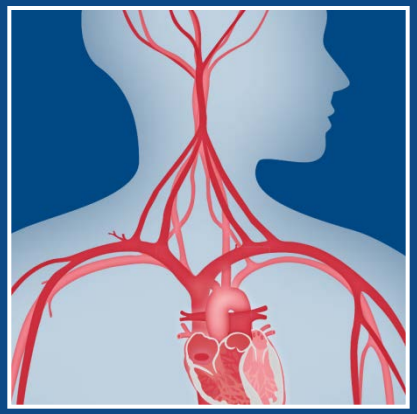
Cardiovascular Disease



Carmine Zoccali, Italy

Subtopics

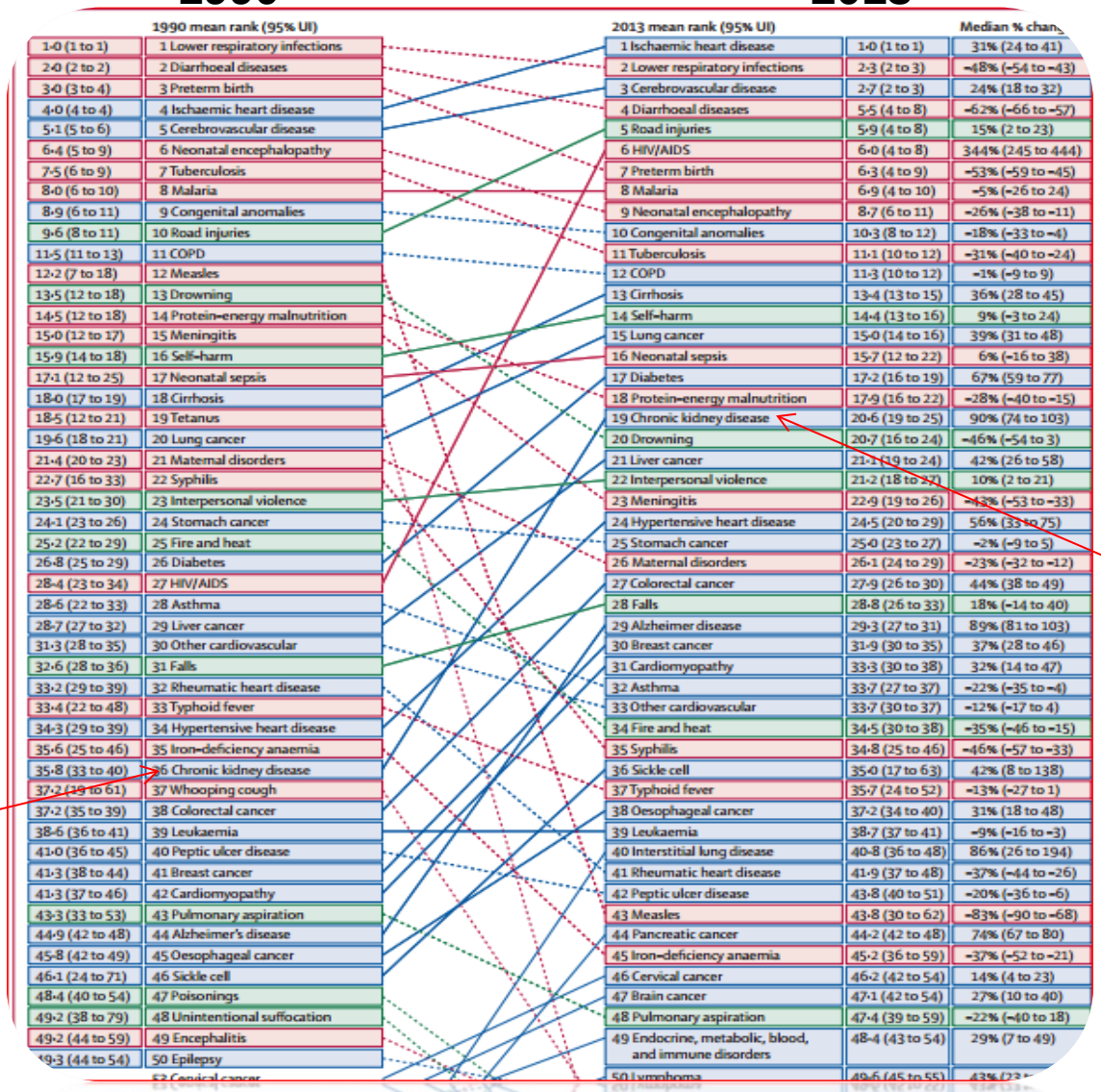
Cardiovascular Disease Epidemiology in CKD and Cardiovascular Outcomes in CKD

