Personalising treatment of diabetic complications with a focus on

“A potential role for the gut microbiota in diabetic kidney complications”

Peter Rossing MD DMSc
University of Copenhagen
Steno Diabetes Center

Korean Diabetes Association

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Disclosures

- Professor Rossing has received the following:
  - consultancy and/or speaking fees (to his institution) from AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, MSD, Novo Nordisk and Sanofi Aventis
  - research grants from AbbVie, AstraZeneca and Novo Nordisk

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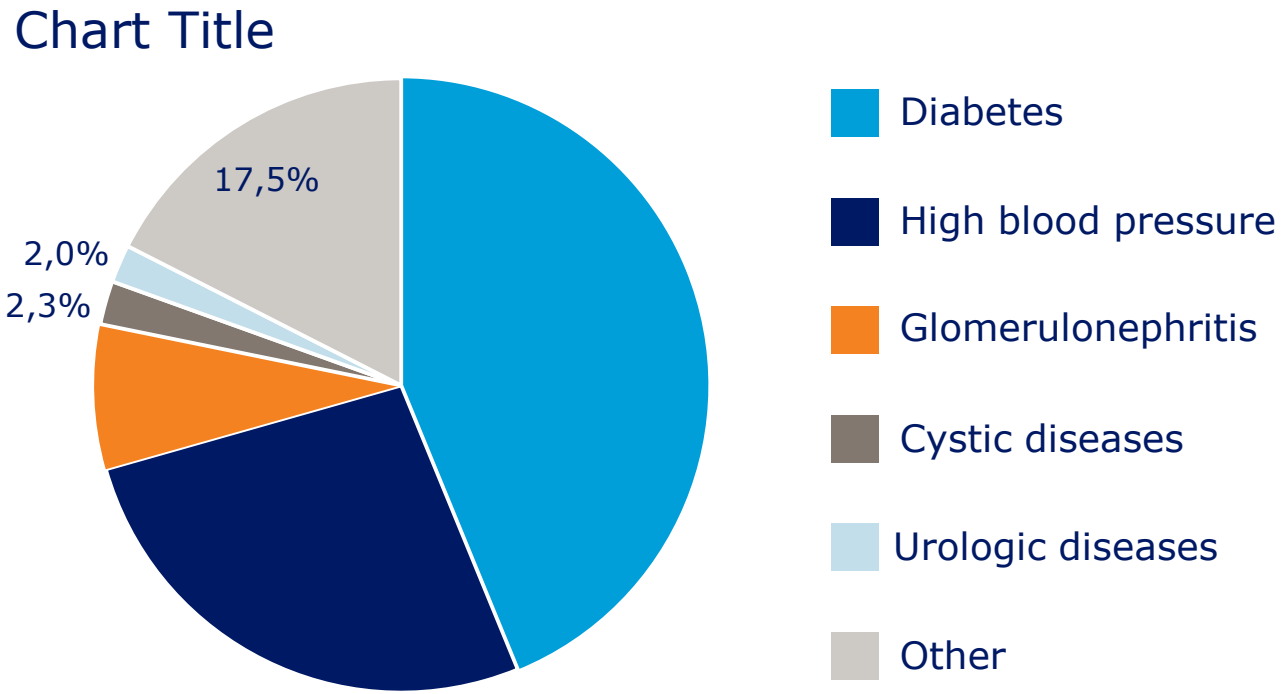
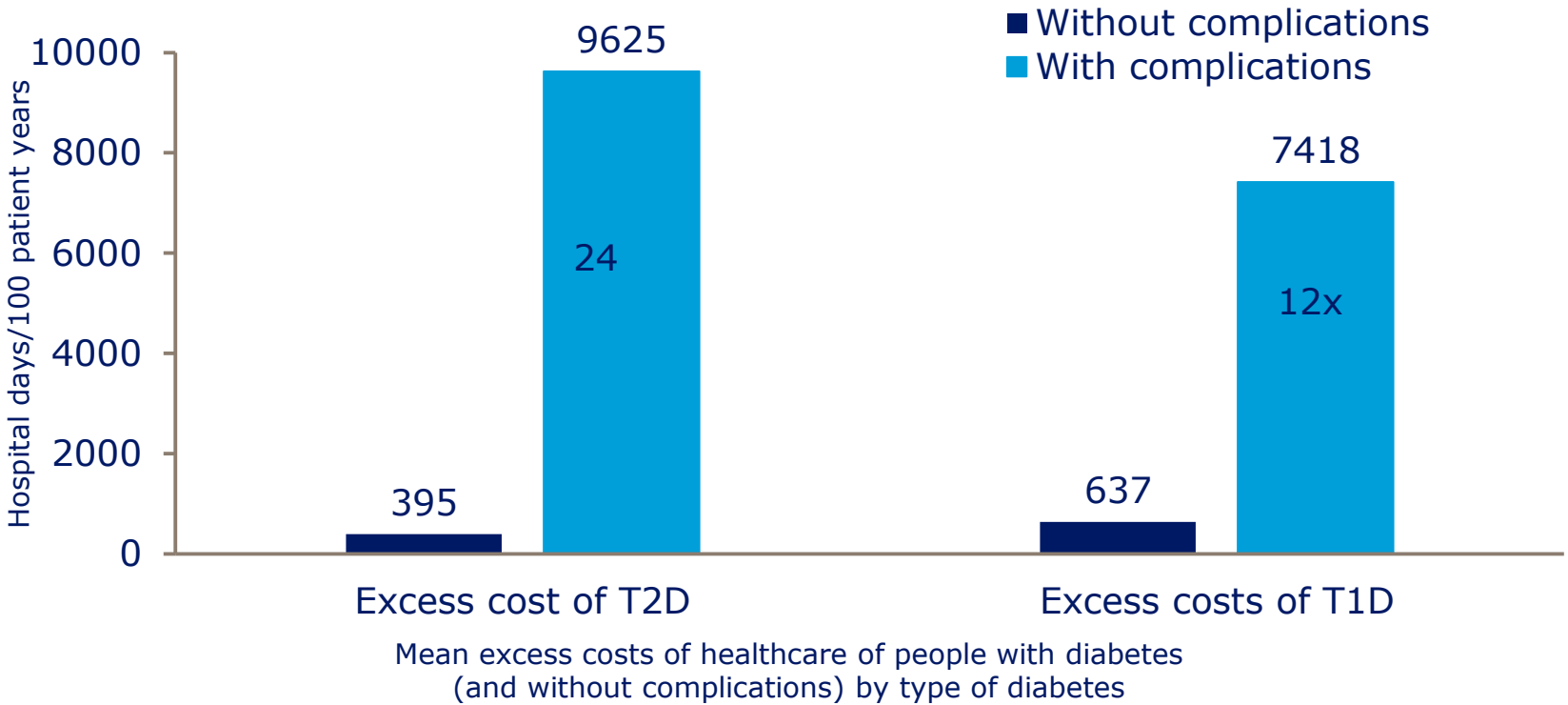
Diabetes is a leading risk factor for renal impairment



US Renal Data System 2007 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

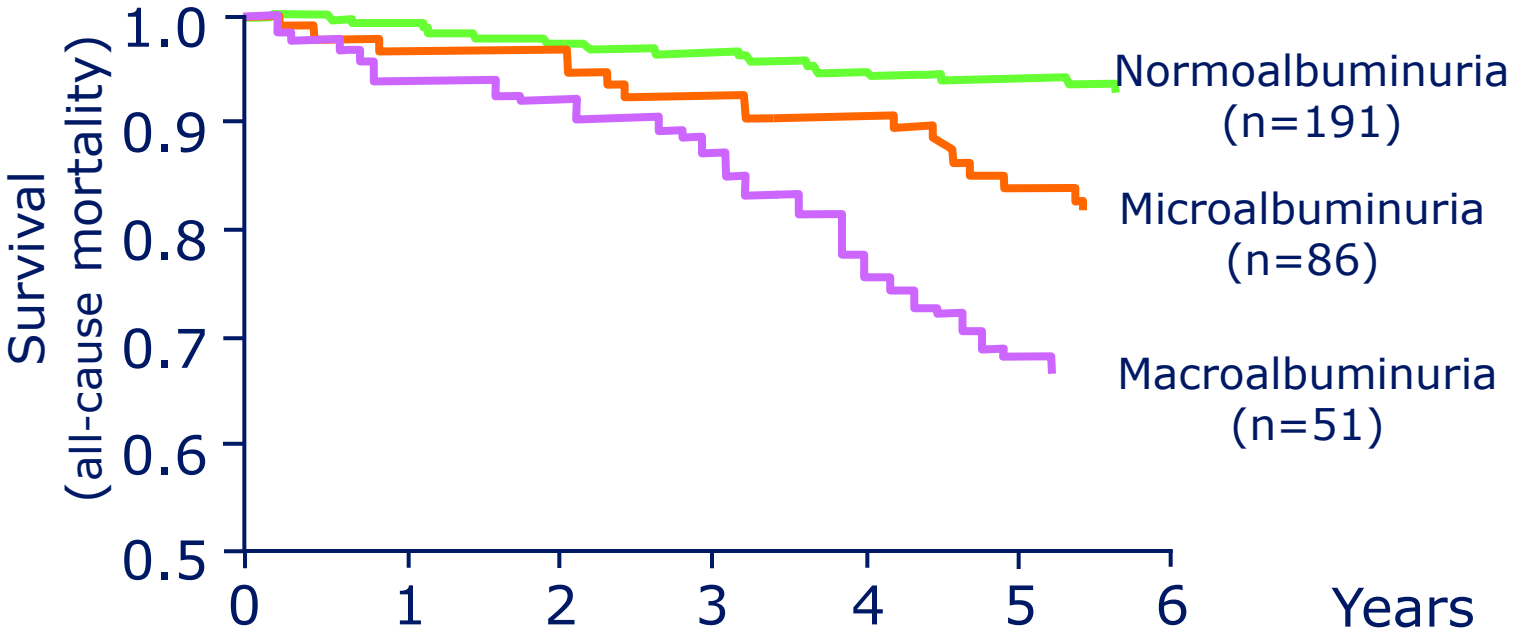
Costs of complications in patients with diabetes: the Helsinki Study



Mean excess costs of healthcare of people with diabetes (and without complications) by type of diabetes

Finnish Diabetes Association. DEHKO 2000–2010. Finnish Diabetes Association 2001

Proteinuria Is an Independent Risk Factor for Mortality in Type 2 Diabetes



P<0.01 normo vs. micro- and macroalbuminuria
P<0.05 micro vs. macroalbuminuria

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Gall, MA et al. Diabetes 1995;44:1303

