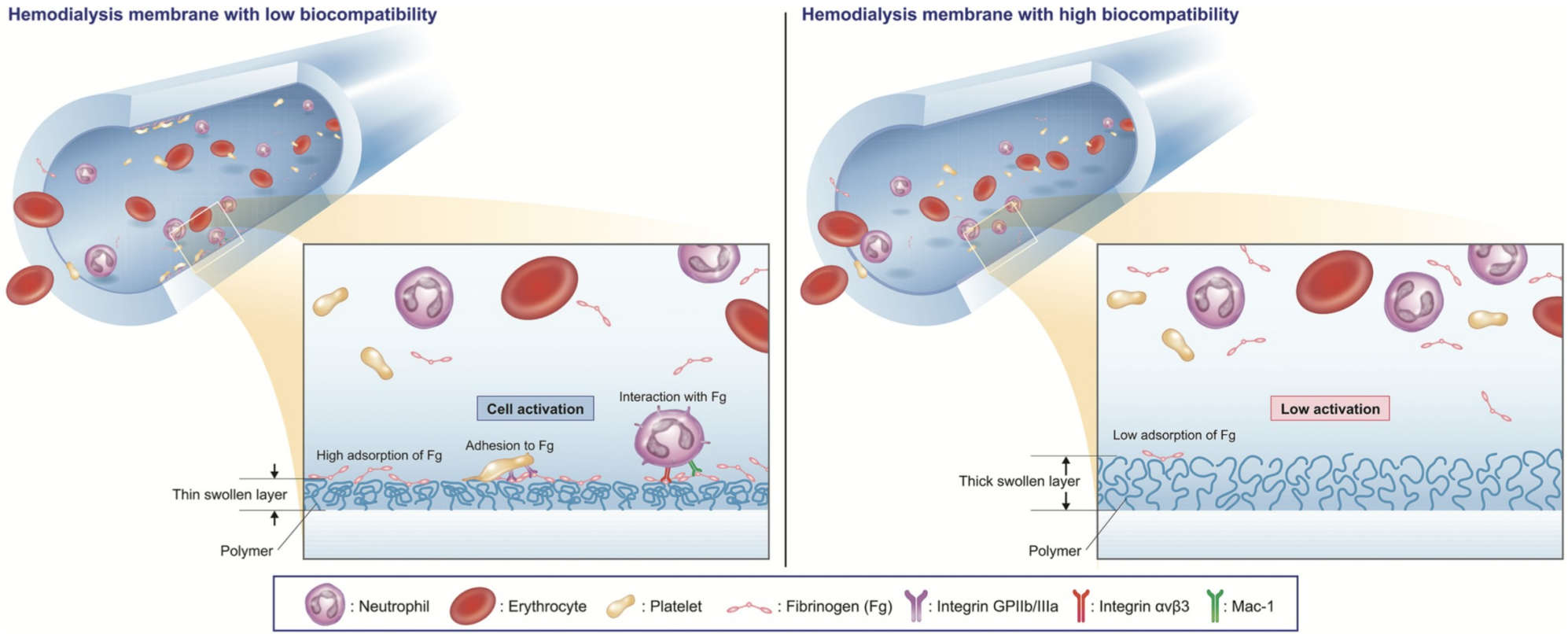


FIG. 8. Schematic illustration showing the means by which hemodialysis membranes affect platelet and neutrophil activation.

Koga et al, Artificial Organs 2018, 42(9):E246–E258

Anticoagulation: membrane biocompatibility

1 Coated membranes

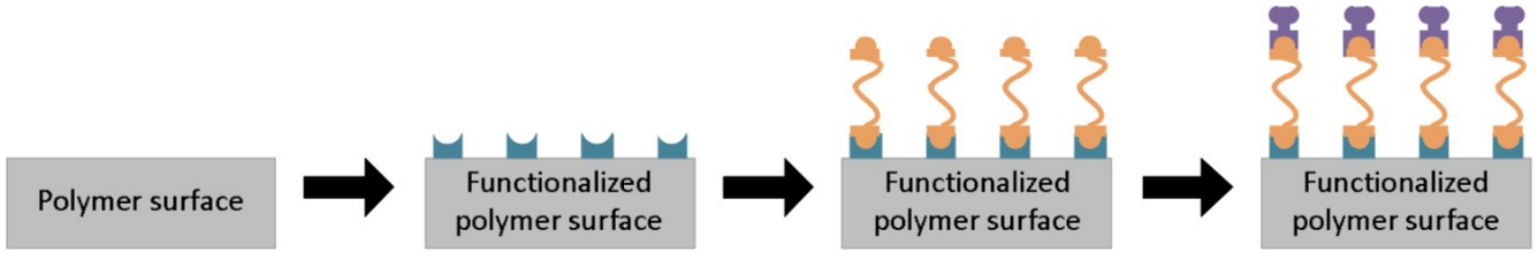


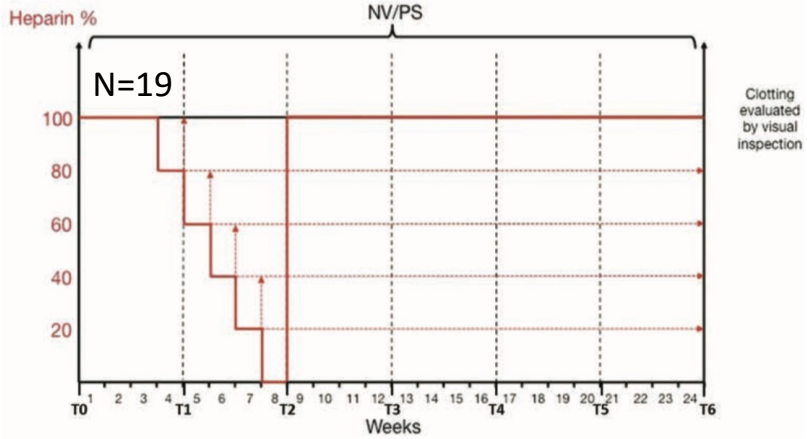
Fig. 3. General concept of biological surface modification.

