

The Heart in Uremia

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Cardiovascular mortality is excessive in patients with even minor renal dysfunction and it is extremely high in patients on dialysis. The main cause of excess mortality is cardiac death, particularly sudden death and myocardial infarction. In past years some, though by means not all, causes contributing to such increased cardiac mortality have been elucidated. In uremia the heart is characterized by the following abnormalities :

- left ventricular hypertrophy (LVH), both concentric and excentric
- congestive heart failure
- cardiac fibrosis
- accelerated coronary atherosclerosis
- microvessel disease and
- ischemia intolerance

LVH is due to both increased afterload (mainly elevated blood pressure and reduced aortic elasticity) and preload (mainly hypervolemia and anemia). The increase in LV mass is in part blood pressure independent, at least in experimental studies. LVH is not merely characterized by an increase in LV mass, but is also associated with genetic reprogramming (embryonal type). A potential contributing cause is sympathetic overactivity, resulting from activating signals which arise from the damaged kidney.

Congestive heart failure carries the most adverse prognosis. At least one of the reasons is cardiomyocyte drop out which is clearly demonstrable in experimental models of renal failure.

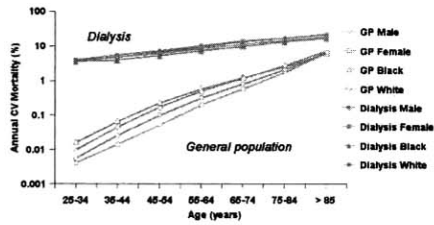
A further hallmark of uremia is cardiac interstitial fibrosis, resulting from primary activation of interstitial fibroblasts in the heart. The consequences are impaired LV compliance, altered stress-strain relationship and electrical instability resulting from the interposition of high electrical resistance obstacles into the spreading front of the excitation wave, favouring reentry type arrhythmias.

A major cause of cardiac death is coronary atherosclerosis. Experimental studies clearly document accelerated atherogenesis, presumably related to increased oxidative stress in endothelial cells. In addition, however, there is also evidence for impaired ischemia tolerance of myocardial cells, consistent with the clinical observation of a higher case fatality rate in acute cardiac ischemic events.

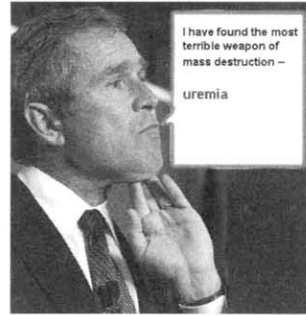
One additional factor, aggravating the consequences of luminal narrowing from coronary atherosclerosis is abnormal vascular remodelling, causing excessive intimal hyperplasia and "secondary" poststenotic luminal narrowing, as well as microvessel disease, i.e. arteriolar wall thickening and inadequate capillary formation in response to myocardial hypertrophy.

Given the complexity of the pathogenesis of the cardiac lesions it is highly unlikely that one will ever find one single "golden bullet" to take care of excess cardiac death. It is likely that a complex multifactorial approach will be required.

CVD - the Major Cause of Mortality in ESRD



Samak. Am J Kidney Dis 2000;35(suppl1):S117



The nephrologist's view of the heart

The heart is a minor organ in the shape of a bladder the major purpose of which it is to supply the kidney with blood

Bryan Williams, 2003

The heart in uremia

- LV hypertrophy
- Heart failure
- Cardiac fibrosis
- Ischemic heart disease
 - coronary atherosclerosis
 - ischemia intolerance

Echocardiographic findings in patients entering dialysis

normal	16%
LV hypertrophy	41%
LV dilatation	28%
systolic dysfunction	16%

Harnett, Kidney Intern (1995) 47: 854

Echocardiographic findings and mortality

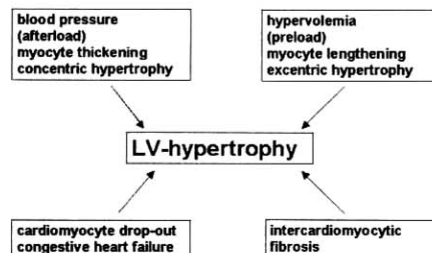
normal echo	1
LV hypertrophy	1.8
LV dilatation	2.9
systolic dysfunction	6.6