Proteinuria based prevention of DM nephropathy

Albuminuria ➡ RAS-inhibition

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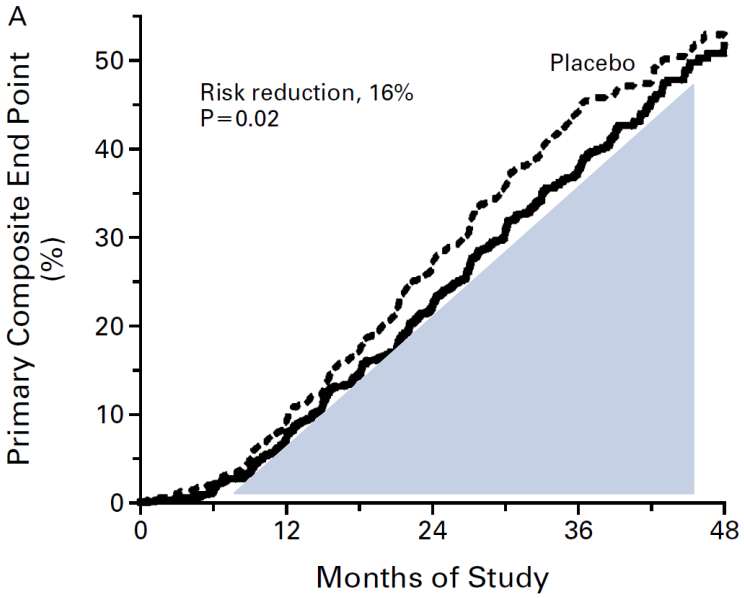
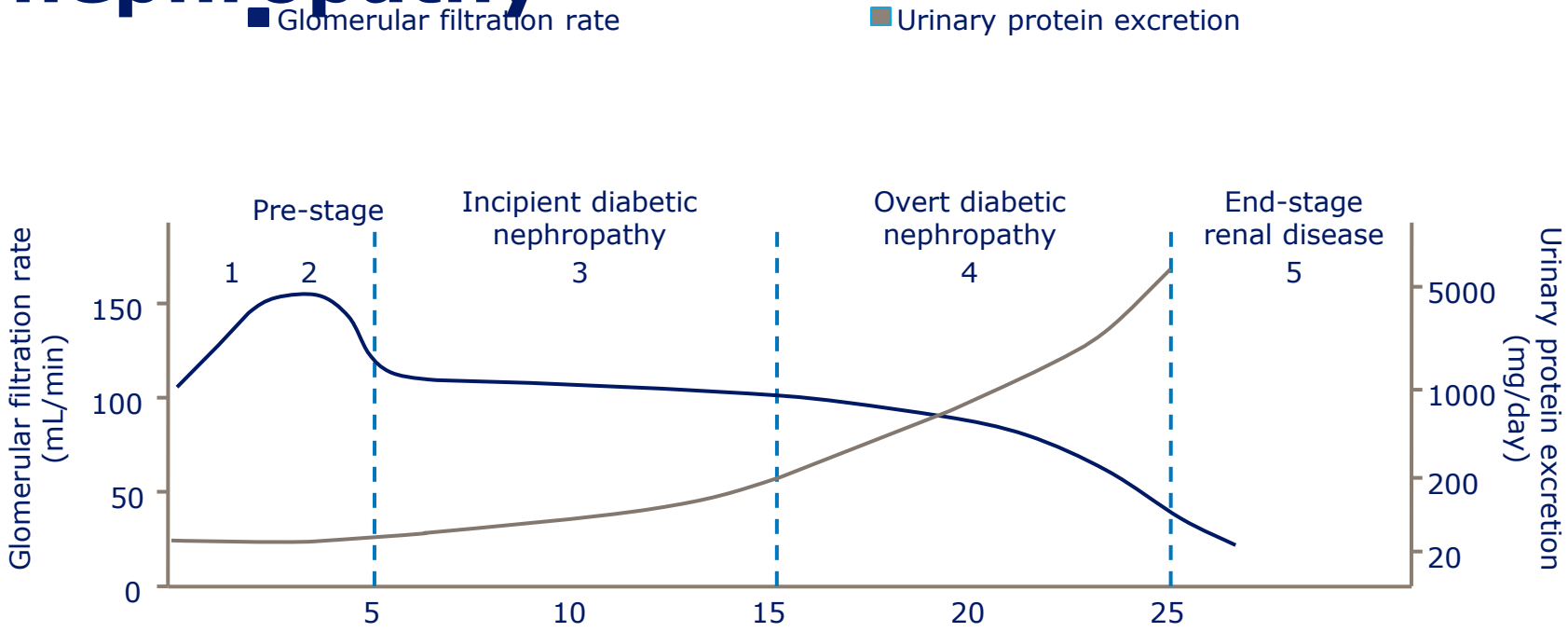
RENAAL: Effects of Losartan on renal and CVD in type 2 diabetes and nephropathy



The unmet need

Brenner et al NEJM 2001

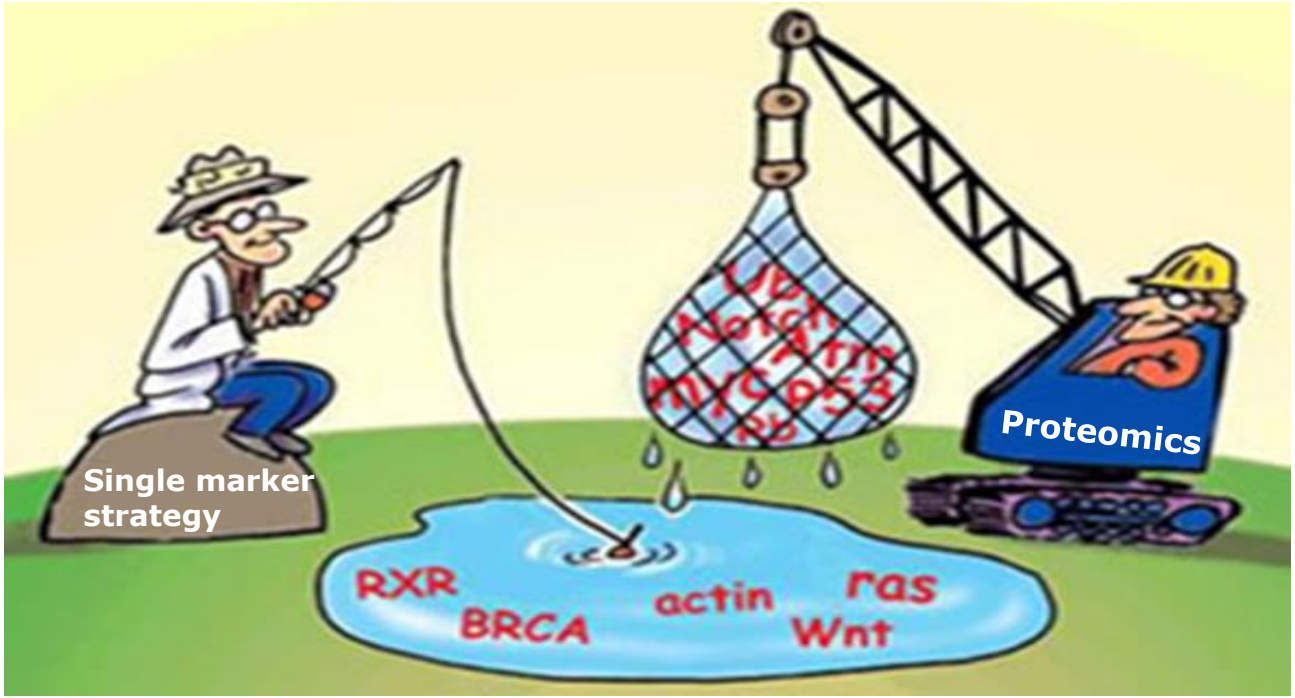
Natural history of diabetic nephropathy



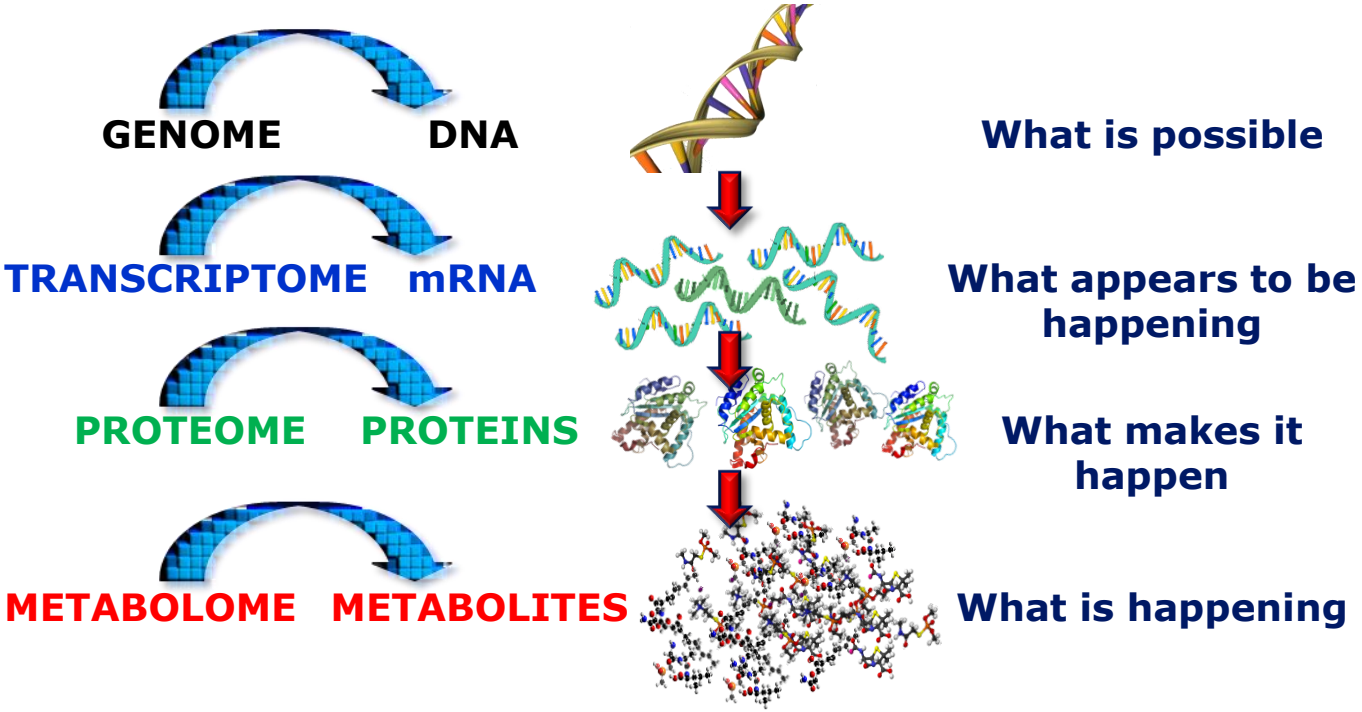
New and early markers
New treatments

Johnson & Feehally, eds. Comprehensive Clinical Nephrology, 2000

Unbiased (open) search for new markers



OMICS: from genes to metabolites



Proteomic utility in DN

- Add to our understanding of patho-physiology
- Identify patients at risk
- Monitor progression of disease and treatment efficacy
- May identify new treatment targets

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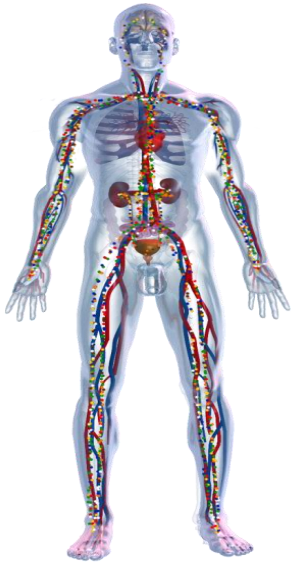
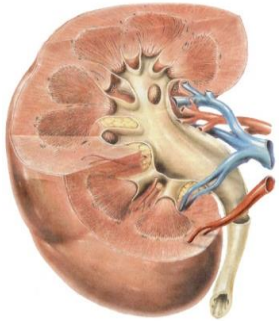
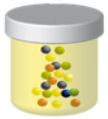
CE-MS proteomic technique –
High separation power and sensitive detection



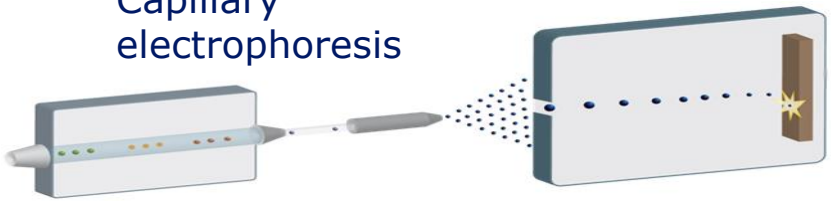


Urine sample



Capillary electrophoresis

Mass spectrometry



Data evaluation

Separation and analysis of proteins and peptides (>**1,000**)

Run time ~**60 min**

CE
- fast
- robust
- inexpensive
- reproducible

MS
- resolution
- scan speed

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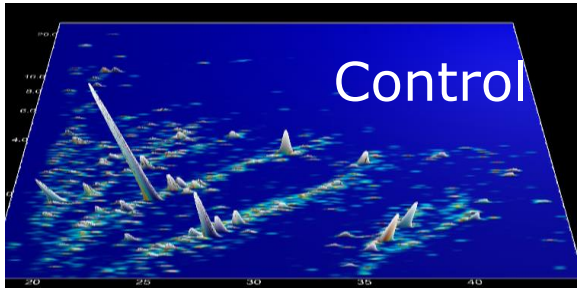
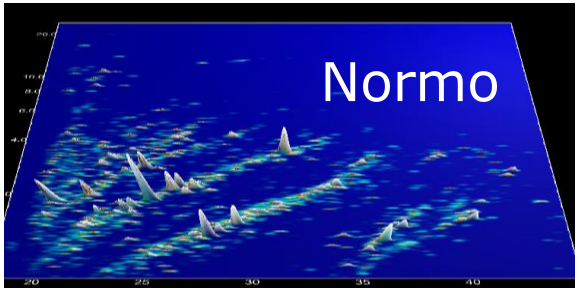
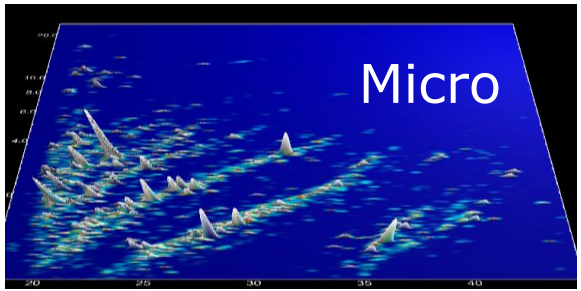
Contrib Nephrol. 2008; 160: 107–126