Wenten et al, J Membrane Science and Research, 2016, 278-89

2 Modified membrane polymers

Pilot, prospective, multi-center, randomized clinical trial on safety and efficacy of Hydrolink™ NV vs polysulfone

Stepwise hep reduction



No inferiority on biocompatibility

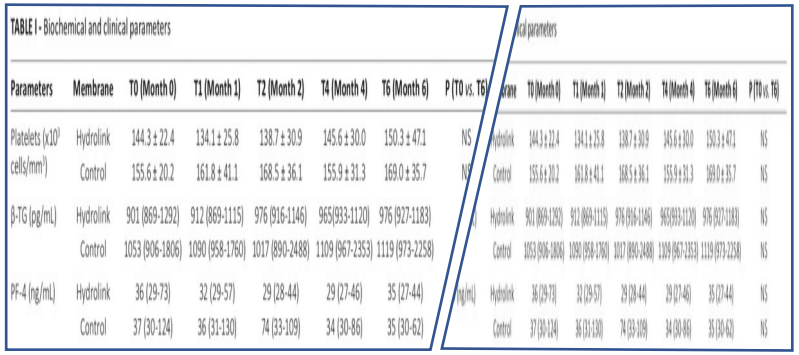
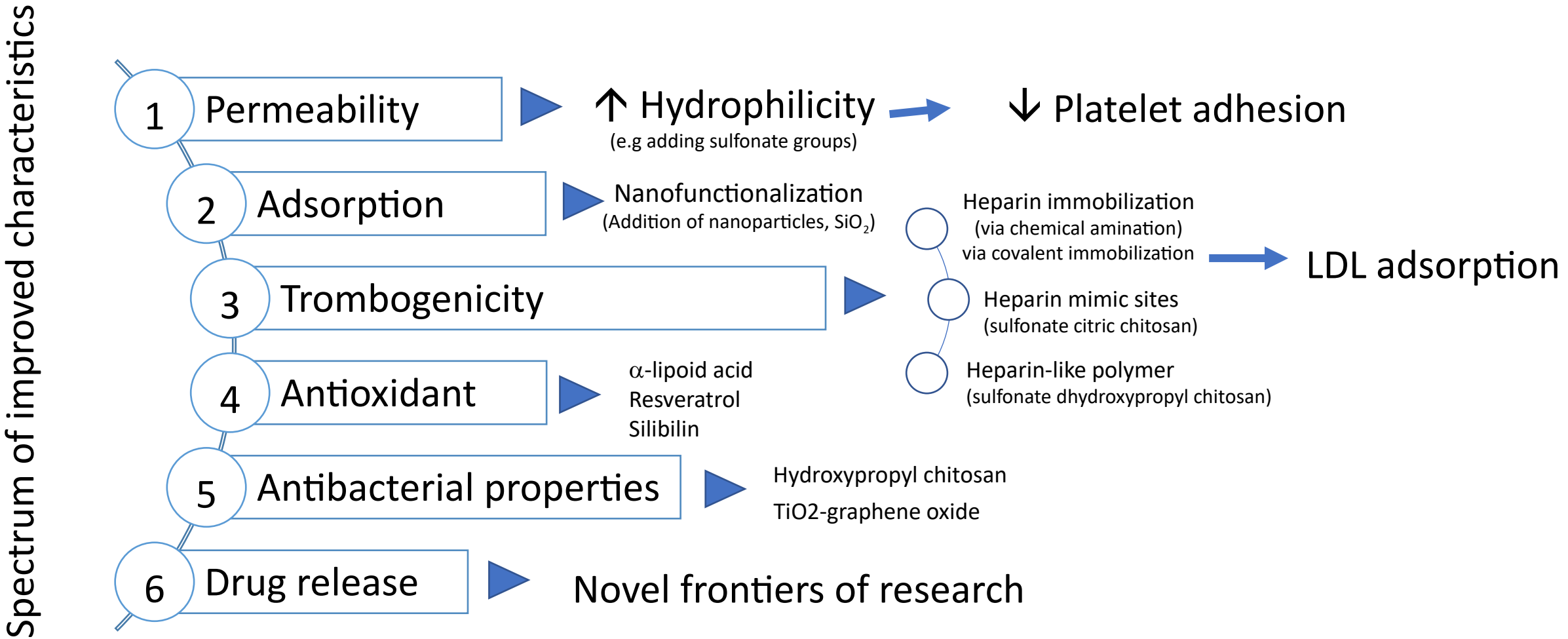