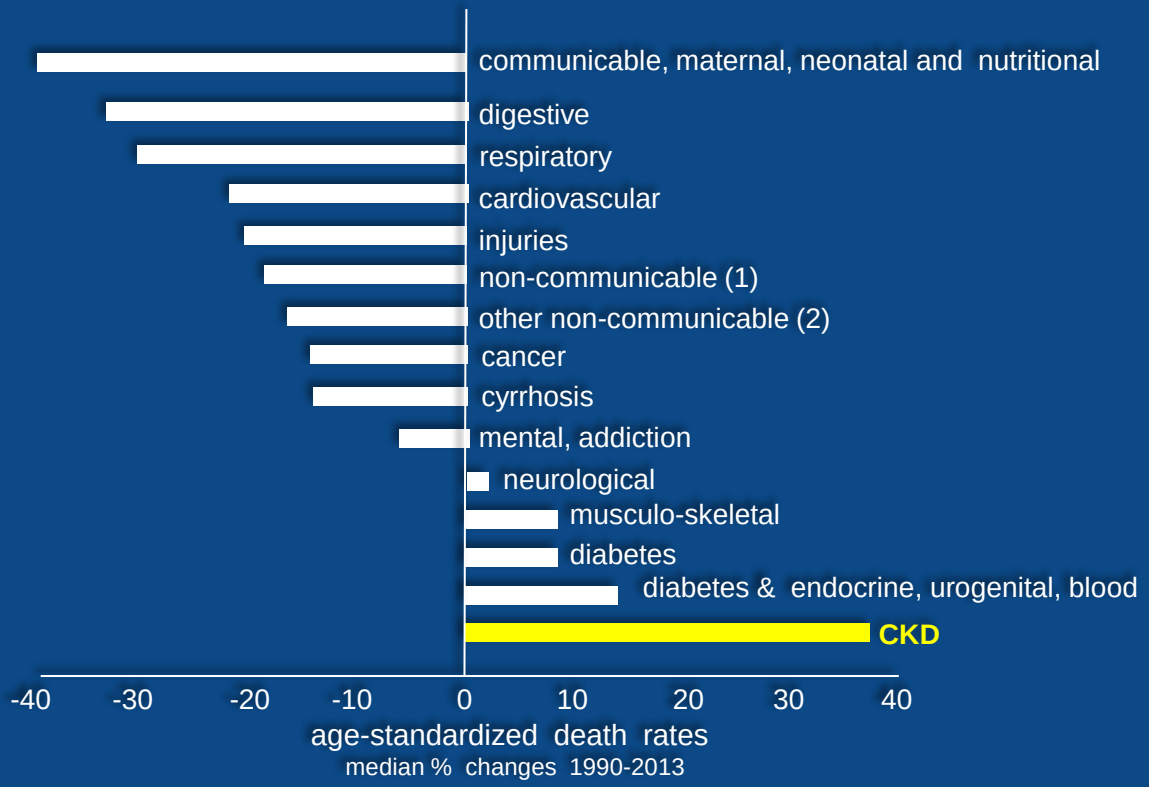
Cardiovascular Risk Prediction in CKD

Cardiovascular Risk Prevention in CKD

Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013

GBD 2013 Mortality and Causes of Death Collaborators.Lancet 2015; 385:117-171



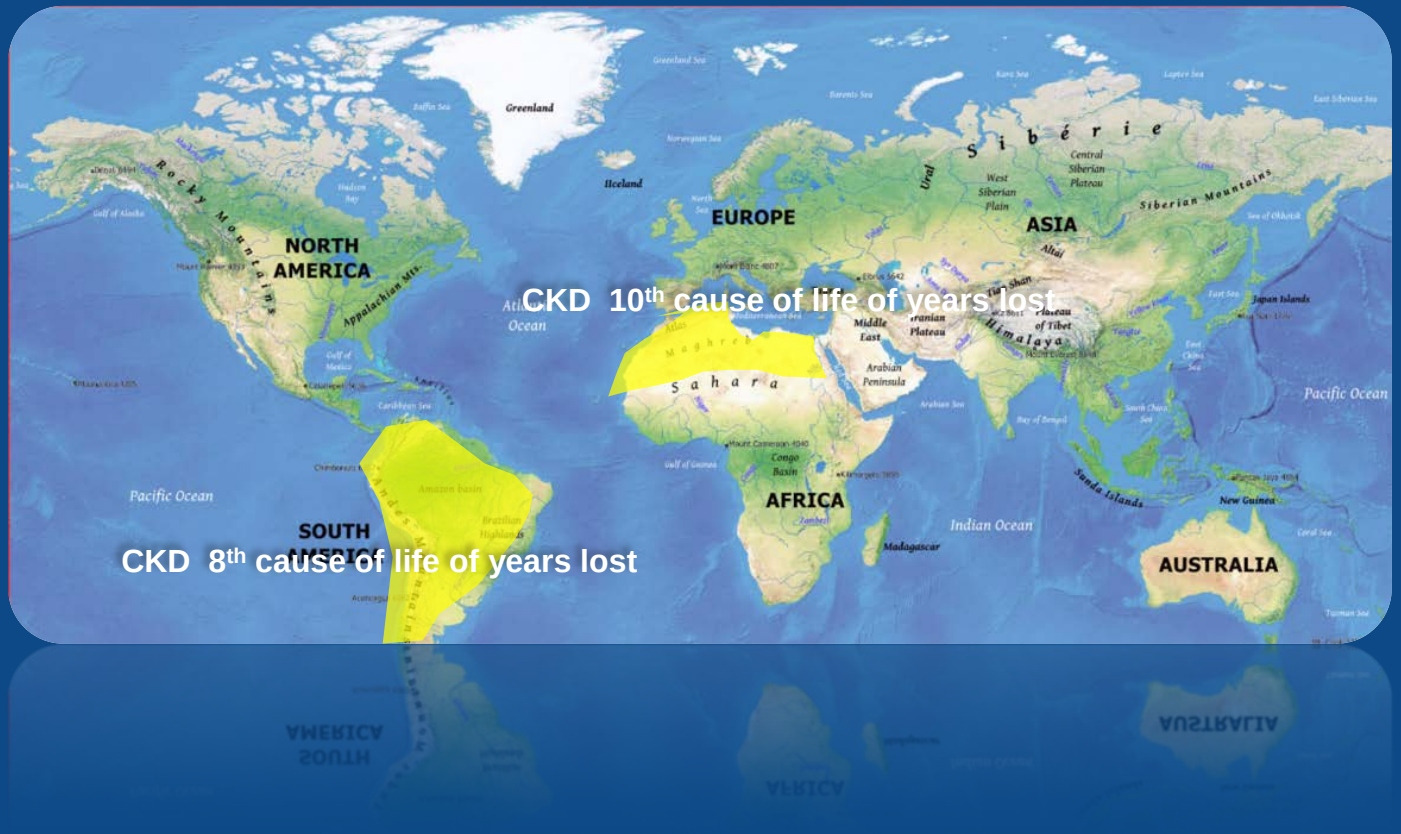


GBD 2013 Mortality and Causes of Death Collaborators.Lancet 2015; 385:117-171

Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015

GBD 2013 Mortality and Causes of Death Collaborators. Lancet 2016; 388:1459-1544

CKD 17th cause of death

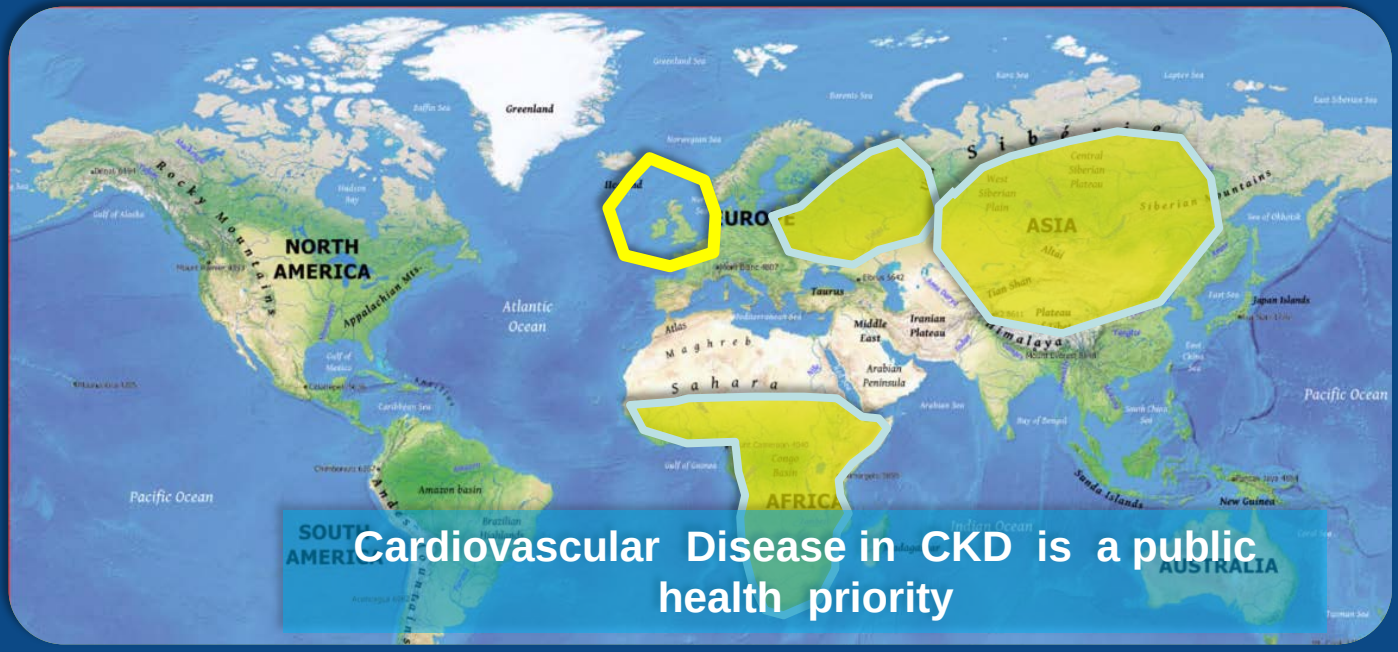


GBD 2015 Mortality and Causes of Death Collaborators.Lancet 2016; 388:1459-1544

Global Cardiovascular and Renal Outcomes of Reduced GFR

Global Burden of Disease 2013 GFR Collaborators, Thomas et al., J Am Soc Nephrol. 2017 Jul;28(7):2167-2179.