Proteomic profile: T1DM +/- DN

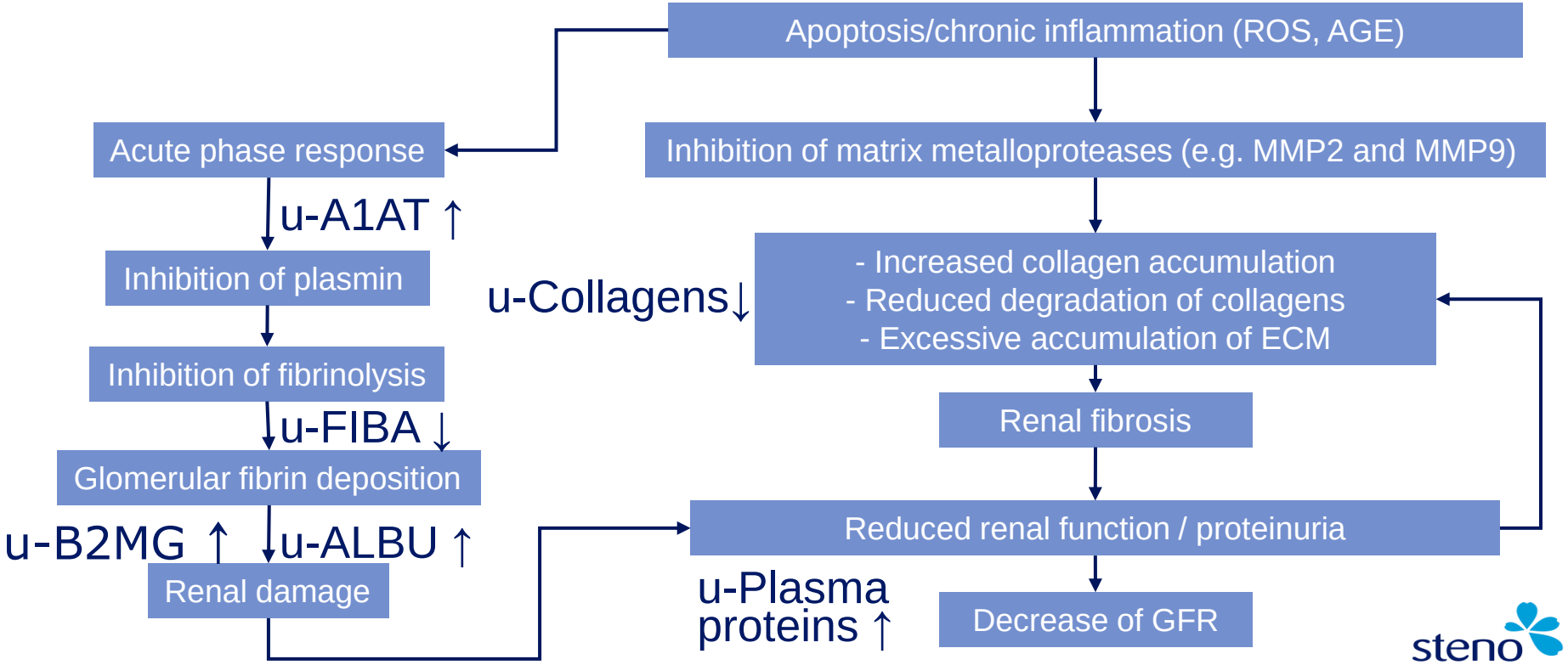




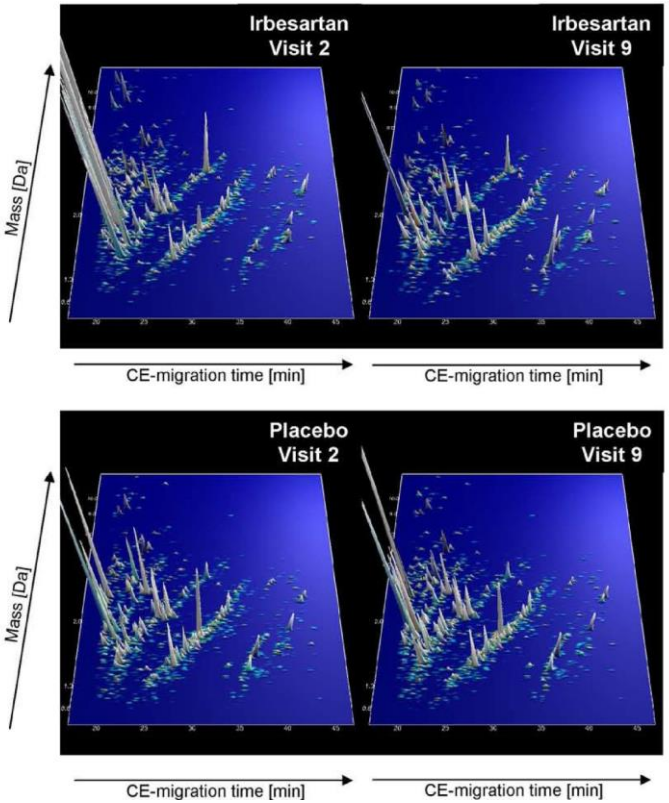


K Rossing et al., *JASN*, 2008

Pathosphysiological suggestions



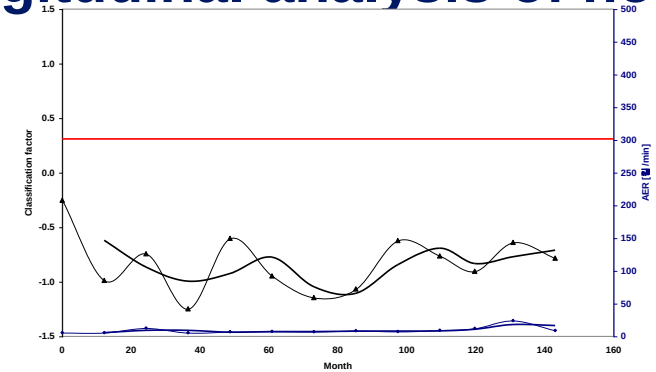
Monitoring Treatment Effects by Irbesartan in microalbuminuric type 2 DM

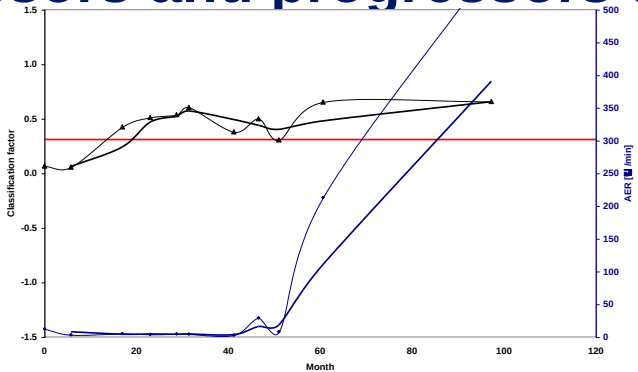


S Andersen et al BMC Nephrol 2010

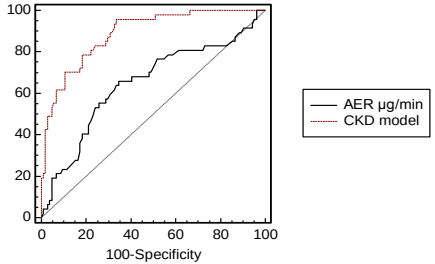
Prediction

Longitudinal analysis of non-progressors and progressors to DN





Proteome analysis and AER from diabetic normoalbuminuric patients (151 samples), assessed for progression to DN over 5 years



	AUC	95% CI
AER [µg/min]	0.648	0.566 to 0.724
CKD model	0.887	0.826 to 0.933

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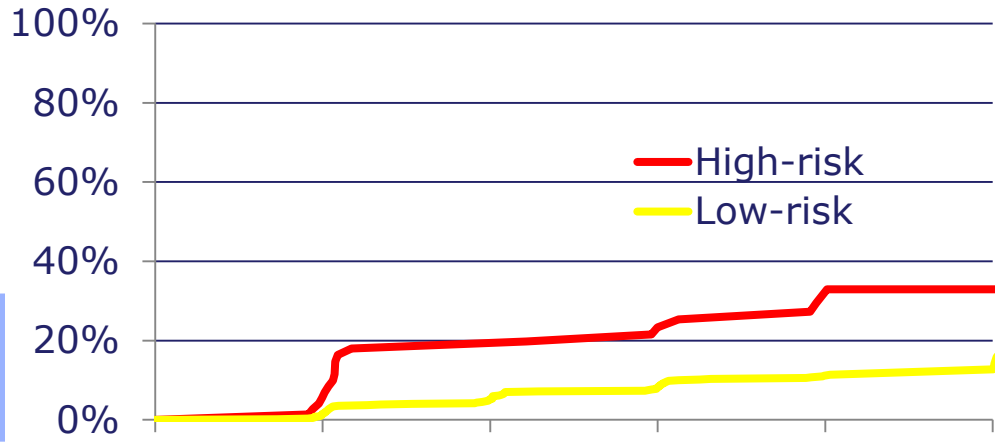
Zürbig et al Diabetes 2012

CKD273 and progression to microalbuminuria

Event rate (Microalbuminuria)



P= 0.0001

Time from randomisation (y)	0	1	2	3	4	5
High-risk, n (events, n)	74(0)	69(12)	58(13)	53(16)	35(19)	6(19)
Low-risk, n (events, n)	666(0)	650(25)	610(45)	570(63)	465(68)	82(72)