TABLE I - Biochemical and clinical parameters

Parameters	Membrane	T0 (Month 0)	T1 (Month 1)	T2 (Month 2)	T4 (Month 4)	T6 (Month 6)	P (T0 vs. T6)
Platelets ($x10^3$ cells/mm^3)	Hydrolink	144.3 ± 22.4	134.1 ± 25.8	138.7 ± 30.9	145.6 ± 30.0	150.3 ± 47.1	NS
	Control	155.6 ± 20.2	161.8 ± 41.1	168.5 ± 36.1	155.9 ± 31.3	169.0 ± 35.7	NS
β-TG (pg/mL)	Hydrolink	901 (869-1292)	912 (869-1115)	976 (916-1146)	965(933-1120)	976 (927-1183)	
	Control	1053 (906-1806)	1090 (958-1760)	1017 (890-2488)	1109 (967-2353)	1119 (973-2258)	
PF-4 (ng/mL)	Hydrolink	36 (29-73)	32 (29-57)	29 (28-44)	29 (27-46)	35 (27-44)	
	Control	37 (30-124)	36 (31-130)	74 (33-109)	34 (30-86)	35 (30-62)	

Ronco et al, Int J Art Org, 2017, 40 (5), 234-239

Membrane functionalization



Radu, Polymers, 2022, 14, 1130.

Example of polysulfone functionalization

Heparin Covalent Immobilization (anticoagulant and LDL adsorption)

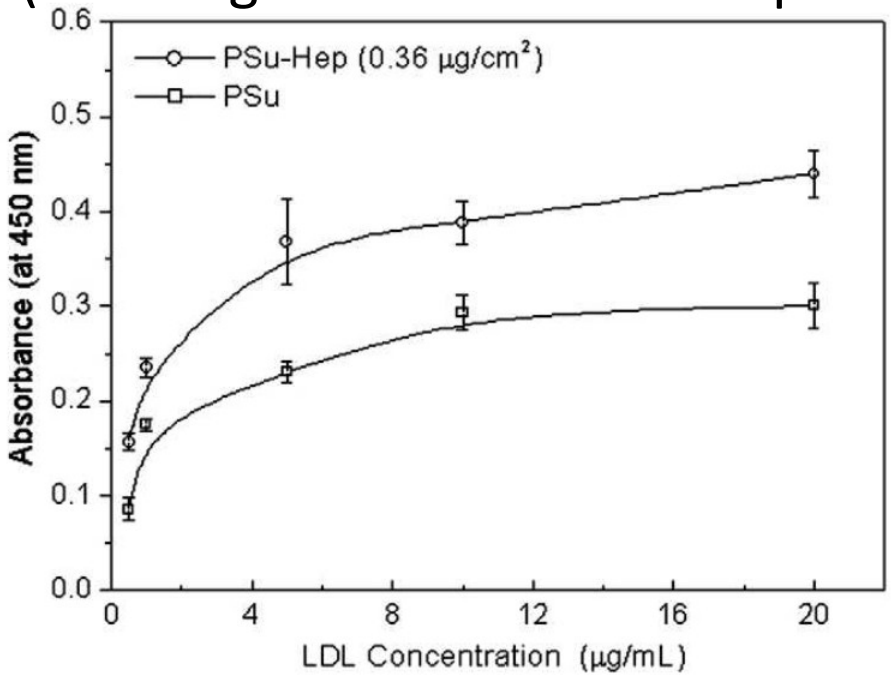
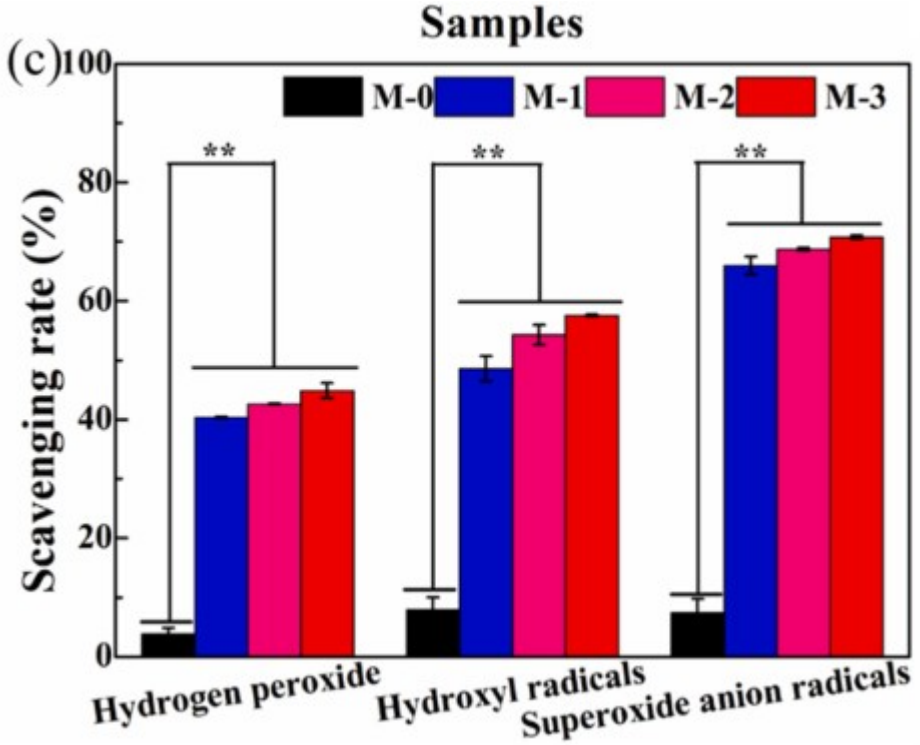


Fig. 6. Adsorption of LDL from single protein solution with different concentrations (0.5, 1.0, 5.0, 10 and 20 μg ml^{-1}) on the pure and heparin-modified PSu films. The adsorption of LDL on both the pure and heparin-modified PSu films surface followed the Langmuir isotherm model. A higher quantity of LDL is adsorbed on the heparin-modified PSu film surface compared to plain PSu.