2013, 1.2 million CV deaths attributed to ⇓ GFR,



In 2009 in England 7000 strokes and 12,000 myocardial infarctions attributable to CKD were registered

The resulting cost was ~£176 million

Kerr M et al. NDT 27 (Suppl. 3): iii73–80, 2012

Take Home Message

CKD is ascending the ranking list of the leading causes of death worlwide

On a world scale over 1 million CV deaths are attributable to CKD

The impact of disability due CKD attributable CV disease is staggering (~ 19 million DALYS)

Subtopics

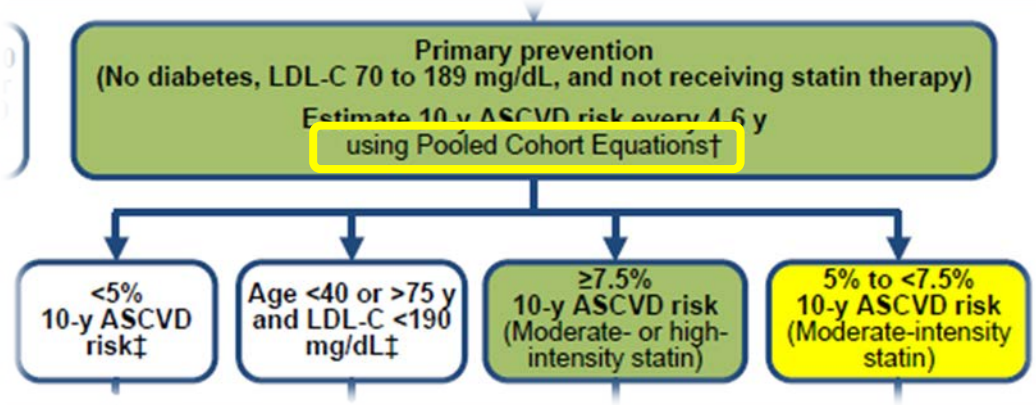
Cardiovascular Disease Epidemiology in CKD and Cardiovascular Outcomes in CKD

Cardiovascular Risk Prediction in CKD

Cardiovascular Risk Prevention in CKD

2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.

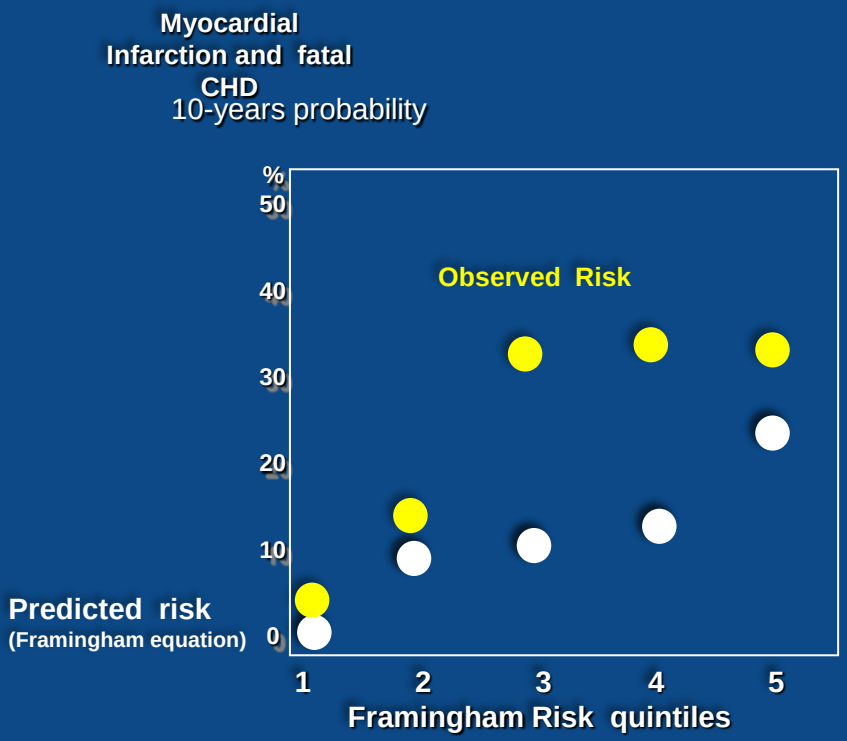
Stone et al., J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934.



Equation based on **Framingham risk Factors:**
Age, sex, race, cholesterol (T & HDL), Syst BP/BP treatment, Diabetes, Smoking

		Enter patient values in this column
Risk Factor	Units	Value
Sex	M (for males) or F (for females)	M
Age	years	60
Race	AA (for African Americans) or WH (for whites or others)	WH
Total Cholesterol	mg/dL	200
HDL-Cholesterol	mg/dL	45
Systolic Blood Pressure	mm Hg	120
Treatment for High Blood Pressure	Y (for yes) or N (for no)	Y
Diabetes	Y (for yes) or N (for no)	N
Smoker	Y (for yes) or N (for no)	N

The Framingham Predictive Instrument in Chronic Kidney Disease
-Weiner et al, J am Coll Cardiol 2007;50:217-24
Development and validation of cardiovascular risk scores for haemodialysis patients
-Anker et al, Int Jour of Cardiol 2016;216:68-77
A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease
-Schlackow et al, Heart published on line Aug 5th 2017



934 with CKD in ARIC and CHS

Risk predictions based on classical risk factors largely underestimate the risk of cardiovascular disease in CKD patients.

Because risk factors in CKD differ in CKD patients as compared to the general population, equations based on Framingham risk factors are «uncalibrated» when applied in CKD patients

Development and validation of cardiovascular risk scores for haemodialysis patients
-Anker et al, Int Jour of Cardiol 2016;216:68-77

RISK SCORE EQUATION BASED ON

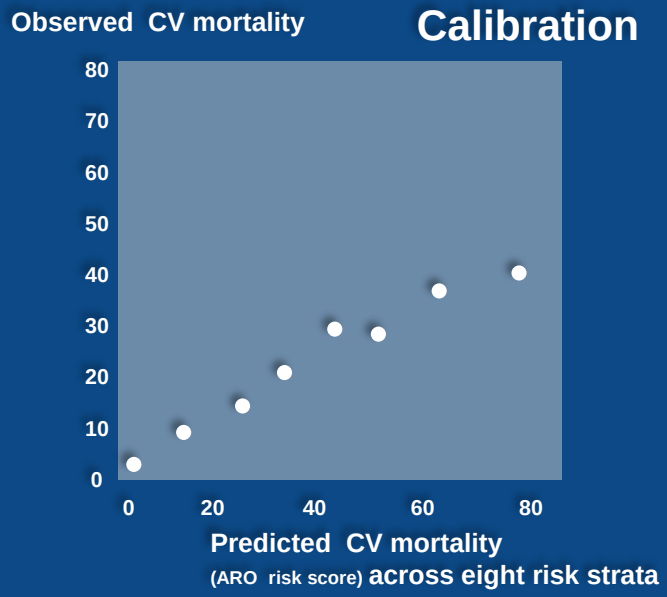
1. **Age**
2. **BMI**
3. **Smoking**
4. **CV history**
5. CKD etiology
6. Pre-dialysis systolic BP
7. Ultrafiltration rate
8. Hb
9. CRP
10. Albumin
11. Creatinine
12. Serum (total) calcium