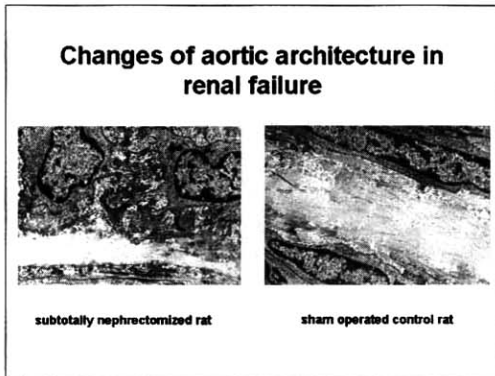
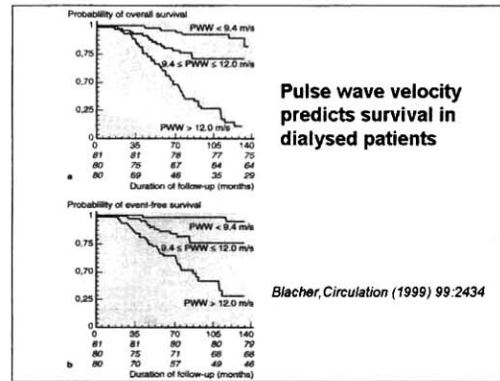
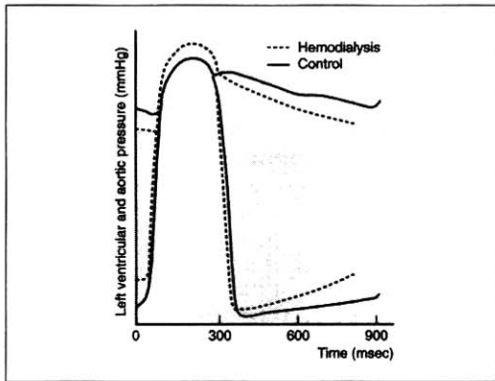
Harnett, Kidney Intern (1995) 47: 854

Cardiac hypertrophy (concentric, excentric) in endstage renal disease

- pressure overload
 - hypertension
 - aortic distensibility / (aortic stiffness ↑)
- volume overload
 - salt / water retention
 - anemia
 - av - shunt
-

London, Kidn.Intern.(1993) 43: S42



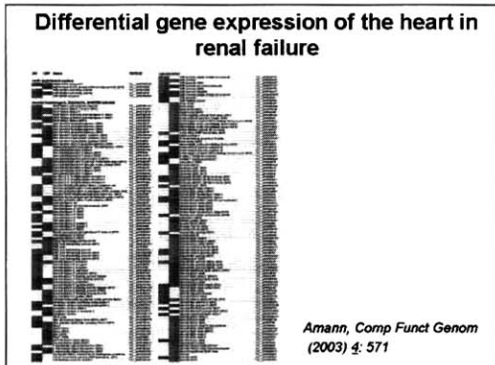
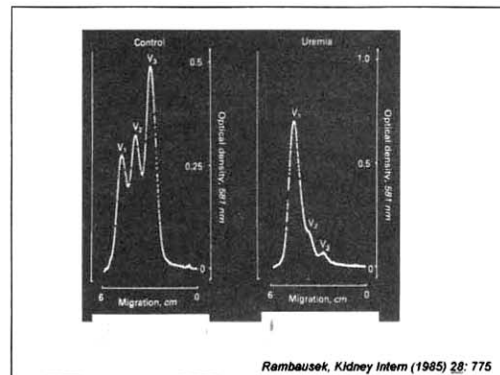


Cardiac hypertrophy in subtotally NX rats

	control	SNX	SNX + frusemide + metoprolol
heart weight / body w. ratio (mg/g x 10 ²)	31.7 ± 0.8	75.8 ± 1.2	73.6 ± 1.1

Rambosek, *Kidn.Intern* (1985) 28:775

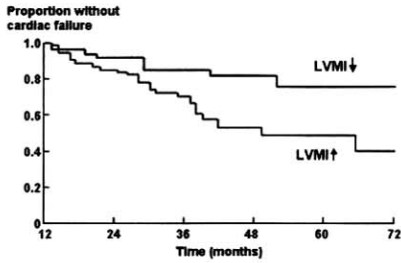
- ### Cardiac hypertrophy – expression of fetal gene programs
- c - fos
 - c - jun
 - c - myc
 -
 - ANP
 - BNP
 - β - MHC
 -



- ### Cardiac hypertrophy
- not benign condition
- # Initially adaptive (wall tension ↑)
 - # later maladaptive, leading to
 - fibrosis
(compliance ↓, arrhythmia)
 - impaired vasodilatation
(extravascular component of vasc. resistance ↑)
 - cardiomyocyte drop out
(congestive heart failure)
 - ...

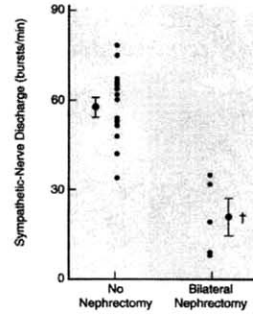
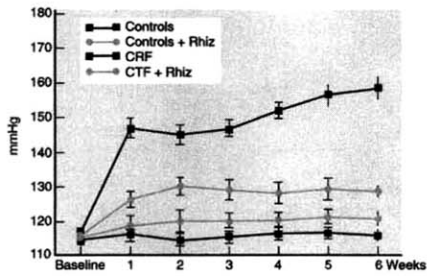
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Heart failure by LV growth