Addition of Resveratrol to pure PSF @ different levels



Resveratrol: plant-based extracted antioxidant

DPPH: 2,2 **D**y**P**henyl-1-**P**icryl**H**ydraz

Huang XJ, Acta Biomater, 2010, 6, 1099 - 1106

Qi X, Mate Sci & Engineer, 2021, 123

Green dialysis

1. Water 

High Dialysis Efficiency → High Water Consumption

Better outcomes ← 120 L / session

1. High Efficiency Water Treatment Plants (WTP)
2. Adsorption as removal mechanism

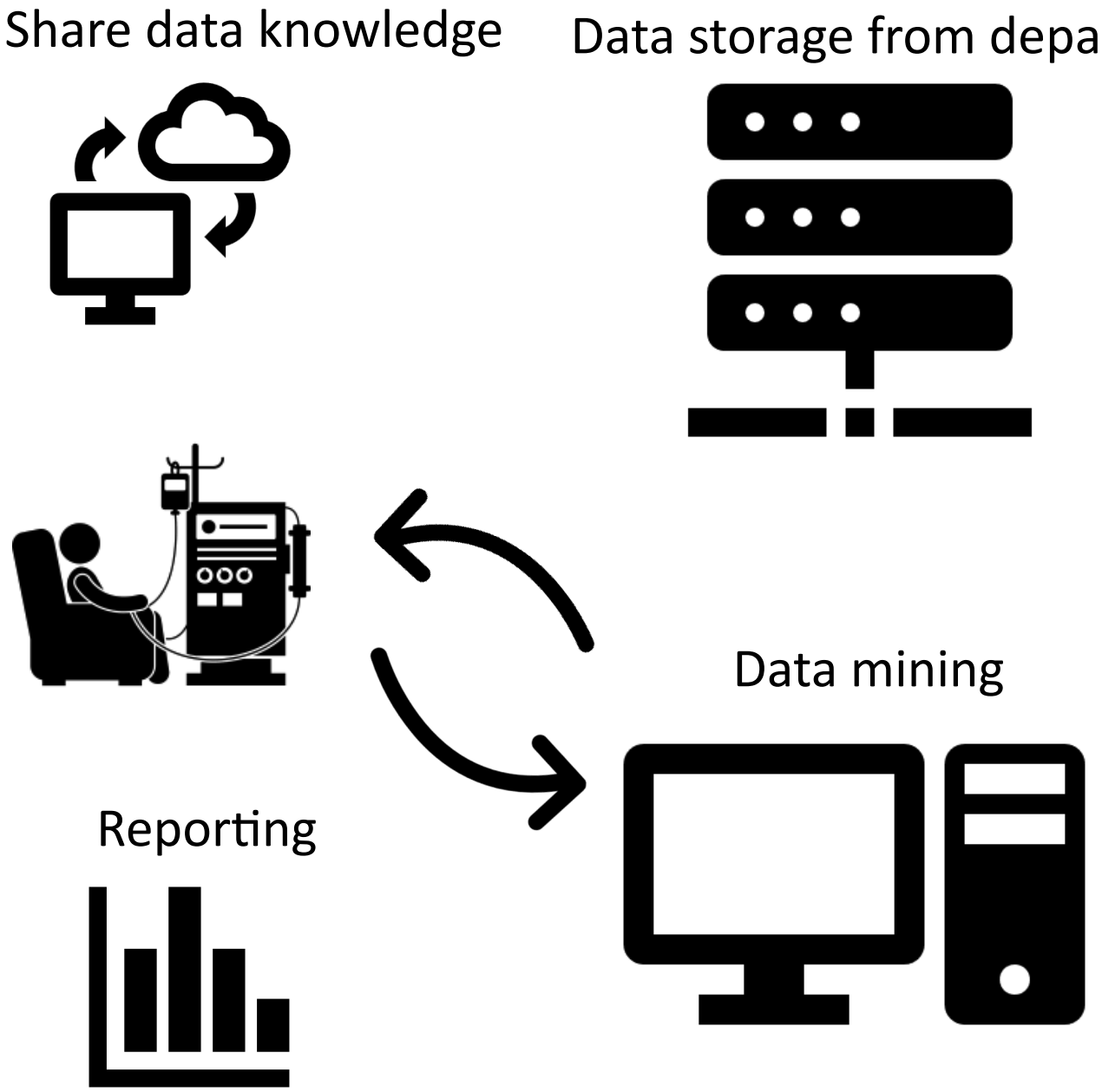
2. Electricity 

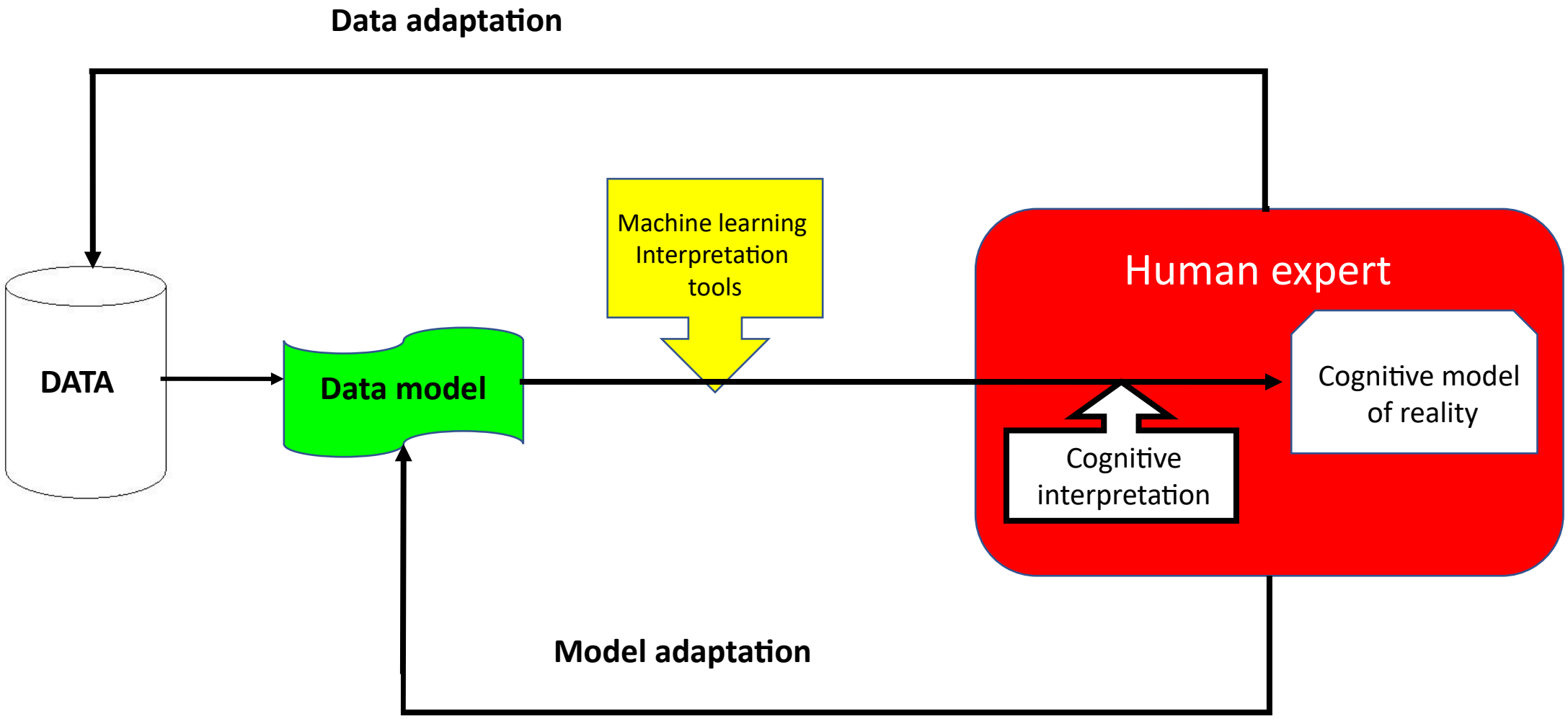
Technology improvement into

Machine: heat recovery

Water Treatment Plant

Computer Assisted Dialysis Care




Data adaptation
DATA
Data model
Machine learning
Interpretation
tools
Human expert
Cognitive model
of reality
Cognitive
interpretation
Model adaptation

Artificial Intelligence in CKD

Distributed sensing
Distributed intelligence
Distributed control

First introduction in HD field

Artificial Intelligence: A New Approach for Prescription and Monitoring of Hemodialysis Therapy

Ahmed I. Akl, MD, Mohamed A. Sobh, MD, Yehya M. Enab, PhD, and James Tattersall, MD

• The effect of dialysis on patients is conventionally predicted using a formal mathematical model. This approach requires many assumptions of the processes involved, and validation of these may be difficult. The validity of dialysis urea modeling using a formal mathematical model has been challenged. Artificial intelligence using neural networks (NNs) has been used to solve complex problems without needing a mathematical model or an understand-

American Journal of Kidney Diseases, Vol 38, No 6 (December), 2001: pp 1277-1283

Artificial intelligence is likely to be the future of dialysis machine processors and developing control devices. As such, it will probably modify clinical practice in a substantial way, particularly in hemodialysis.