ARO* cohort
~ 10,000 patients in 14 EU countries

External validation: DOPPS

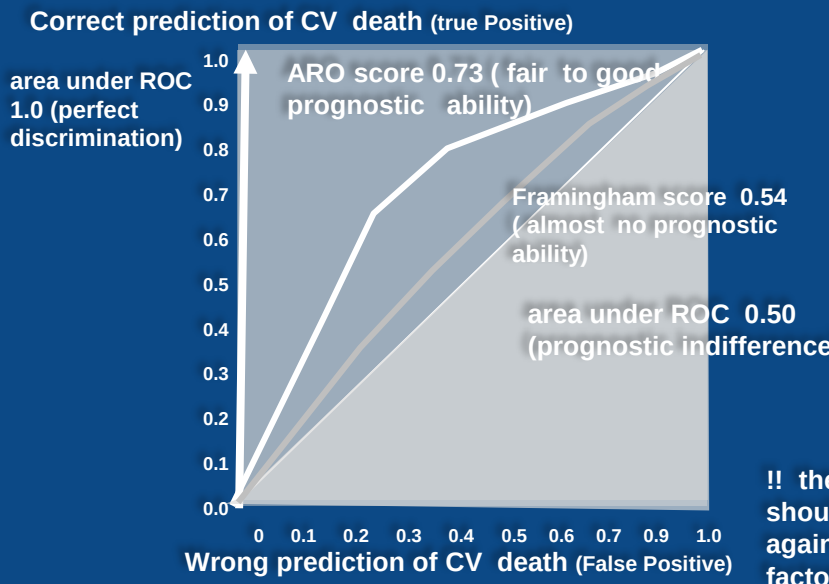
*Analysing Data, Recognising Excellence and Optimising Outcomes

Calibration



Development and validation of cardiovascular risk scores for haemodialysis patients
-Anker et al, Int Jour of Cardiol 2016;216:68-77

Risk Discrimination (area under the ROC curve)



Limitations

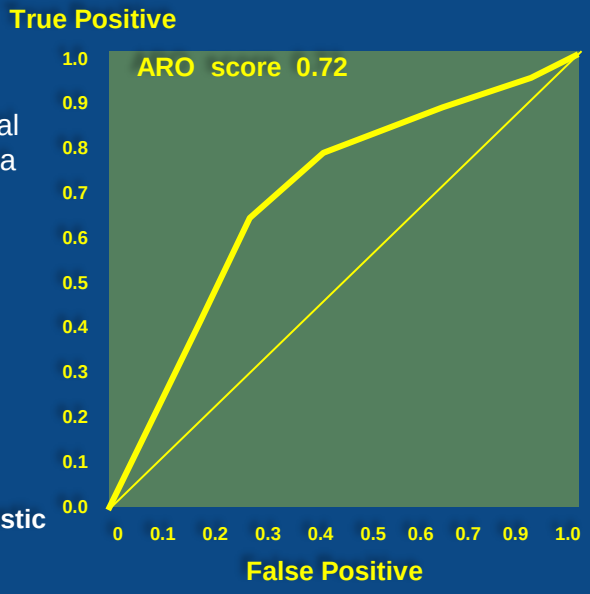
Not all patients started dialysis in the Fresenius dialysis network

Usefulness in clnical practice unknown (a trial is needed)

!! the ARO risk score should be further tested against powerful prognostic factors in the dialysis population

DOPPS cohort (7 of the 14 EU countries covered by ARO)

Risk Discrimination



Reappraisal in two European cohorts of the prognostic power of left ventricular mass index in chronic kidney failure

-Tripepi, et al, Kidney International 91, 704–710; 2017

The left ventricular mass index (LVMI) is considered as the most powerful integrator of cardiovascular risk in ESRD and LVMI measurement by echocardiography is recommended at initiation of regular dialysis treatment by current guidelines.

Is the prognostic performance of the ARO cardiovascular risk score comparable to that of the LVMI?

Does the measurement of the LVMI add meaningful prediction power to the ARO cardiovascular risk score in ESRD?

Reappraisal in two European cohorts of the prognostic power of left ventricular mass index in chronic kidney failure

-Tripepi, et al, Kidney International 91, 704–710; 2017

Giovanni Tripepi[1], Bruno Pannier[2], Graziella D'Arrigo[1], Francesca Mallamaci[1], Carmine Zoccali[1] and Gerard London[3]

Development and validation of cardiovascular risk scores for haemodialysis patients

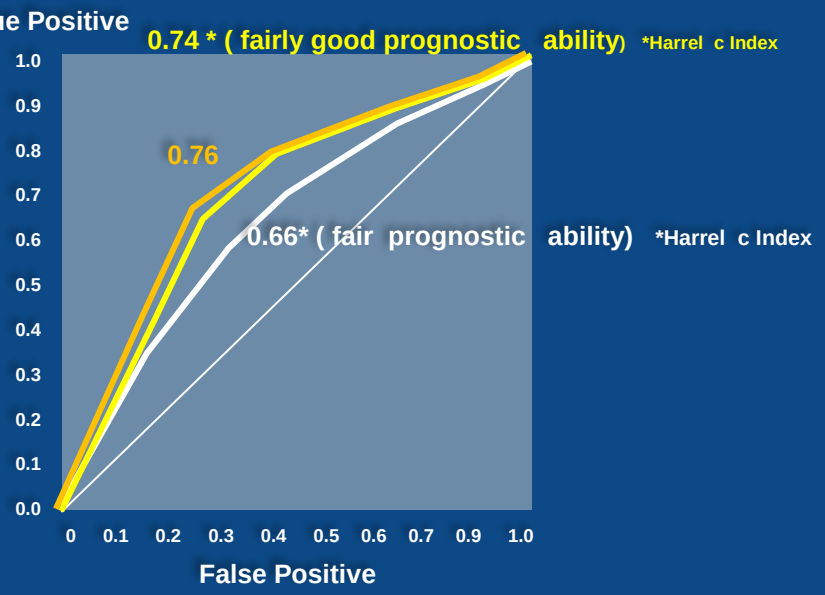
-Anker et al, Int Jour of Cardiol 2016;216:68-77

Stefan D. Anker[a,*,1], Iain A. Gillespie[b,1], Kai-Uwe Eckardt[c,1], Florian Kronenberg[d,1], Sharon Richards[e,1], Tilman B. Drueke[f,1], Peter Stenvinkel[g,1], Ronald L. Pisoni[h,1], Bruce M. Robinson[h,1], Daniele Marcelli[i,1], Marc Froissart[j,1], Jürgen Floege[k,1], On behalf the ARO Steering Committee (collaborators):

ARO CV-Risk score

+

Risk Discrimination (area under the ROC curve)



The ARO cardiovascular risk score is endowed with prediction power superior to LVMI and LVMI adds minimal discrimination ability to the ARO score

Very modest gains in risk reclassification when LVMI is applied on top of the ARO cardiovascular risk score

Reappraisal in two European cohorts of the prognostic power of left ventricular mass index in chronic kidney failure

-Tripepi, et al, Kidney International 91, 704–710; 2017

Giovanni Tripepi[1], Bruno Pannier[2], Graziella D'Arrigo[1], Francesca Mallamaci[1], Carmine Zoccali[1] and Gerard London[3]

Echocardiography useless in ESRD??