MK Lindhardt et al Neph Dial Trans 2016

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The Priority Trial

Type 2 DM
Normoalbuminuria

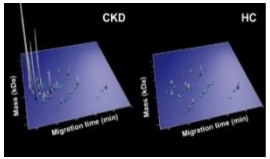
Proteomic test

High-risk
n ~ 250

Randomised
Double-blinded
Placebo controlled

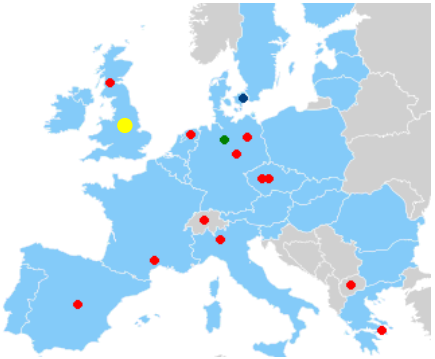
Placebo

Spironolactone



Low-risk
n ~ 1700

Observational



Three years follow-up

Targets in Diabetic Nephropathy

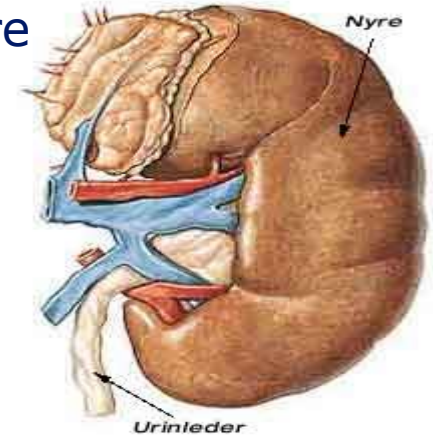
Oxidative stress
NOX1/4i

Systemic Blood Pressure
AII, ET1,Renin, Aldo

Proteinuria
soludexide

Glycemic control
DPP4, GLP1, SGLT2,PPARγ

Glycation
AGEi, RAGE blockers
PKCi



Growth factors
CTGF/TGFb/VEGF Ab

Dietary protein intake

Smoking

Uric Acid

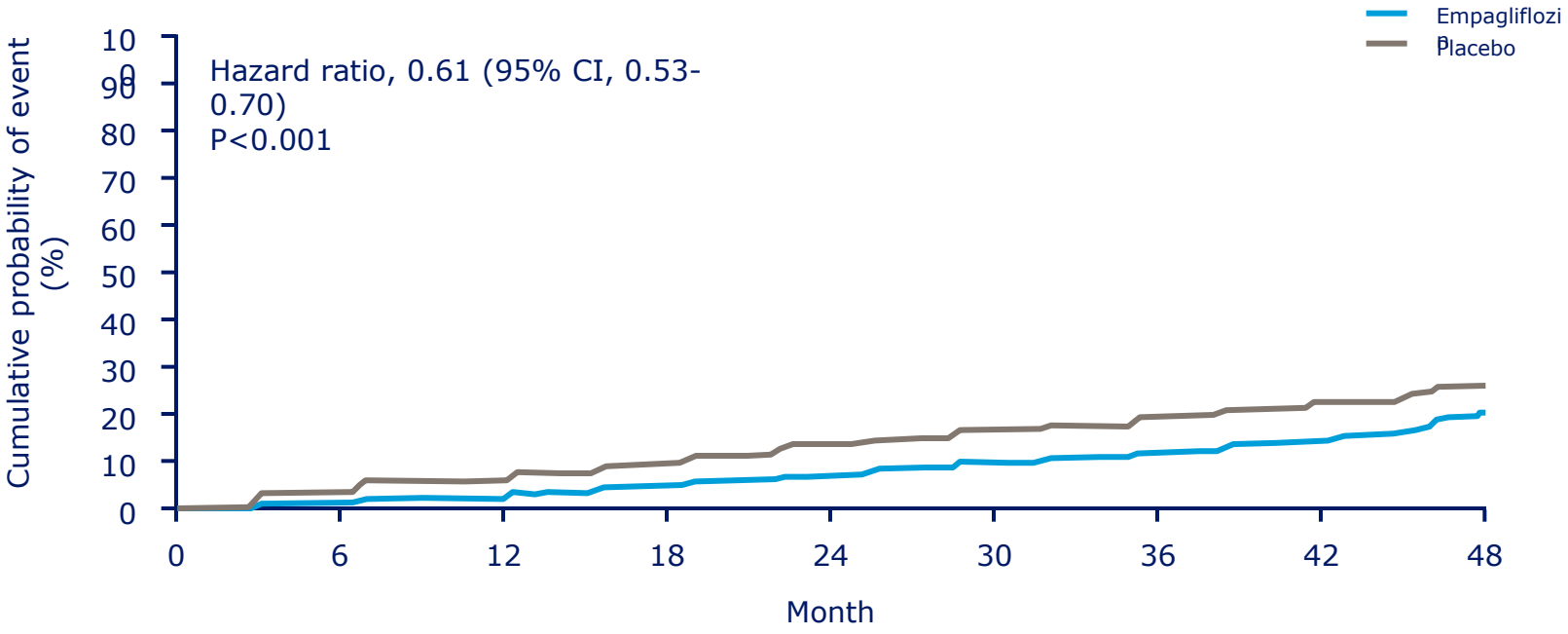
Vitamin D
VDRA

Hyperlipidemia
Statin? Fibrate?

Inflammation
CCR2/CCR5 (CCX140, NOXON),
Pentoxilfyllin, Nrf,
JAK/STAT (Baricitinip)

EMPA-REG OUTCOME

Incident or worsening nephropathy



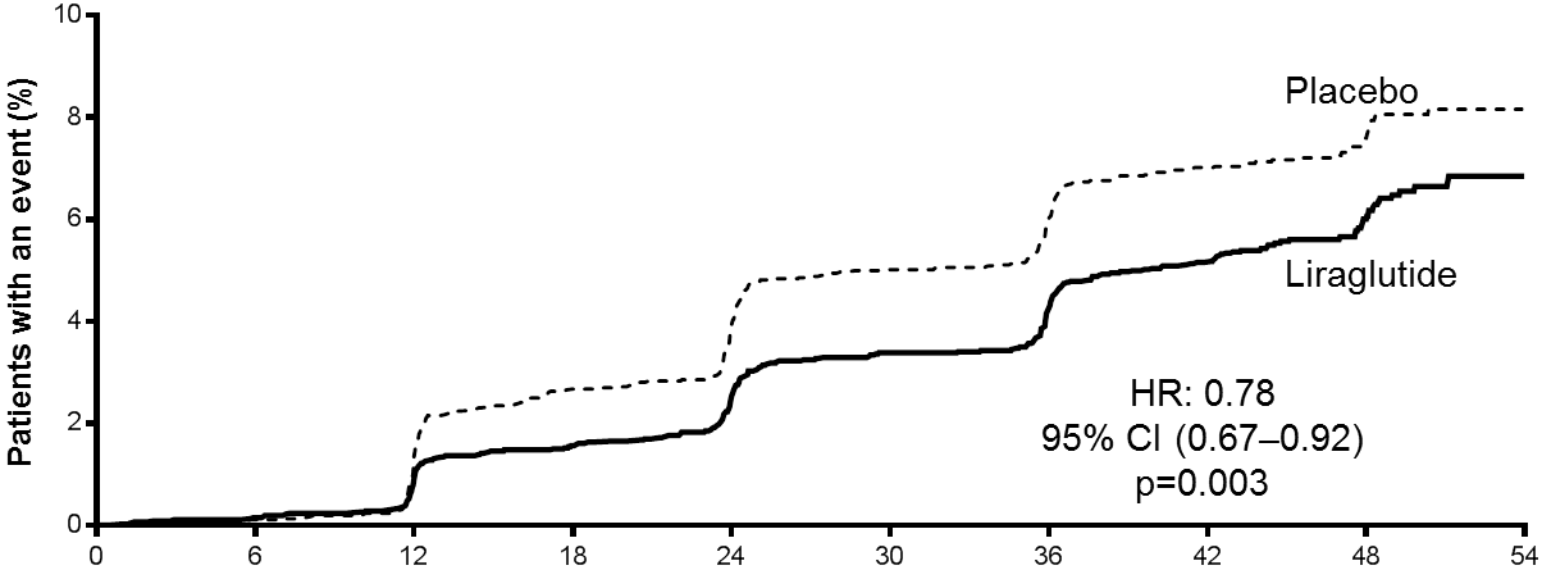
No. at Risk

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Wanner C et al. *N Engl J Med* 2015; 375:323-34.
CI, confidence interval

Time to first renal event

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



Patients at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

PROTON

PeRsOnalising Treatment Of diabetic Nephropathy

Moving from albuminuria to multidimensional characterisation and intervention

Sponsored by Novo Nordisk Foundation

Joslin Diabetes Center

Universitair Medisch Centrum Groningen

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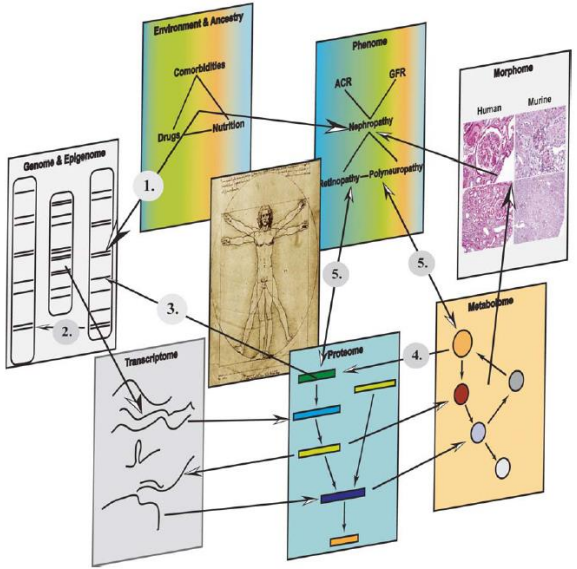
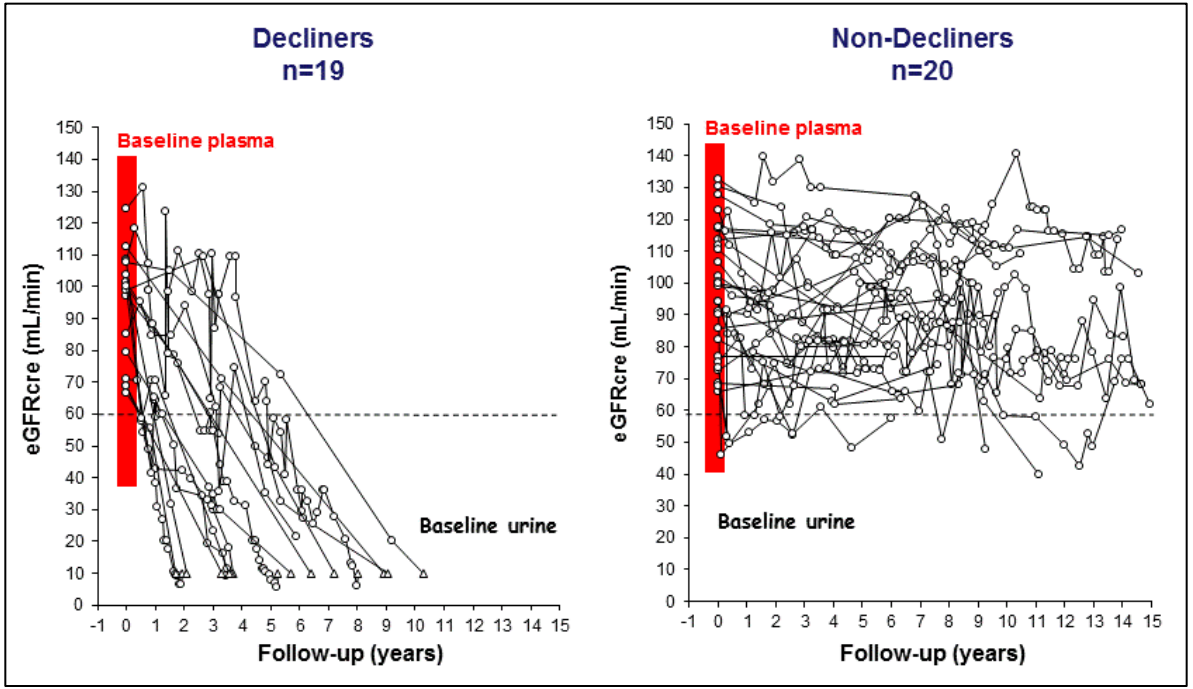
From albuminuria to profile-omics

Albuminuria ➡ RAS-inhibition

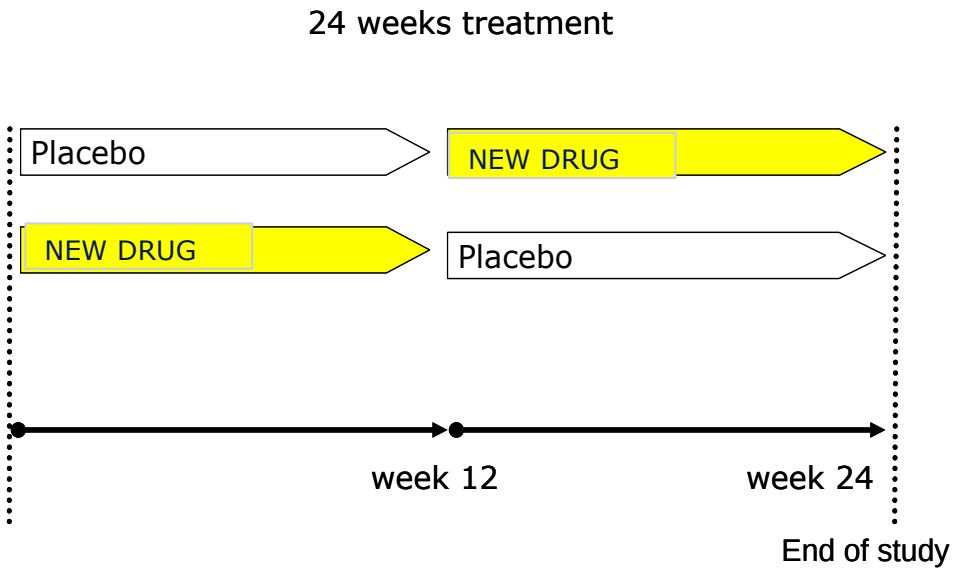


Personalised Treatment

Extreme cases



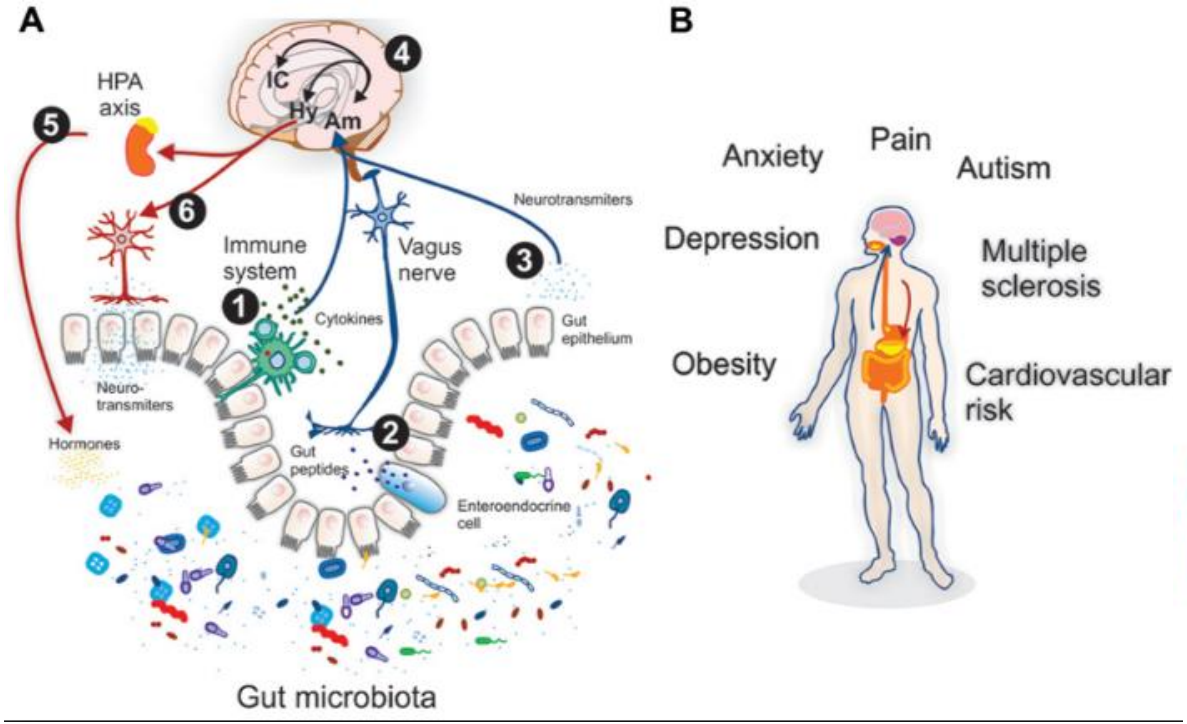
Pilot studies,
based on target/intervention