AI

- Prescription
  - Intra session → HD set-up
  - Long-term → Optimal ESA dose

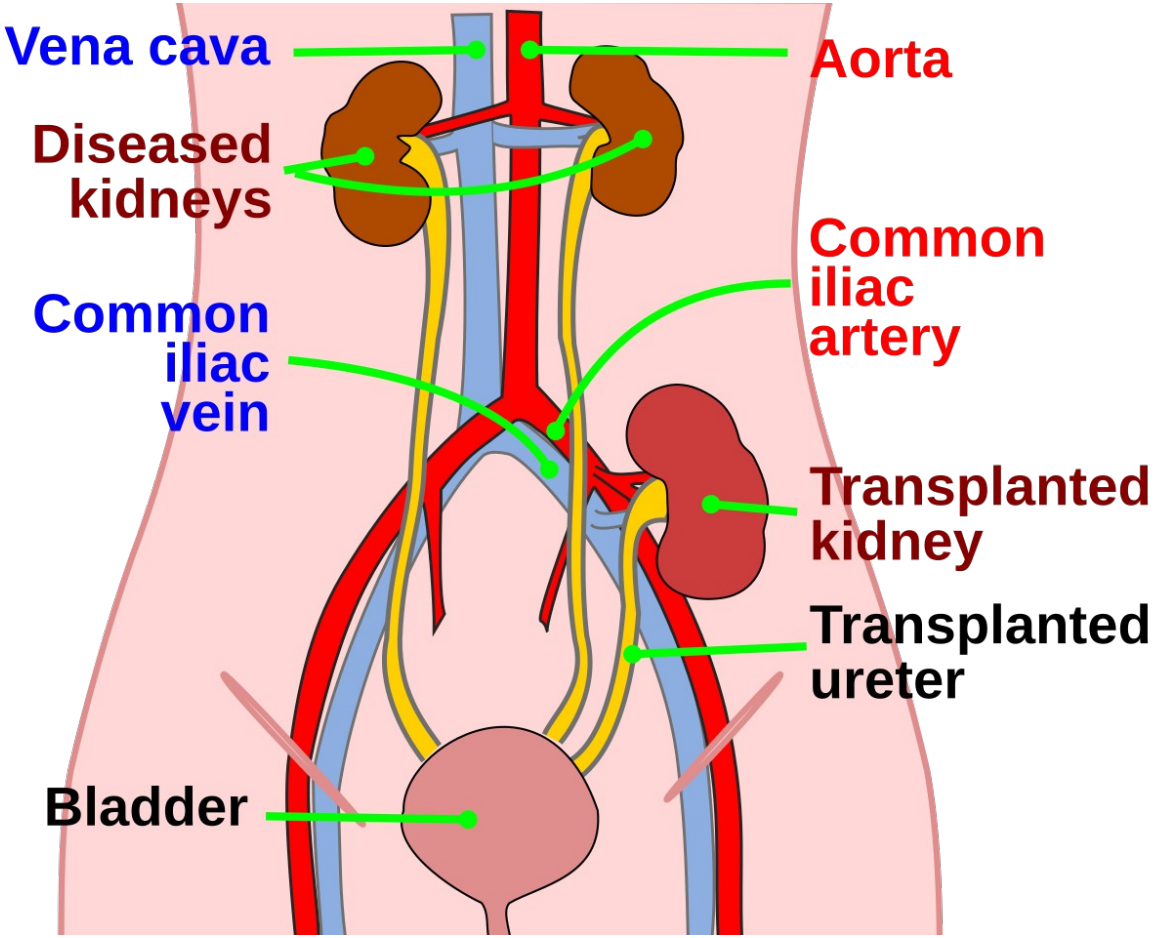
  Martinez JM, Comp. Meth Prog Biomed, 2014
- Monitoring
- Control
  - Short-term → Intra session A.E. Hypotension

    Mambelli E, IJAO, 2022
  - Long-term
- Prediction
  - Short-term → Intra session events
  - Long-term → Clinical outcomes (Mortality, CV events)