…however the measurement of LVMI for risk prediction is less informative than the ARO CV risk score…..

…given its simplicity and costlessness the ARO CV risk score is better suited than the LVMI for CV risk prediction in the dialysis population…

A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease
-Schlackow et al, Heart published online Aug 5th 2017

Prediction model of CV events and CV death (combined) for up to 5 years developped on the SHARP study data.
Applicable to pre-dialysis and dialysis patients

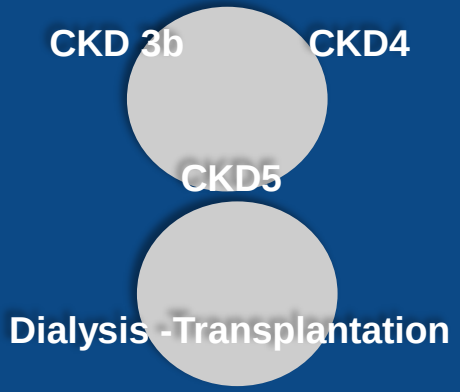
SOCIODEMOGRAPHIC/standard

1. Gender
2. Ethnicity
3. BMI
4. Smoking
5. Diabetes
6. HDL Cholesterol
7. Systolic & Diastolic BP
8. Dependent / Independent
9. Education level

CKD typical risk factors

1. Previous Transplant
2. Hb
3. Serum albumin
4. Phosphate
5. Albuminuria

yearly updates of incident CKD transitions and CV event states



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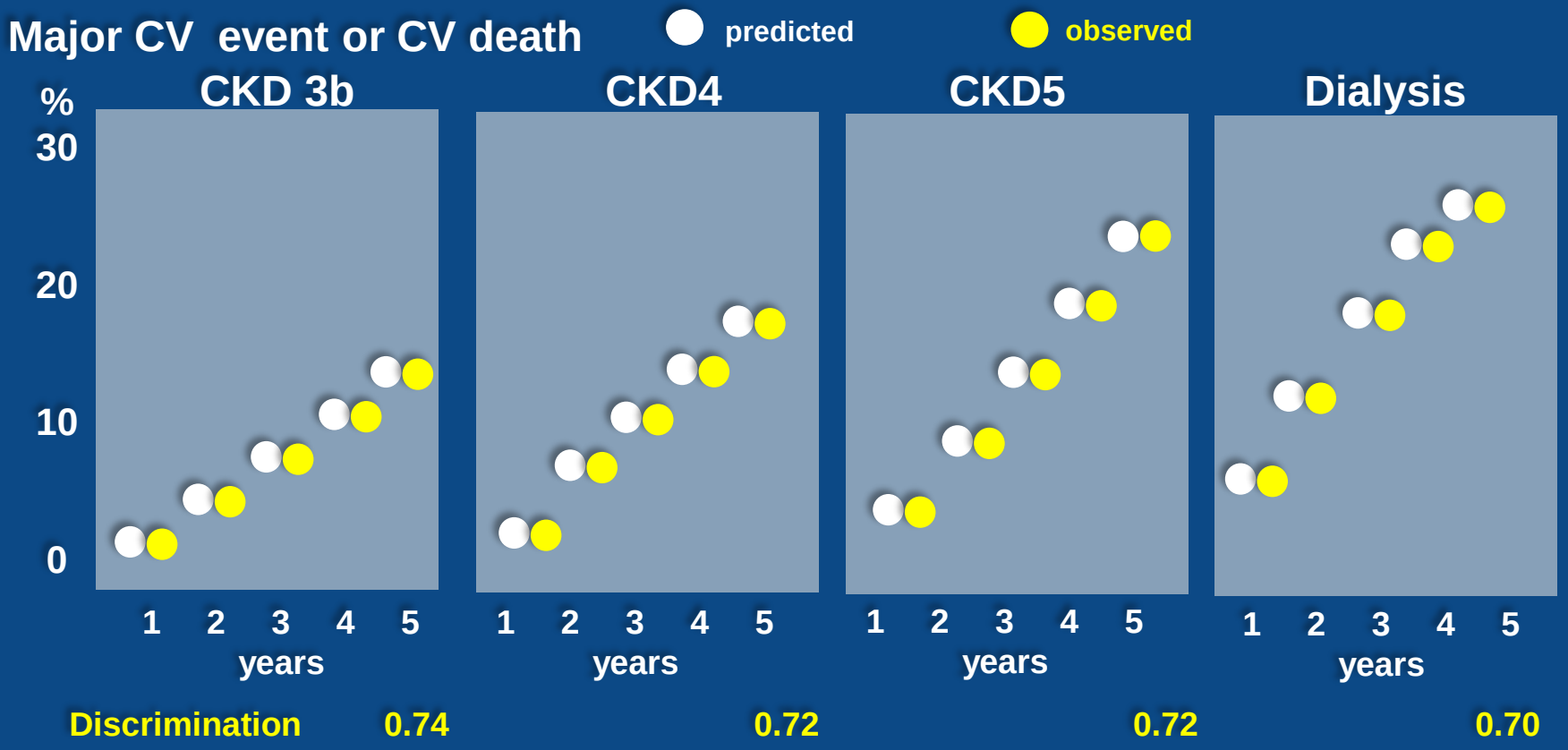

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External Validation

In (stage 3-5 CKD) in the Chronic Renal Insufficiency Cohort (CRIC):
Discrimination 0.75 (5 yrs)