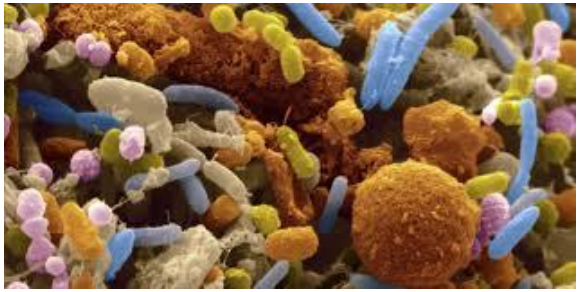


- UAER: Randomization, week 12 and week 24
- 24h BP: Randomization, week 12 and week 24
- Kidney function (^{51}Cr GFR): week 12 and week 24
- Markers of inflammation: Randomization, week 12 and week 24

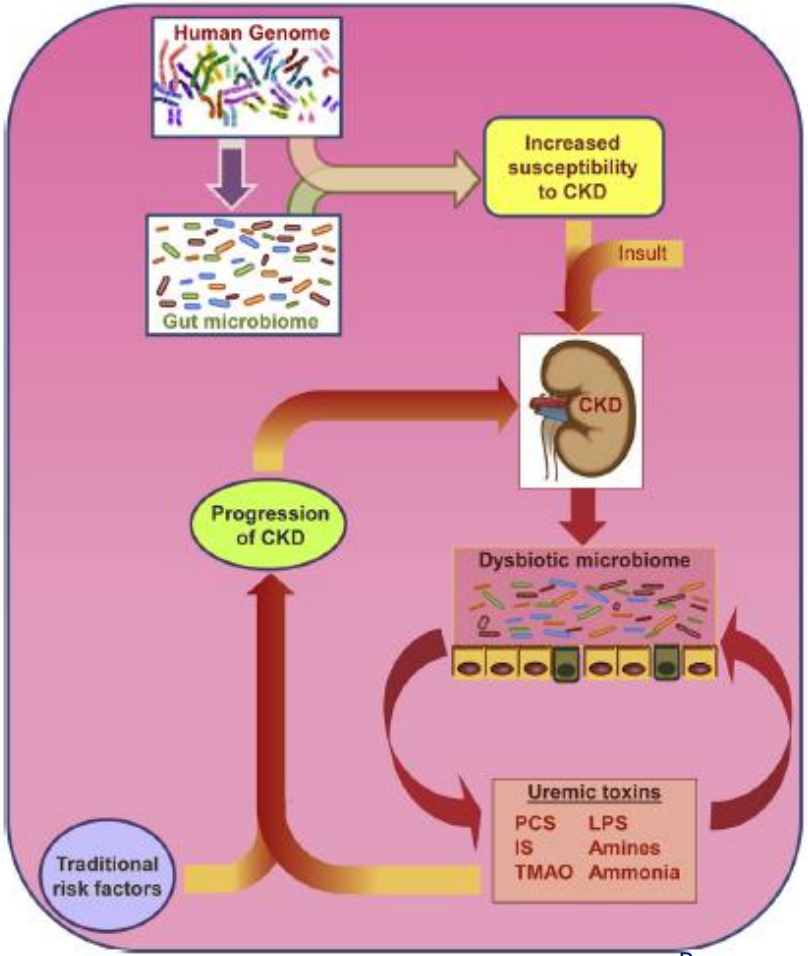
Potential targets:
fibrosis, glucose
inflammation,
oxidative stress
RAS/bradykinins
Microbiome (diet,
probiotica, adsorption)
etc.

GUT MICROBIOTA





From Frontiersin.org



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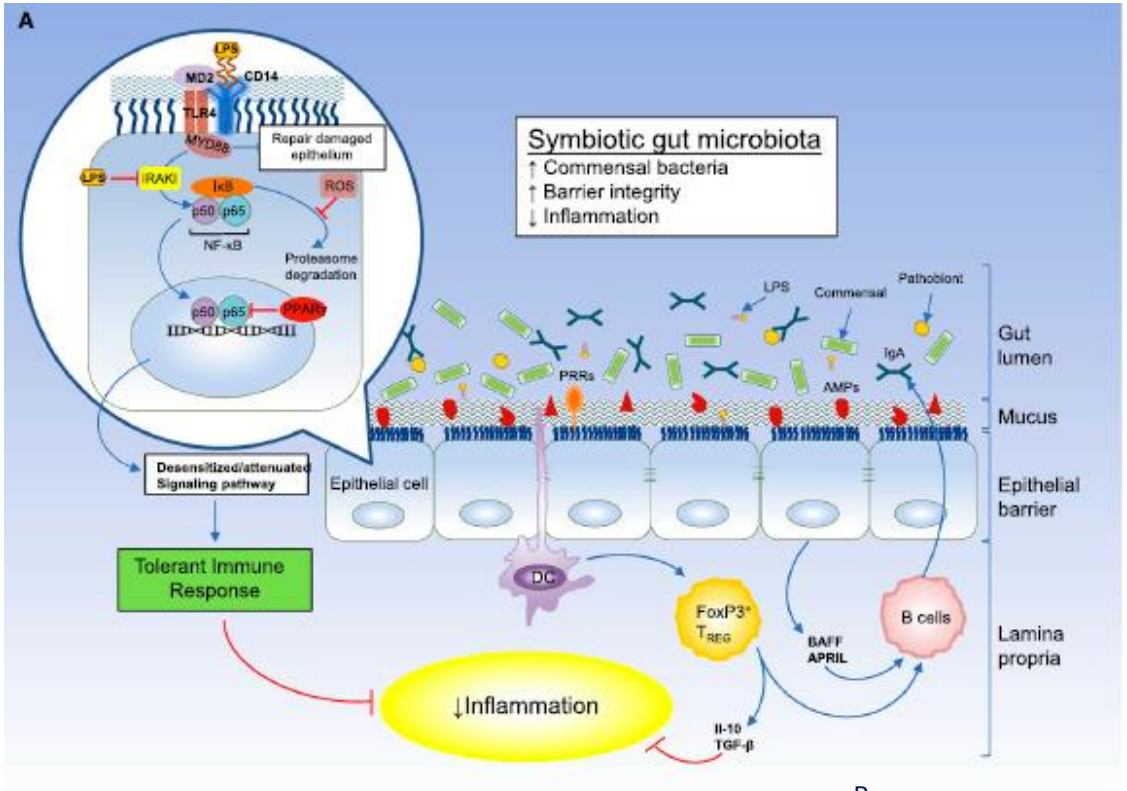
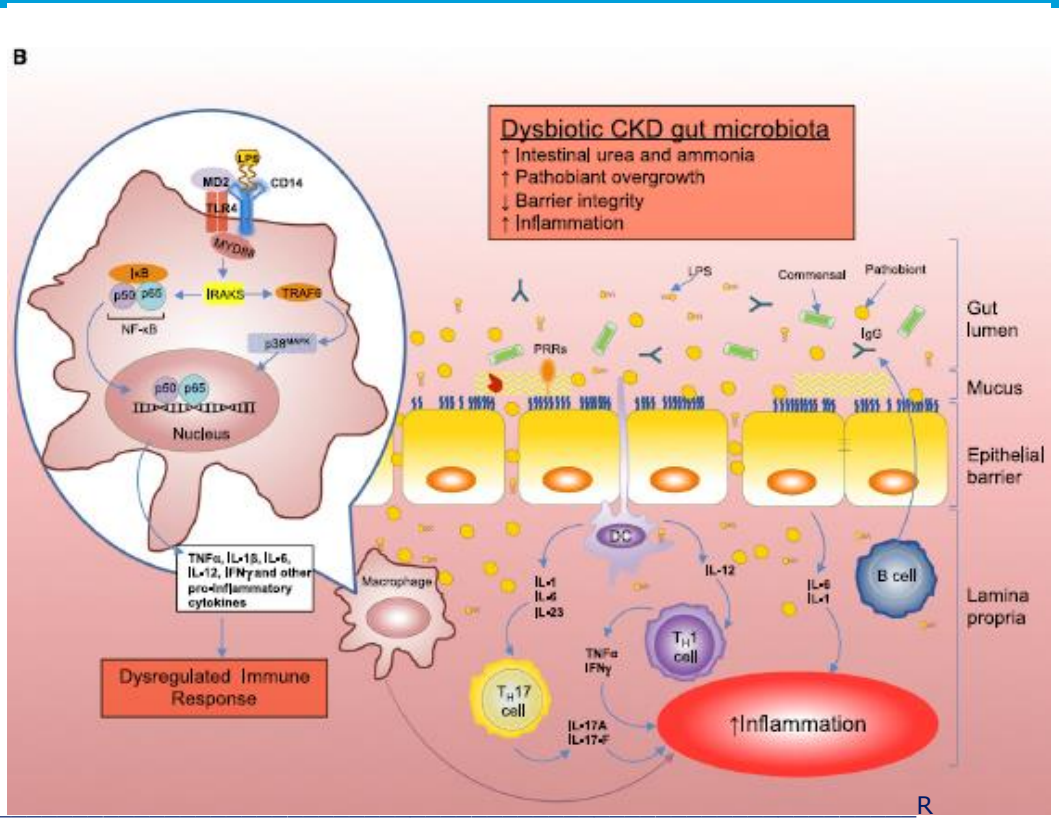
References A Ramezani et al Am J Kid Dis 2016