    Kanda E, PLosOne, 2020

Hoeso M, Kidney Dis, 2018, 4, 1-9

KIDNEY TRANSPLANT

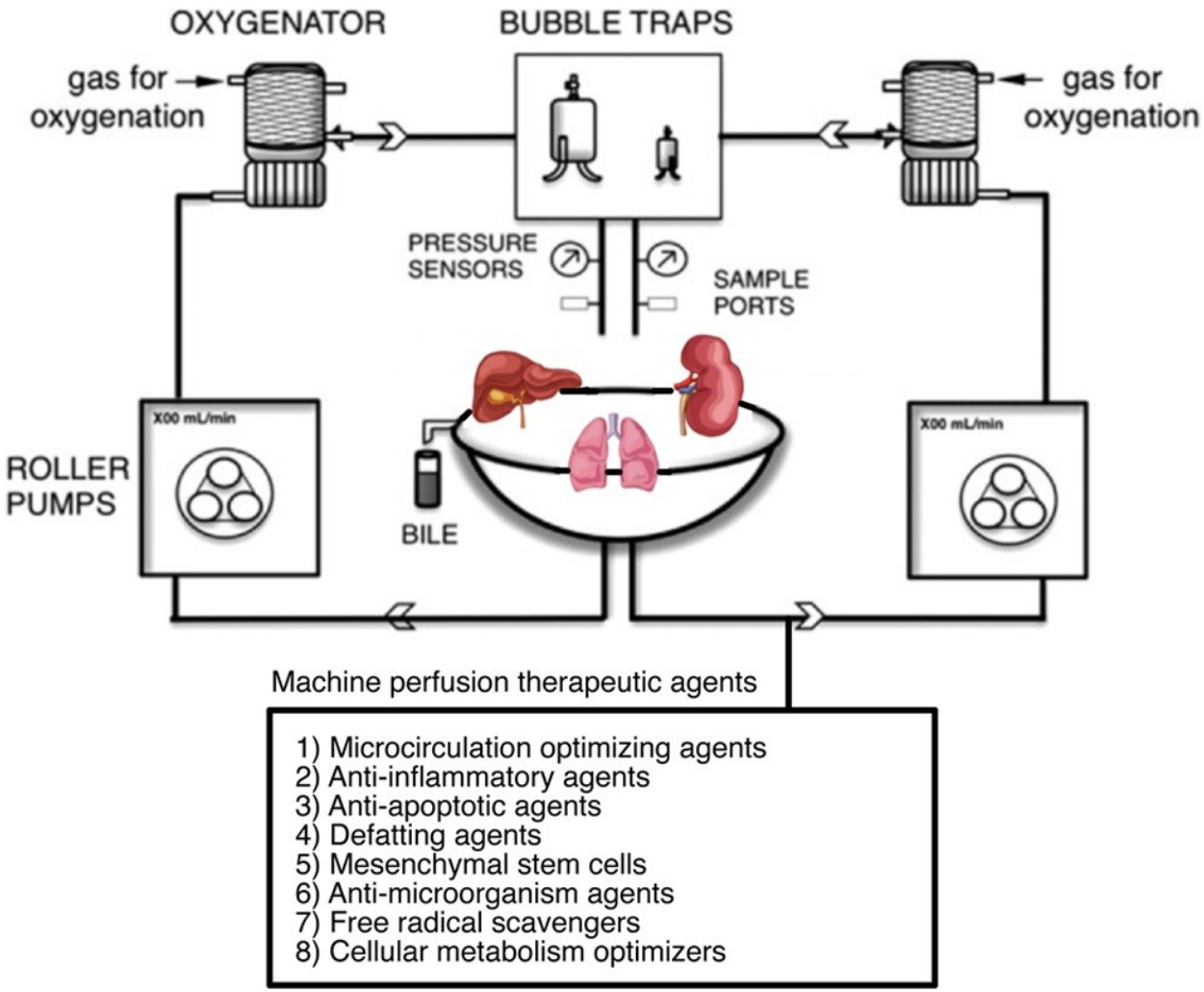


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

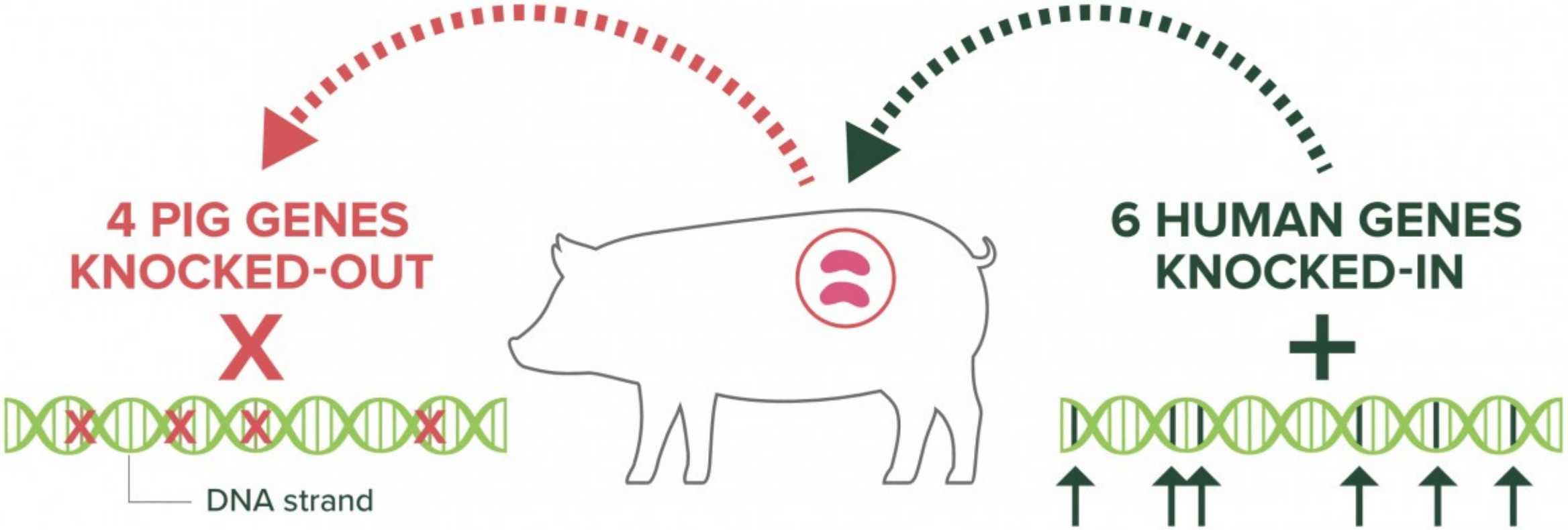
Hypothermia or Machine Perfusion in Kidney Donors