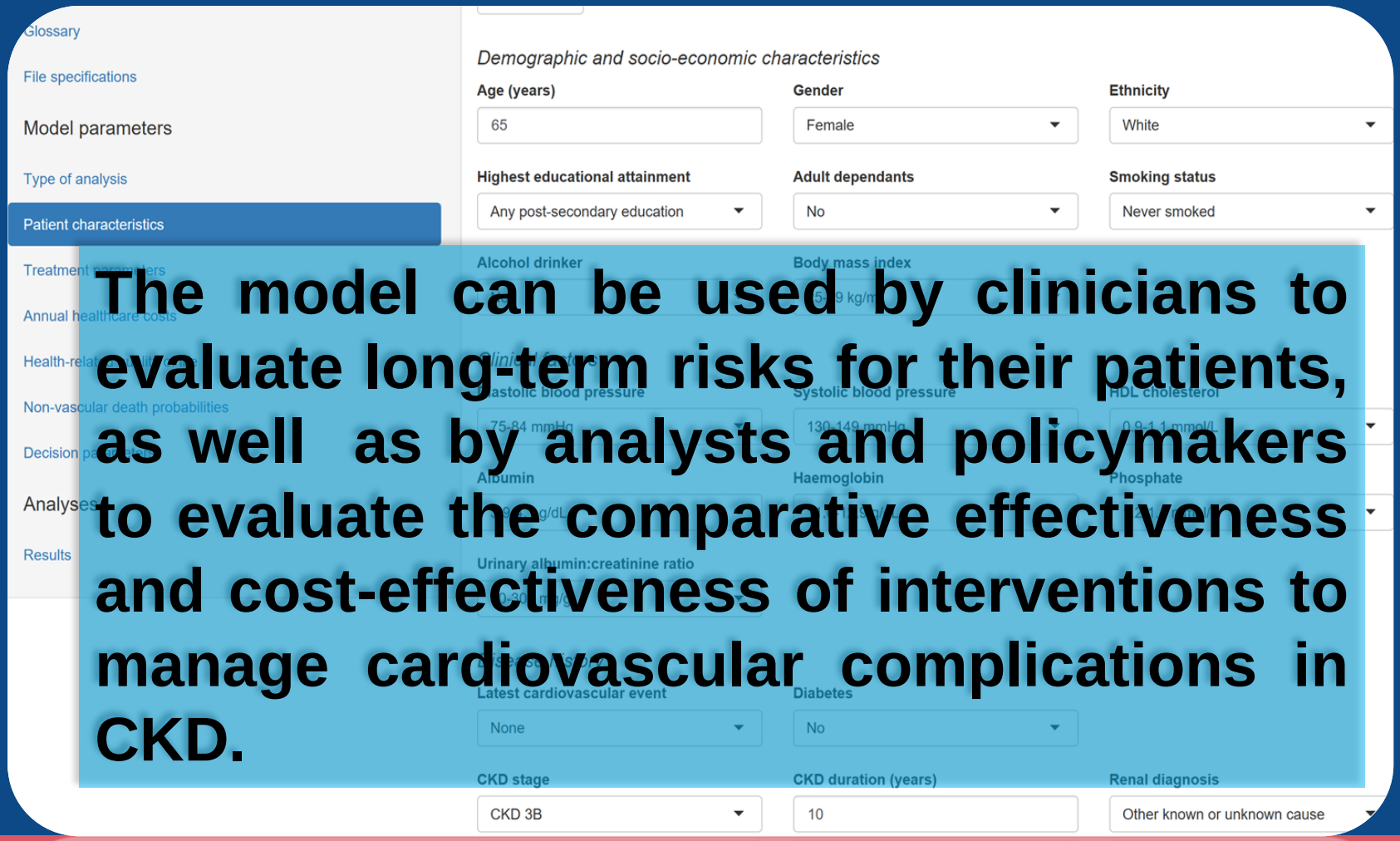
In hemodialysis patients 4D and AURORA study cohorts :
Discrimination 0.61 (4 years) and 0.65 (3 years)

LIMITATION SHARP excluded patients with major coronary disease, whereas in routine clinical practice coronary heart disease is highly prevalent in moderate-to-advanced CKD. Model assessment in further CKD cohorts is desirable

Discrimination	**0.74**	**0.72**	**0.72**	**0.70**

A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease
-Schlackow et al, Heart published online Aug 5th 2017

http://dismod.ndph.ox.ac.uk/kidneymodel/app/



The model can be used by clinicians to evaluate long-term risks for their patients, as well as by analysts and policymakers to evaluate the comparative effectiveness and cost-effectiveness of interventions to manage cardiovascular complications in CKD.

Take Home Message

Given the high CV burden of the CKD population, CV risk prediction is important in this population.

The standard CV calculators based on Framingham risk factors are inherently unsuitable for application in CKD

In HD patients, the recently developped ARO CV risk score is superior to LVMI to predict cardiovascular mortality and it deserves to be tested in a clinical trial to see whether it may refine the clinical decision process.

A new model developped on the basis of the SHARP trial data performs fairly well in CKD patients and fairly in hemodialysis patients in external validation studies

Subtopics

cardiovascular disease epidemiology in CKD and cardiovascular outcomes in CKD

cardiovascular risk prediction in CKD

cardiovascular risk prevention in CKD

Tertiary: treatment of modifiable risk factors to prevent CV disease worsening in CKD patients with established CV disease .

- A meta-analysis apprasing the usefulness of a low BP target in CKD
- The Frequent Hemodialysis Trial extended-study looking at mortality

Subtopics

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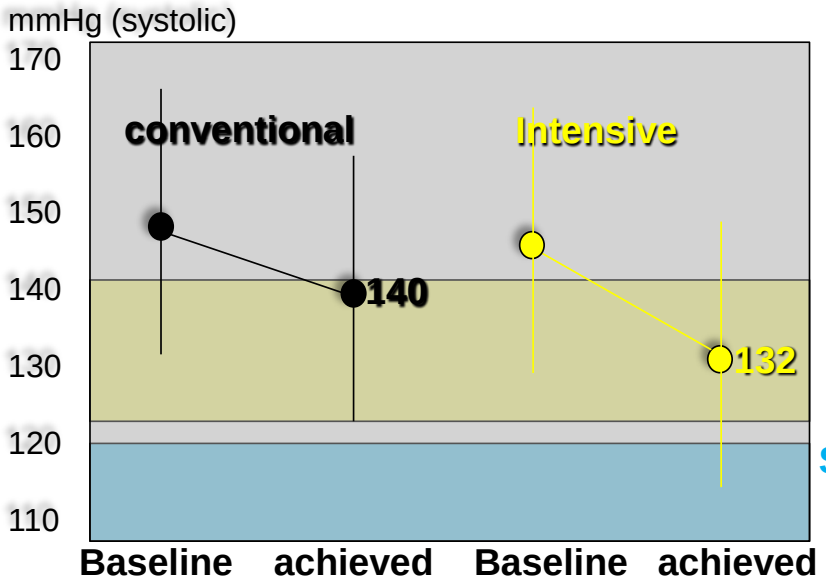
- **The Frequent Hemodialysis Trial extended-study looking at mortalit**

Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5.
A Systematic Review and Meta-analysis
-Malhotra et al, JAMA Int Med September 5 2017 (online)

~16,000 CKD patients abstracted from 18 RCT randomizing patients to an intensive BP target as to standard BP target

This meta-analysis included patients with proteinuria (any severity), diabetes and ADPKD



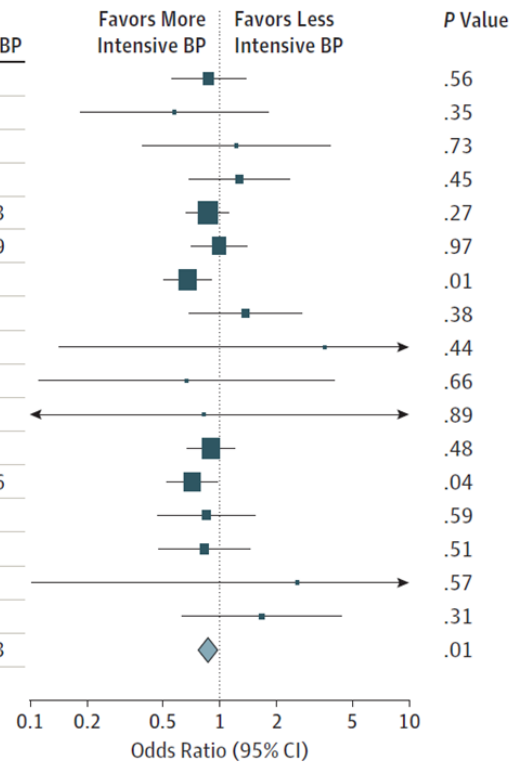
Well within the currently recommended target (<140/90 mmHg)

SPRINT target

Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5. A Systematic Review and Meta-analysis
-Malhotra et al, JAMA Int Med September 5 2017 (online)