Symbiotic gut microbiota



References A Ramezani et al Am J Kid Dis 2016

Dysbiotic CKD gut microbiota



References A Ramezani et al Am J Kid Dis 2016

LPS induces progression of diabetic nephropathy in type 1 DM

Serum LPS activity and diabetic nephropathy

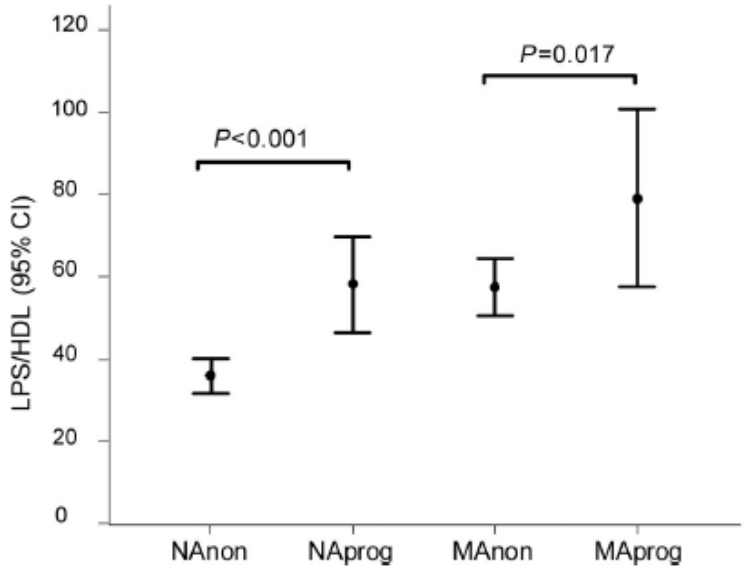
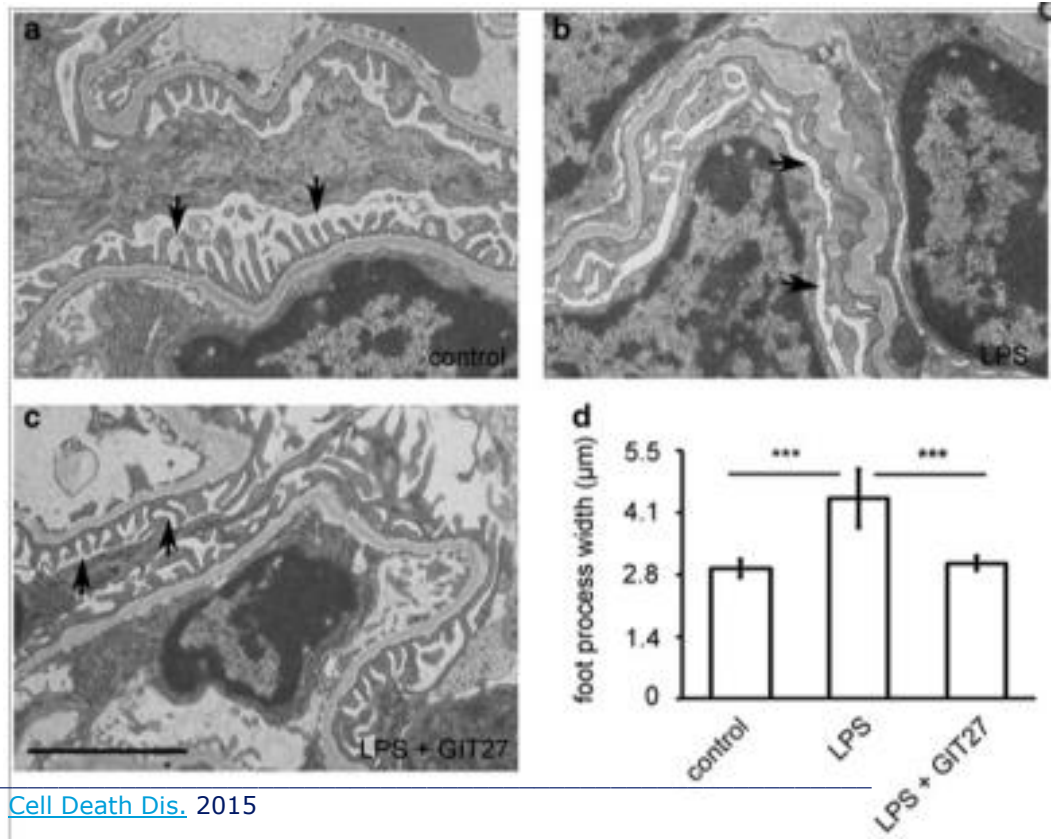


Figure 1—*A high LPS-to-HDL ratio was associated with both the development of microalbuminuria in the normoalbuminuric (NA) group and with the progression of kidney disease in the macroalbuminuria (MA) group. non, nonprogressors; prog, progressors.*

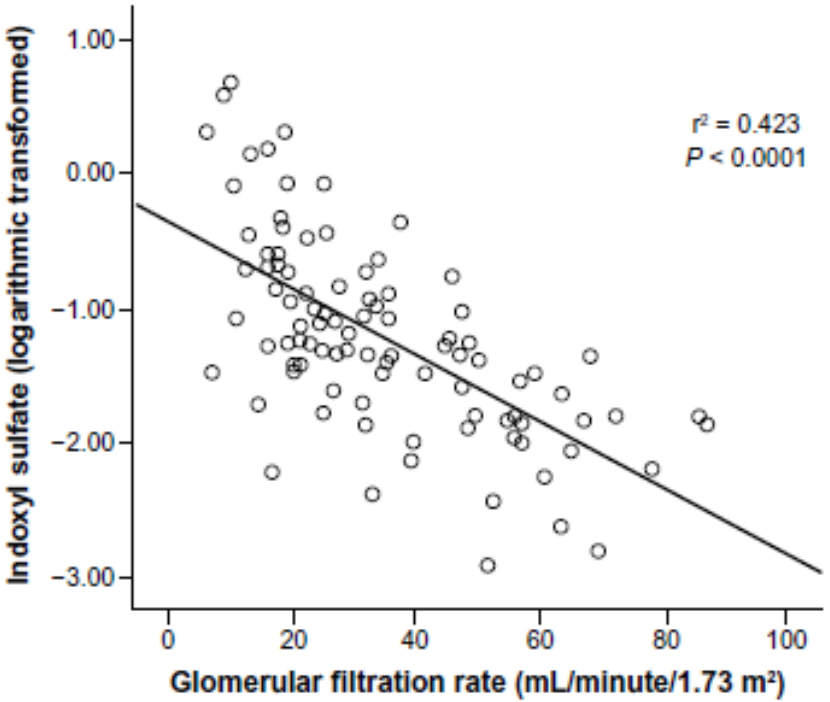
References Nymark et al Diabetes Care 2009

LPS acting via TLR pathway



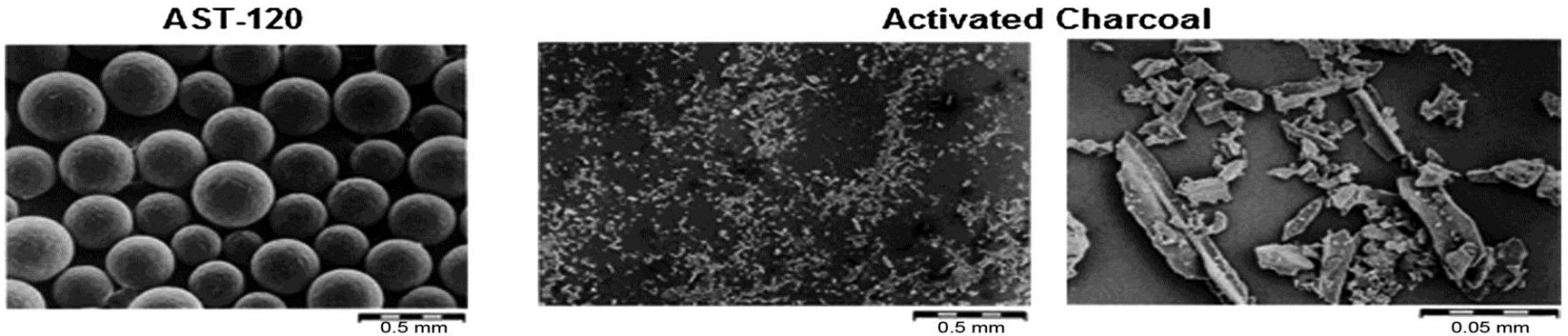
References P Saurus et al Cell Death Dis. 2015

Indoxyl Sulfate related to GFR



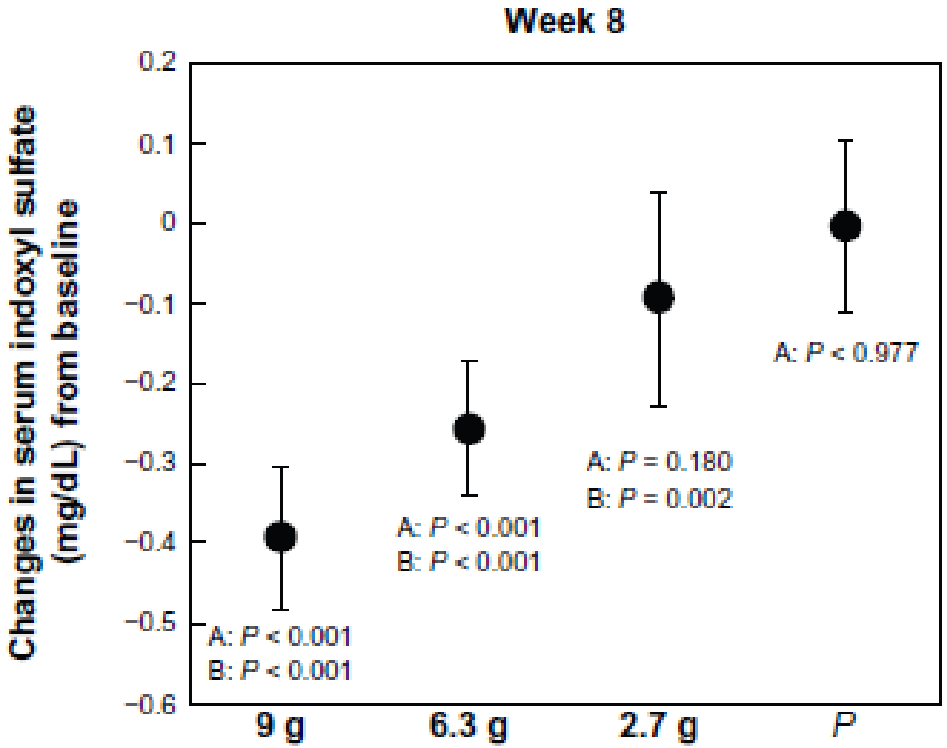
References FC Barreto et al Clin JASN 2009

Structural features of AST-120 and activated charcoal (United States Pharmacopeia).



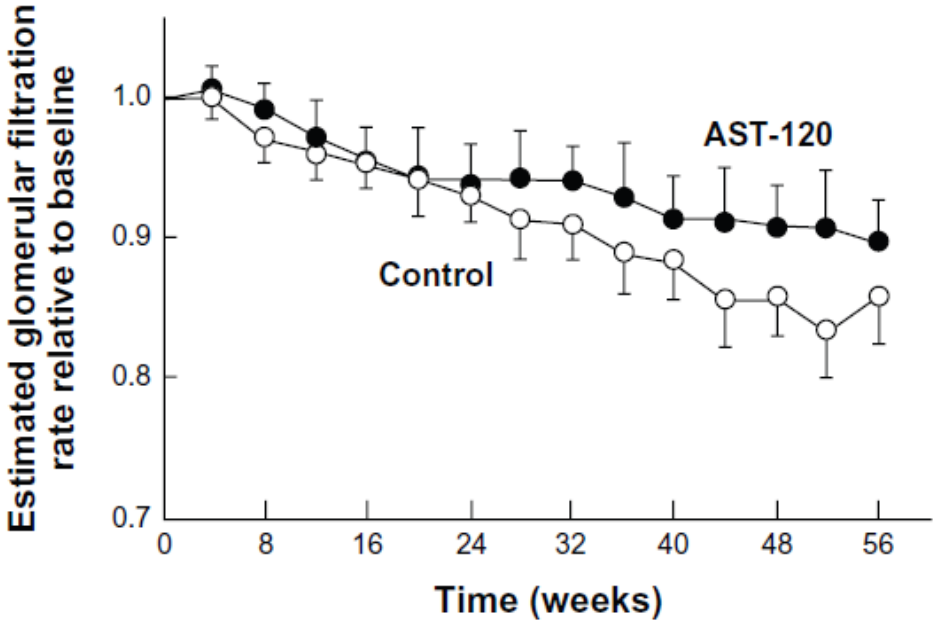
Gerald Schulman et al. JASN 2015;26:1732-1746