February 2, 2023



The 10-Gene-Edited Pig

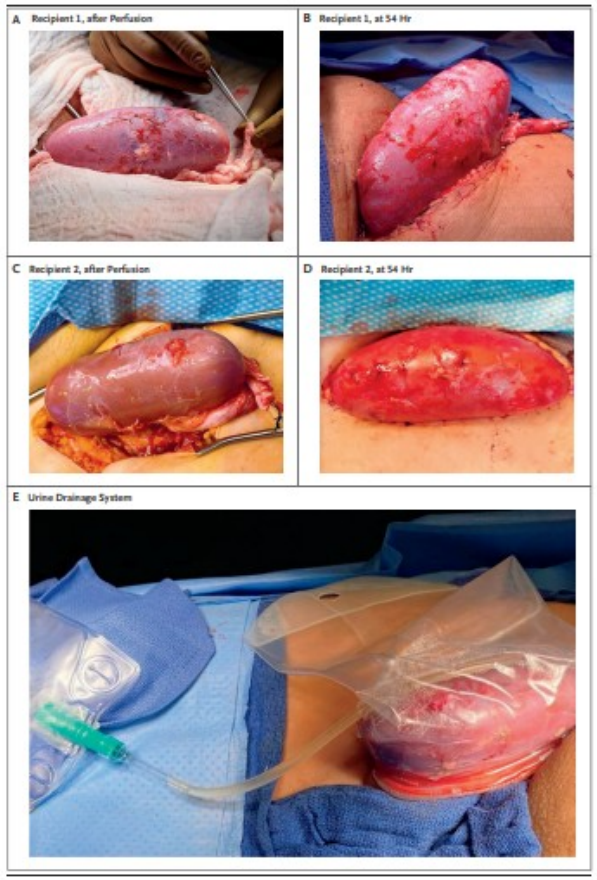
The key to xenotransplantation

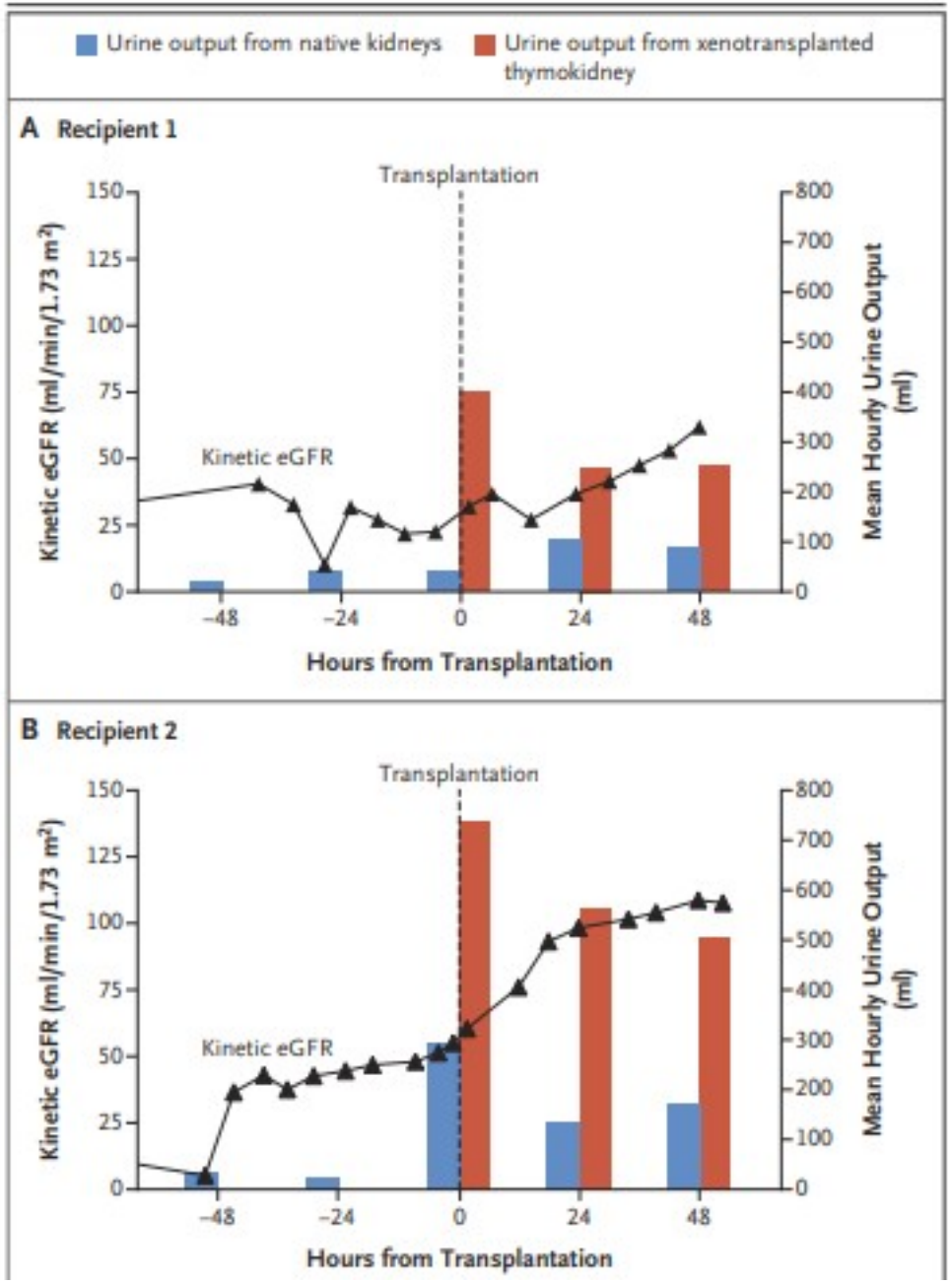


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Results of Two Cases of Pig-to-Human Kidney Xenotransplantation





Tanta tecnologia tra le novità in Nefrologia !!!

With different mechanisms, the SGLT2i acts in the same direction. By antagonizing the tubular reabsorption of glucose and Na+, the SGLT2i maintain the concentration of those molecules in the glomerular filtrate and counteract the production of renin at the level of the dense macula in which the absorption of Na+ and the production of adenosine are activated [36, 37].

The analysis of the neurohormonal and receptor network is involved in the management of the intra-renal Na^+ of the neurohormonal response and, therefore, of the intra-glomerular filtering pressure and the Na^+ retention. The beneficial consequences of the action of SGLT2i have been observed in the largely controlled processes conducted in subjects with T2DM. In these studies, the reduction of the initial filtering pressure led to a replacement of the filter, but below if stabilization is observed and, in some cases, a detail of the recovery, the improvement is also proven inversely proportional to the degree of renal impairment before -existent [37]. Furthermore, the reduced glucose reabsorption in the proximal tubules (due to both decreased glucose levels and SGLT2 inhibition) could result in a decrease in proximal tubular cells inflammation and fibrosis [38]