Source	Odds Ratio (95% CI)	Score	No. of Deaths/Total No.		P Value
			More Intensive BP	Less Intensive BP	
Wright et al,[14] 2002	0.874 (0.554-1.380)	-0.578	37/540	43/554	.56
Estacio et al,[24] 2000	0.575 (0.182-1.820)	-0.941	5/62	9/68	.35
Schrier et al,[26] 2002	1.227 (0.398-3.865)	0.349	6/57	7/80	.73
Cushman et al,[32] 2010	1.271 (0.685-2.360)	0.761	26/208	20/198	.45
Heerspink et al,[27] 2010	0.862 (0.662-1.123)	-1.102	117/1010	135/1023	.27
Lonn et al,[37] 2016	0.993 (0.699-1.410)	-0.039	49/1220	97/2399	.97
Beckett et al,[30] 2008	0.676 (0.502-0.911)	-2.570	83/788	121/816	.01
Klahr et al,[13] 1994	1.366 (0.681-2.742)	0.878	20/432	14/408	.38
Mant et al,[34] 2016	3.588 (0.140-91.945)	0.772	1/26	0/30	.44
Ruggenenti et al,[22] 2005	0.667 (0.110-4.042)	-0.441	2/167	3/168	.66
Schrier et al,[25] 2002	0.825 (0.050-13.701)	-0.134	1/41	1/34	.89
SHEP Cooperative Research Group,[28] 1991	0.900 (0.670-1.209)	-0.700	96/879	103/859	.48
Wright et al,[17] 2015	0.714 (0.519-0.982)	-2.072	70/1330	95/1316	.04
Benavente et al,[33] 2013	0.850 (0.468-1.544)	-0.534	24/216	25/195	.59
Staessen et al,[29] 1997	0.826 (0.470-1.451)	-0.665	26/242	29/228	.51
Toto et al,[23] 1995	2.566 (0.101-64.993)	0.572	1/42	0/35	.57
UK Prospective Diabetes Study Group,[35] 1998	1.667 (0.626-4.435)	1.023	20/68	7/35	.31
Overall	0.859 (0.764-0.965)	-2.560	584/7451	709/8473	.01

Heterogeneity: $\tau^2 = 0\%$; $P = .77$; $I^2 = 0\%$



Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5. A Systematic Review and Meta-analysis
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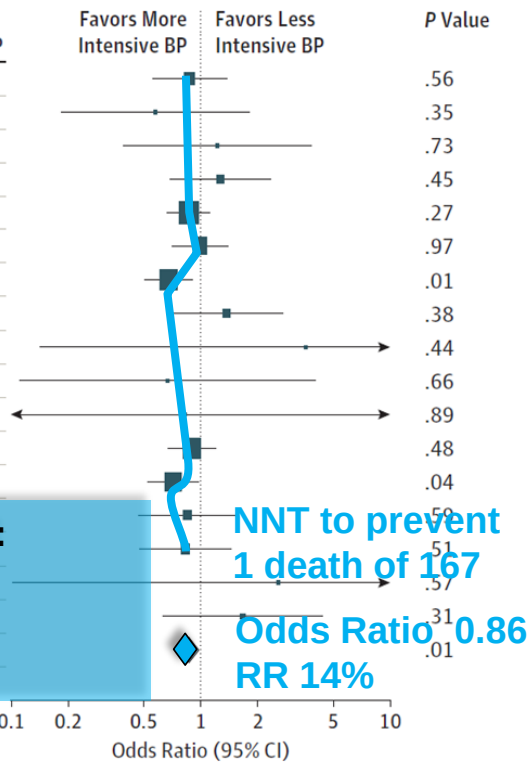
Overall	0.859 (0.764-0.965)	-2.560	[illegible]/7451	709/8473	.01
Heterogeneity: $\tau^2 = 0\%$; $P = .77$; $I^2 = 0\%$					



Odds Ratio almost the same (0.88) also excluding SPRINT

No heterogeneity by:
- **CKD severity**
- **initial BP**
- **Diabetes**

NNT to prevent 1 death of 167

Odds Ratio 0.86
RR 14%

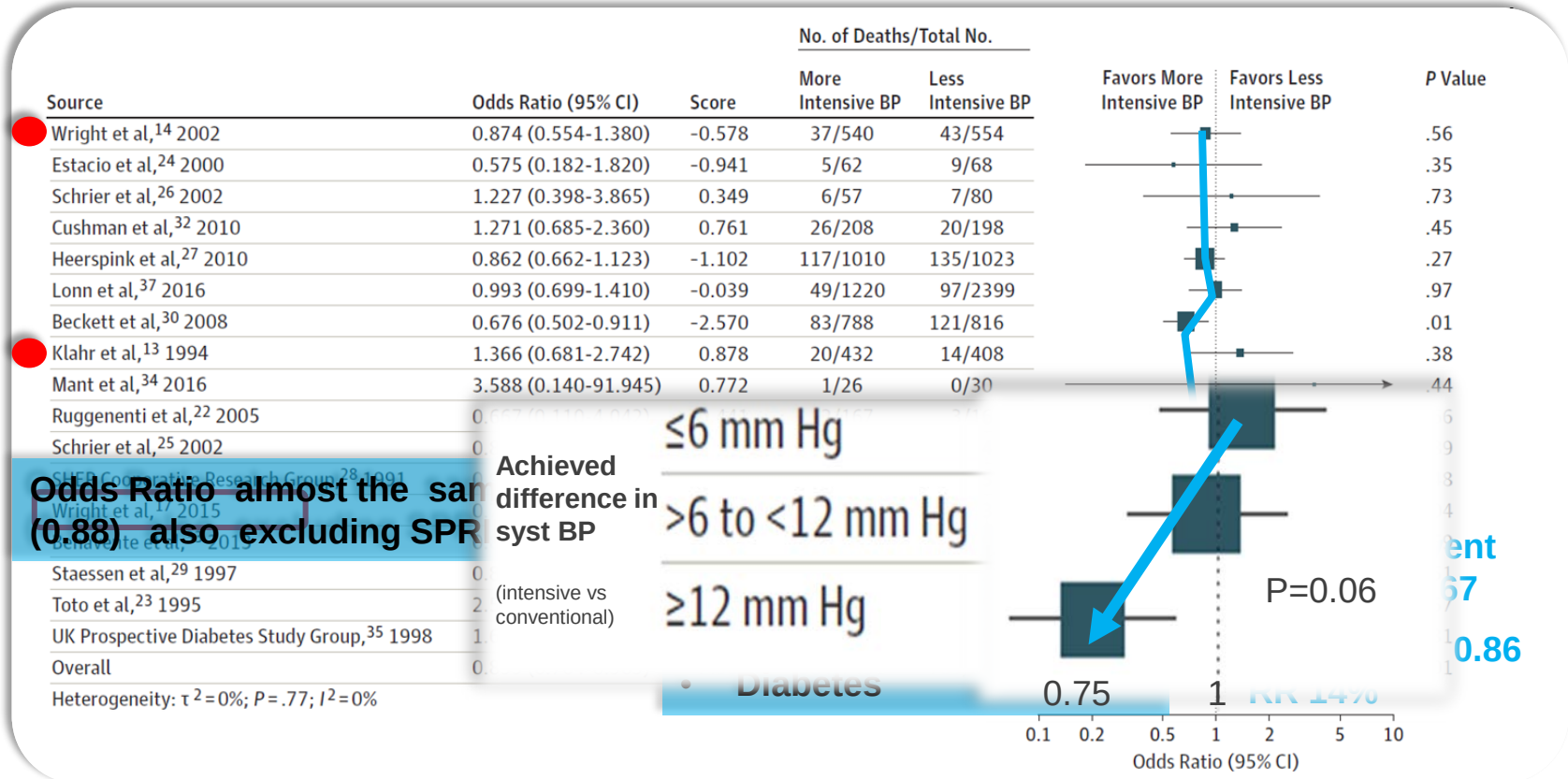
? GFR ↓ ?