Gastrointestinal binding of Indoxyl Sulfate with AST 120



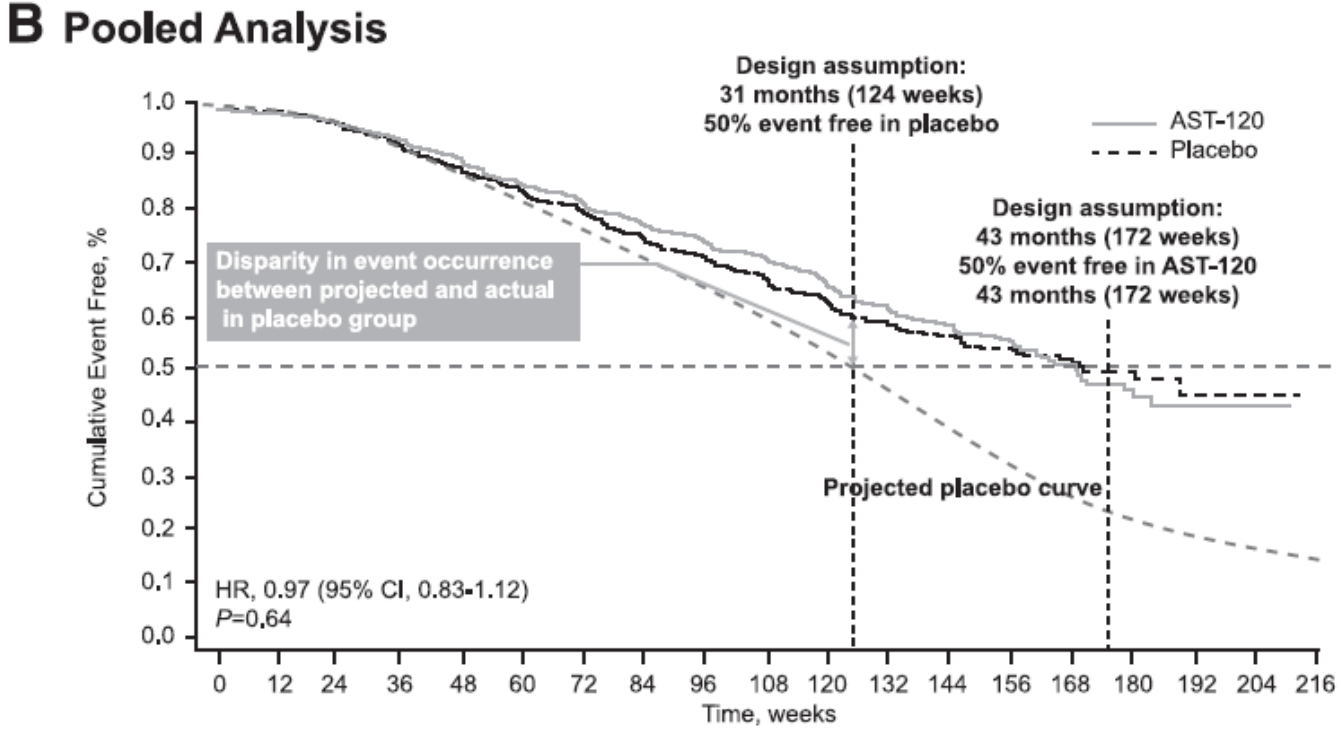
References G Schulman et al Am J KidDis 2006

AST 120 reducing loss of GFR in CKD



References Akizawa T et al Am J Kid Dis 2009

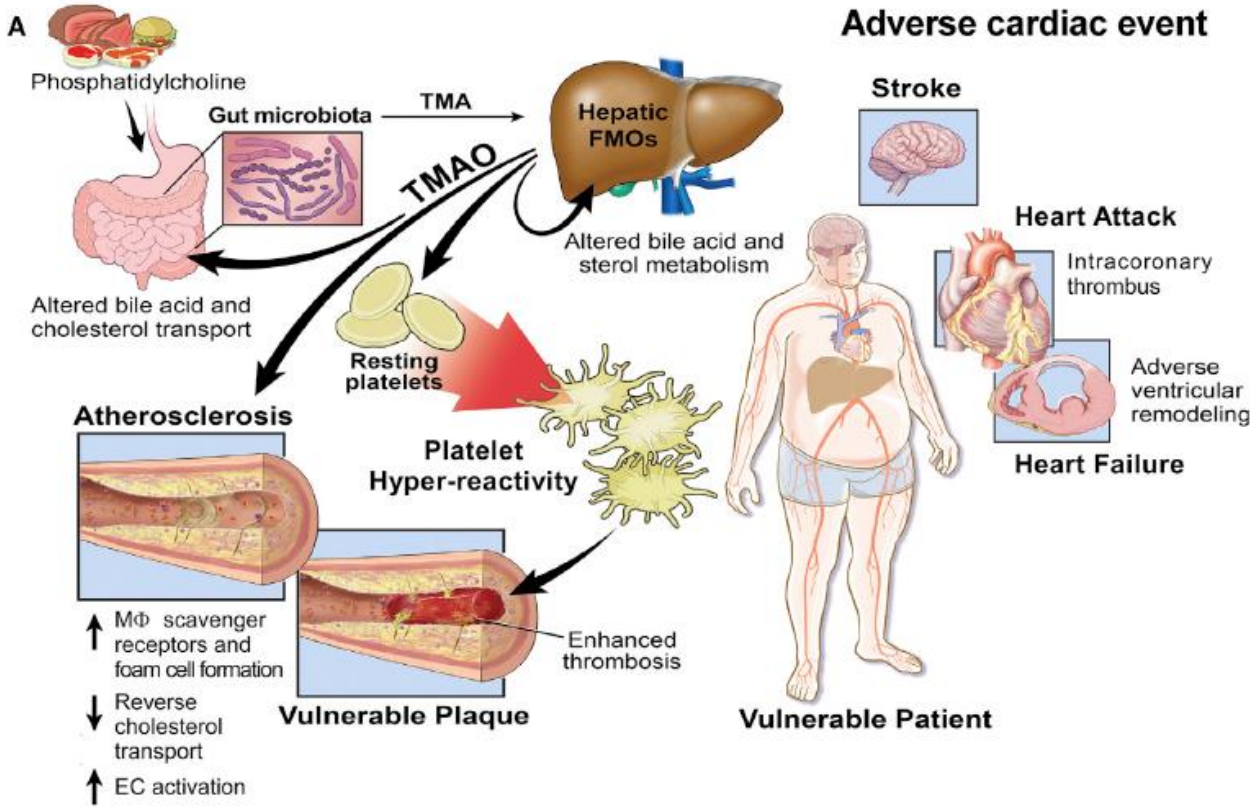
EPPIC trial of AST-120 in CKD



JASN

Gerald Schulman et al. JASN 2015;26:1732-1746

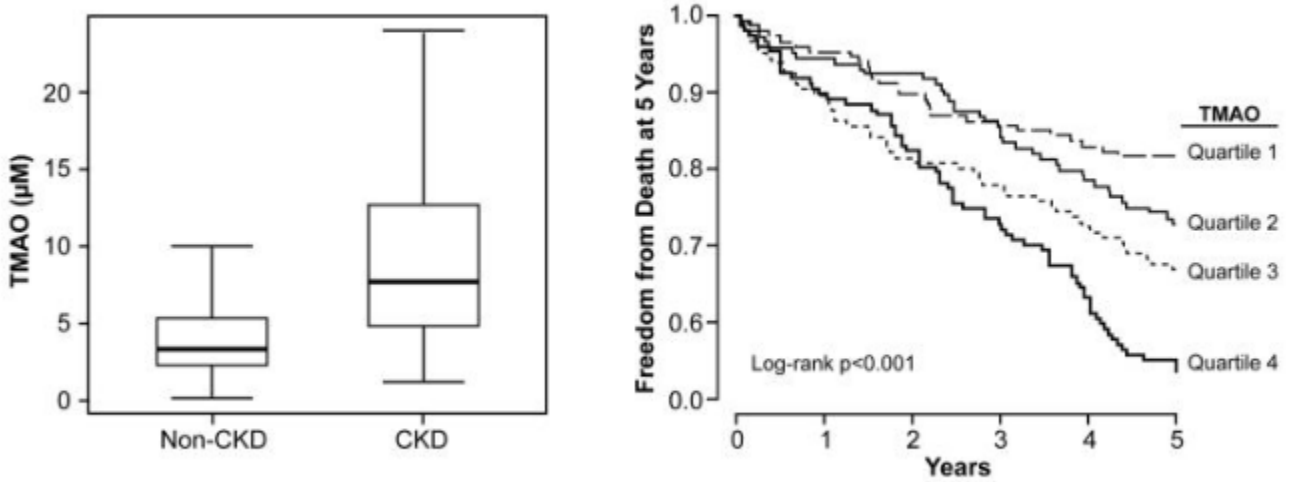
TMAO cause platelet hyperreactivity



References W Zhu et al Cell 2016

TMAO and CKD

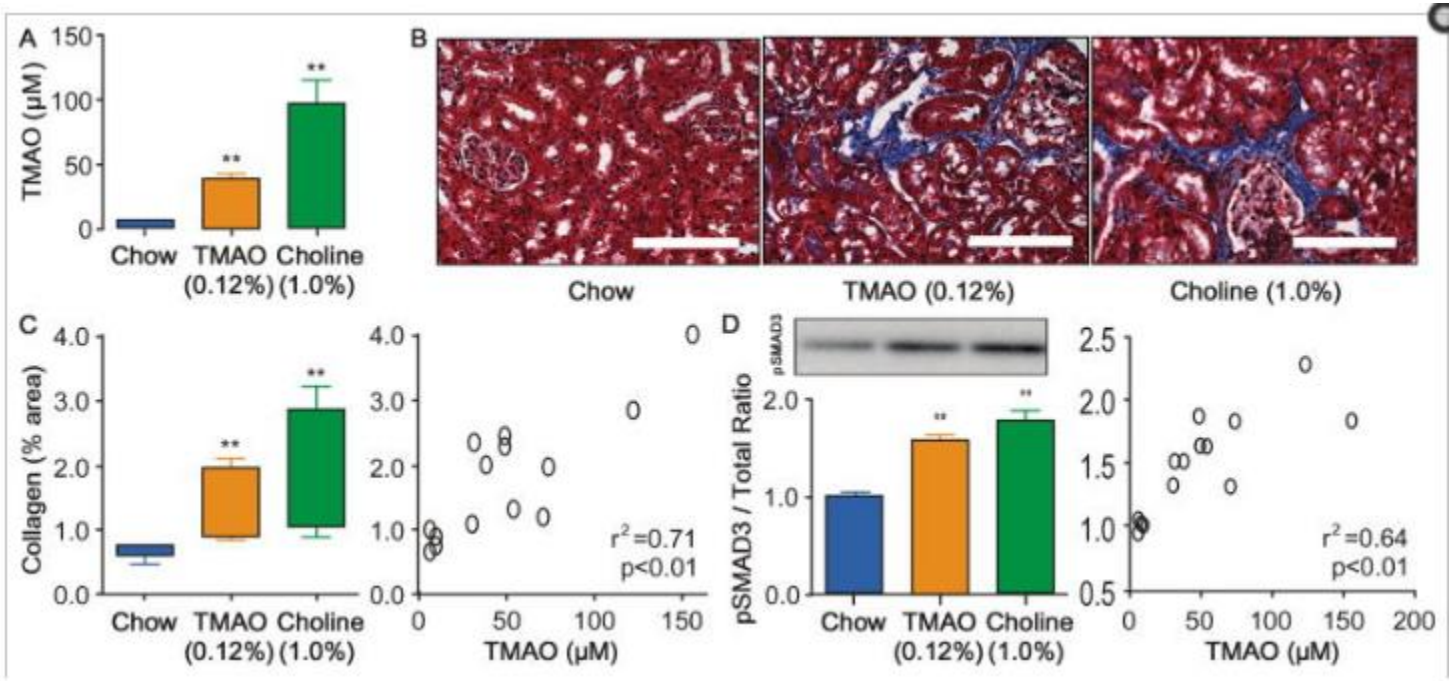
Figure 1



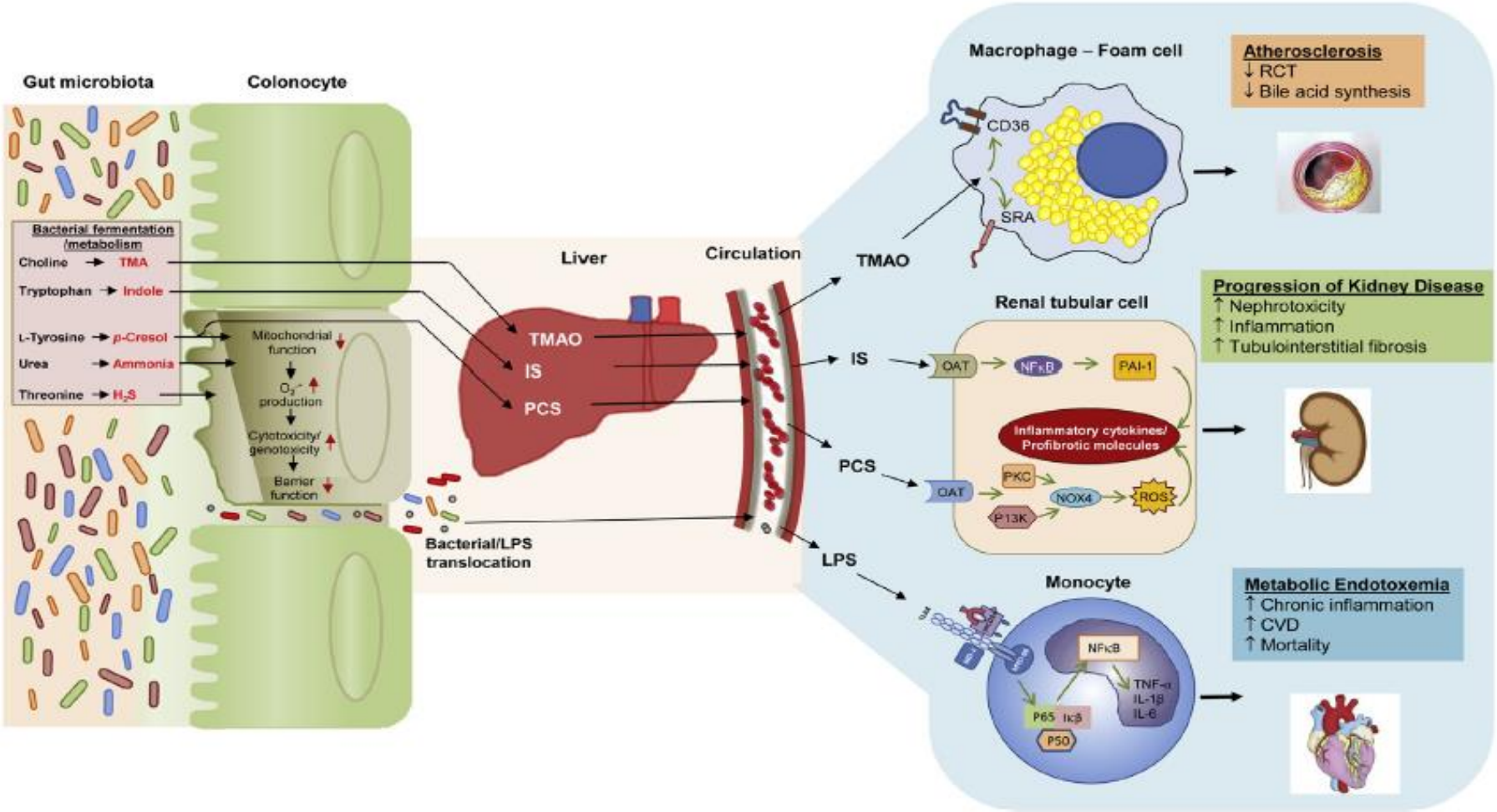
Prognostic Value of Plasma trimethylamine *N*-oxide (TMAO) Levels in the CKD Cohort

References W. H. Wilson Tang,[1,2] Circ Res. 2015 Jan 30; 116(3): 448–455.

TMAO induce renal damage in experimental setting

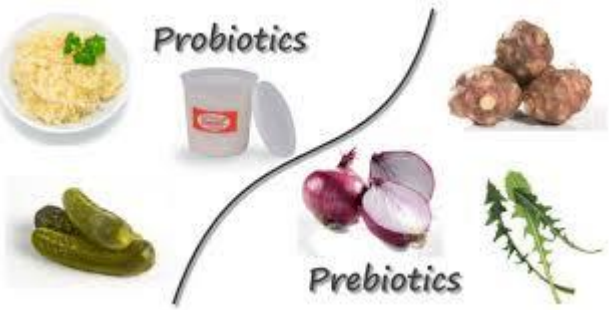


References W. H. Wilson Tang,[1,2] Circ Res. 2015 Jan 30; 116(3): 448–455.



References A Ramezani et al Am J Kid Dis 2016

Modification of Gutmicrobiota



Antibiotics

Personalised treatment in the future

n ~ ?

Omics

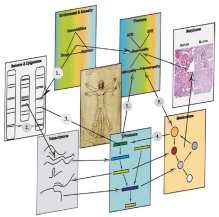
High-risk profile

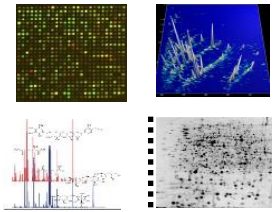
Randomised
Double-blinded
Placebo controlled

Targeted intervention

Low-risk

Observational



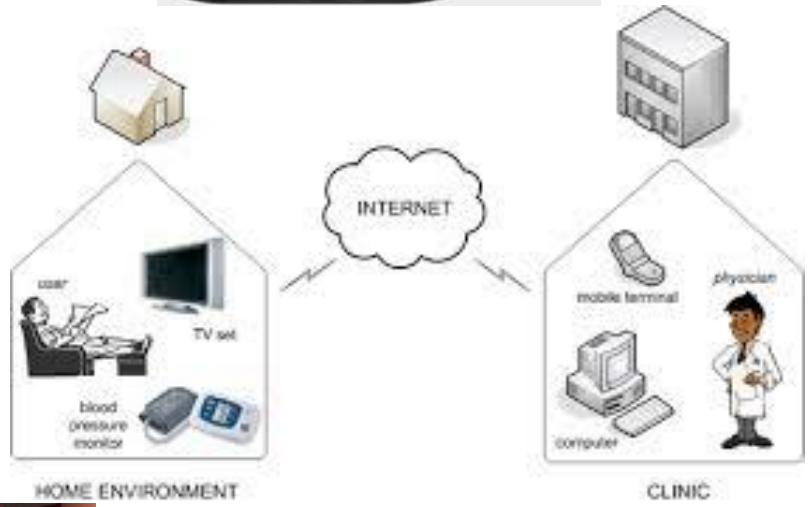


follow-up


GENOME
GCGTAGTC
ATGCGTAG
GGCATGCT
ATGCCATG
ATAGCTGC
CUUAGUGC
UAUGCGUA
GCUAGGCG
CAUGCUUC
GAGUGAUA
TRANSCRIPTOME
PROTEOME
arg-his-pro-val-
gly-leu-ser-thr-
ala-trp-tyr-val-
met-phe-arg-
Na 143 K 3.7
BP 110/70
HCT 32
BUN 12.9
Pulse 110
PLT 150
WBC 92
PHENOME
EPIGENOME
0100101011010101101
0110101010101011010
1010101101010101010
SOCIAL MEDIA
11010100010
10101011010
10101001000
10110100111
10110101010


Actual Sleep
8h 12m


110
77
68
iHealth


INTERNET
user
TV set
blood pressure monitor
HOME ENVIRONMENT
mobile terminal
physician
computer
CLINIC

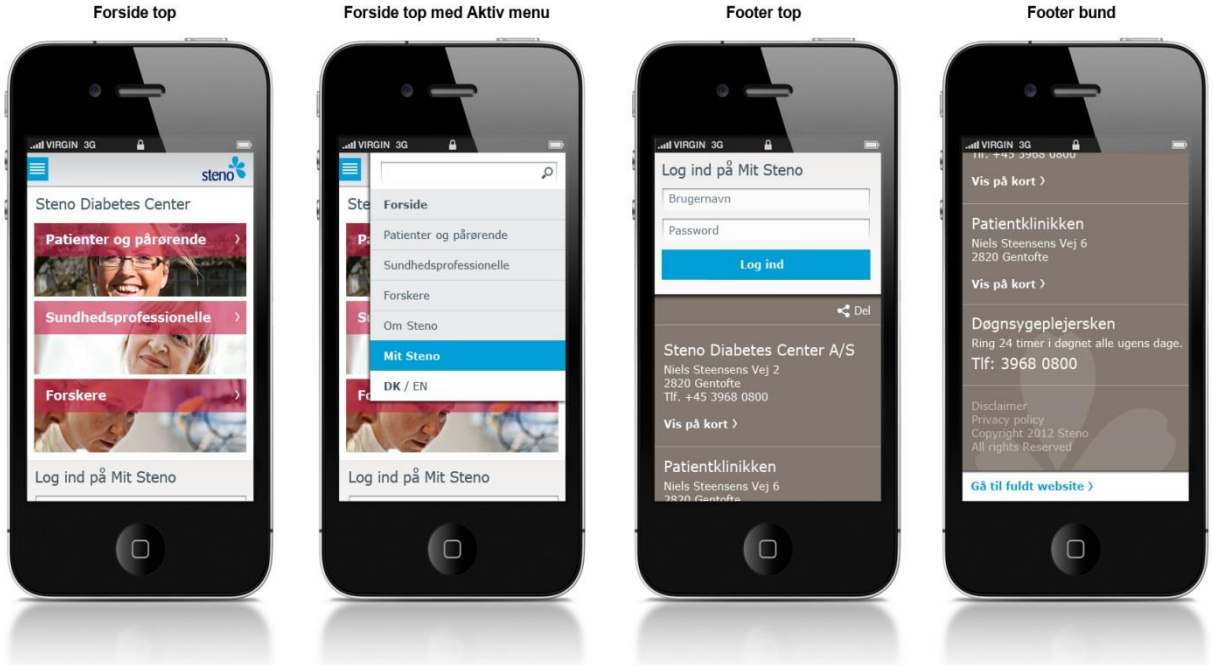

138
138


7-Eleven, Inc.
SNICKERS

steno

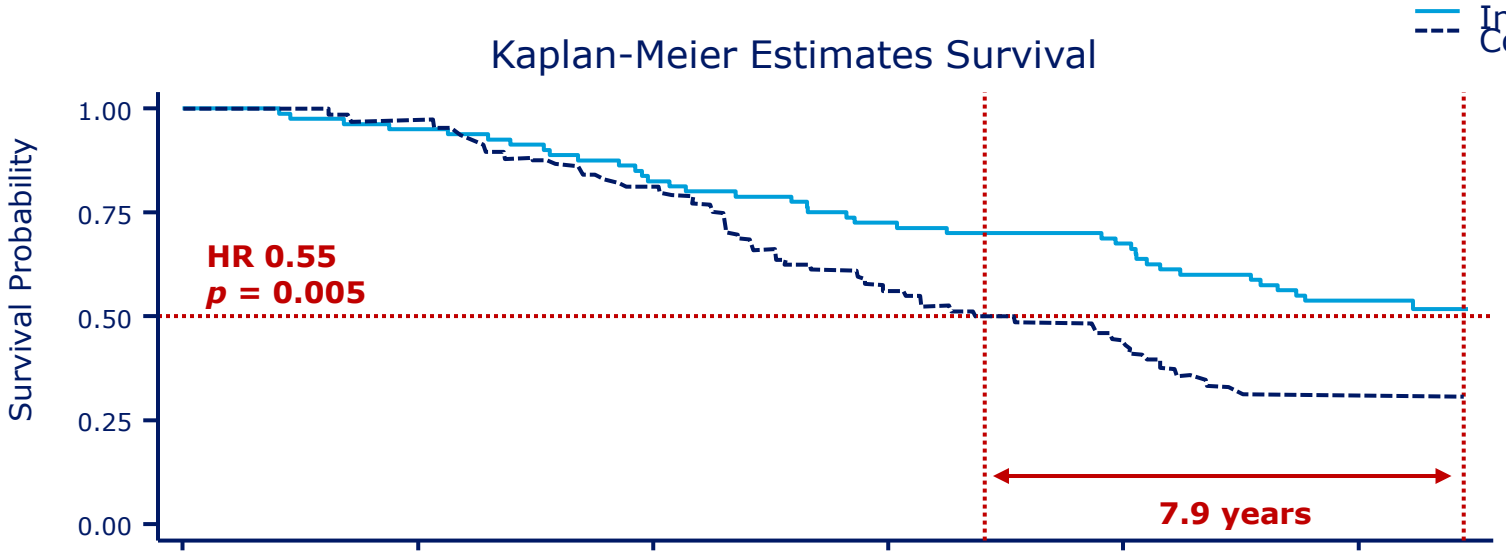
Steno Diabetes Center

“My Steno” – web-based diabetes care



Steno-2 post-trial:

Sustained effect of multifactorial intervention



Number at risk:

Intensive	80	76	66	58	54	43
Conventional	80	78	65	45	34	24

Gæde P , Ølgaard J et al *Diabetologia* 2016; Epub ahead of print

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Achievement of Goals in U.S. Diabetes Care, 1999–2010

Mohammed K. Ali, M.B., Ch.B., M.B.A., Kai McKeever Bullard, M.P.H., Ph.D., Jinan B. Saaddine, M.D., M.P.H., Catherine C. Cowie, M.P.H., Ph.D., Giuseppina Imperatore, M.D., Ph.D., and Edward W. Gregg, Ph.D.

However, 33.4 to 48.7% of persons with diabetes still did not meet the targets for glycemic control, blood pressure, or LDL cholesterol level. Only 14.3% met the targets for all three of these measures and for tobacco use.

Ali et al. **N Engl J Med 2013;368:1613-24**

Conclusion

- Diabetic nephropathy remains a major challenge
- New treatments are needed, new targets necessary
- Systems medicine with multidimensional characterisation can identify targets and select patients for interventions
- Gut microbiota may be both a target and a culprit
- Personalising treatment may optimise efficacy and reduce adverse events, thereby improving outcome for patients

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Thanks to collaborators and colleagues

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