Achieved BP in the low BP target arms in AASK and MDRD (BP fall ≈ to that in the present meta-analysis) there was no excess risk for AKI-dependent ESRD.

Ku E, et al. JASN;28:2794-2801; sept 2017.

Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5. A Systematic Review and Meta-analysis

-Malhotra et al, JAMA Int Med September 5 2017 (online)



In-Center Hemodialysis Six Times per Week versus Three Times per Week
-FHN Trial Group, Chertow et al, N Engl J Med. 2010 Dec 9;363(24):2287-300.

N=245
(age ~50 years, 40% diabetics)

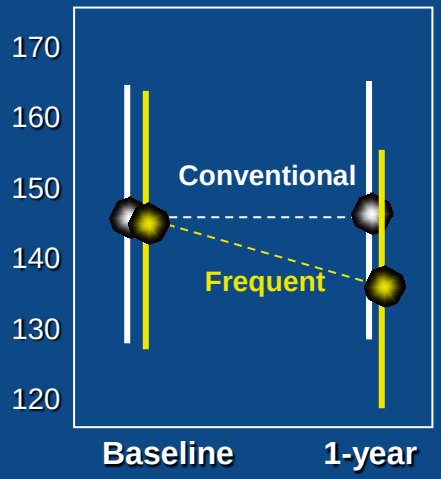
Frequent (x6/week) dialysis

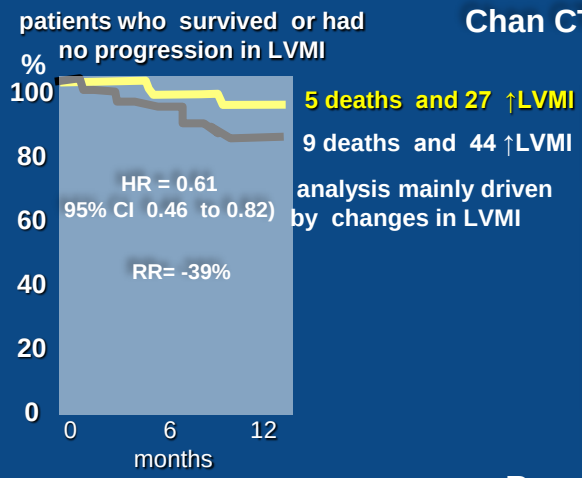
Conventional (x3/week) dialysis

← 1 year →

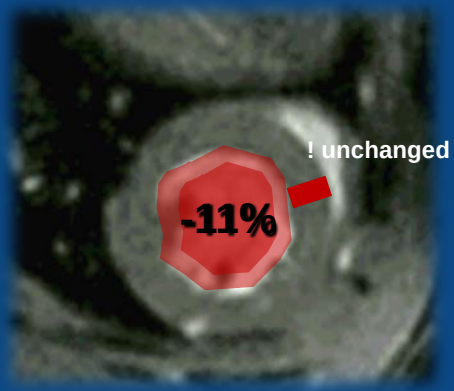
Death or increase in LVMI (by NMR)

Systolic BP mmHg





Chan CT et al., CJASN 8: 2106–2116, 2013

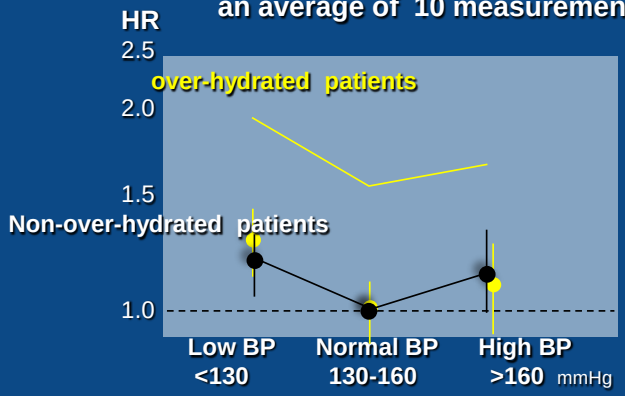


Regression of LVH in the trial was mainly due to a lower ventricular volume, i.e. to a ⇓ in blood volume

Long-Term Effects of Frequent In-Center Hemodialysis
-Chertow et al, JASN 2016;27:1830-1836
Chronic Fluid Overload and Mortality in ESRD
-Zoccali et al, JASN 2017;28:2491-2497
In-Center Hemodialysis Six Times per Week versus Three Times per Week
-FHN Trial Group, Chertow et al, N Engl J Med. 2010 Dec 9;363(24):2287-300.

39,566 patients in 26 countries, > 200,000 tetrapolar BIA studies

Fluid Volume as a preditor was estimated by an average of 10 measurements over 1 year



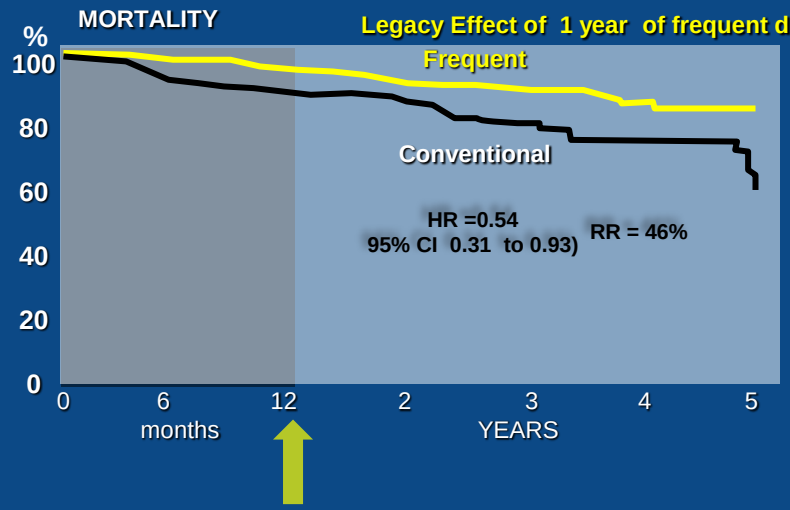
Chronic Fluid Volume Overload is a powerful risk factor for death.

Better outcomes by long and more frequent dialysis in large part underlie better volume control

NMR studies repeated during long term follow up in about 1/3 of patients confirmed LVMI reduction (⇓ LV volume)

patients who survived or had no progression in LVMI

after returning to convential dialysis, patients seem to maintain the blood volume achieved during frequent dialysis



Robust findings confirmed in Bayesian and sensitivity analyses

Trial stopped . Patients on Frequent HD returned to conventional dialysis

Take Home Message

A low BP target (achieved average systolic BP 132 mmHg) reduces the risk of death by the 14% in CKD patients. Even though there not seems to be a higher risk for adverse renal outcomes with this BP target, further confirmations are needed.

Analyses in the Frequent hemodialysis trial extended to 5 years show a relevant risk reduction notwithstanding that the study intervention was stopped after 1 year. These are robust findings because confirmed in Bayesian and sensitivity analyses.

Chronic Fluid Volume Overload is a powerful risk factor for death.
Better outcomes by long and more frequent dialysis most likely underlie better volume control.

List of References

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