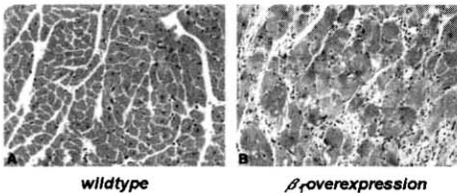
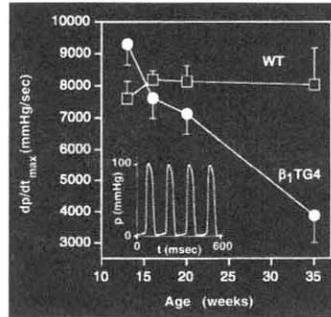
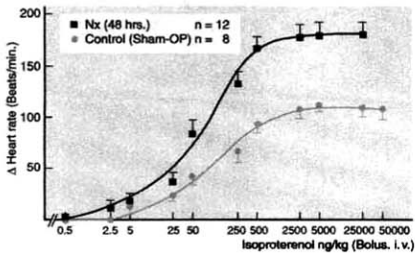


Adrenergic activity in renal failure

- afferent signals from damaged kidney
 - activation of hypothalamic centers
 - increased efferent sympathetic nerve traffic,
- involved in :
- hypertension*
 - LVH*
 - predisposition to arrhythmia*
 - progression*



Postreceptor defect of the heart in uremia – decreased heart rate and cAMP response despite unchanged β receptor binding

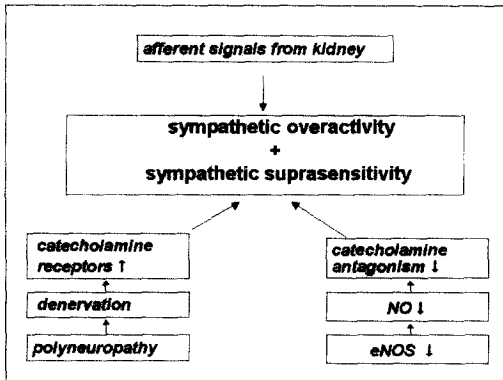


Engelhardt, PNAS (1999) 96, 7059

β adrenergic receptor polymorphism

- 389 glycine / arginine exchange
- more left ventricular hypertrophy
- greater rel. risk of congestive heart failure
- cardiac phenotype reproduced in organ specific transgenic mice expressing the human 389 arg gene in the heart

Perez, Nature Med (2003) 9:1300



114 dialysis patients with dilated cardiomyopathy
standard therapy plus carvedilol vs placebo
at 2 years :

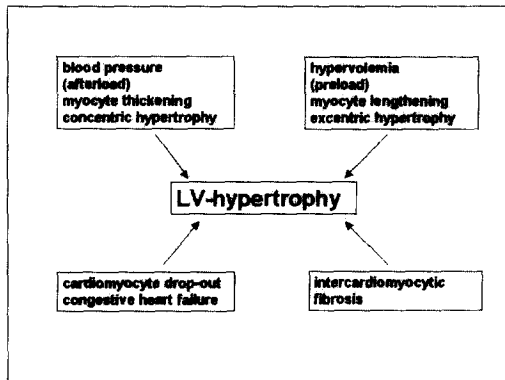
death	51.7 % vs 73.2 %
CV death	29.3 % vs 67.9 %
hospitalisation	34.5 % vs 58.9 %

Cico, JACC (2003) 41:1438

The heart in uremia

LV hypertrophy
Heart failure
Cardiac fibrosis
Ischemic heart disease

- coronary atherosclerosis
- ischemia intolerance



Cardiomyocyte drop-out in uremia

	control	SNX	SNX + Ramipril
cardiomyocytes per left ventricle	84.8±	70.9±	118±
	18.1	70.9	39

⇒ predisposition to congestive heart failure

Amann, Kid. Intern.(2003)63:1708

Heart failure

activation of fetal program
 β-myosin heavy chain ↑
 α-actin skeletal isoform ↑
 ANP, BNP ↑

repression of adult program
 SERCA 2a

Heart - Renal failure
 activation of fetal program
 β-myosin heavy chain ↑

Rembausek, Kidney Intern (1985) 28: 775

Effect of β-blockers
 reversal of fetal program

Bristow, New Engl J Med (2002) 348: 1957

- β₁ adreno receptor (↑)
- β₂ adreno receptor ↑
- ANP ↓
- SERCA 2a ↑
- α₂ myosin heavy chain ↑

Metoprolol – progressive reduction of intima media thickness

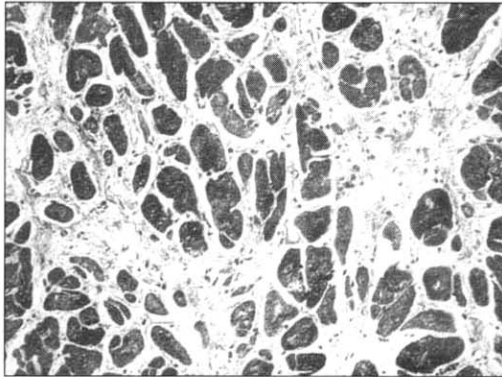
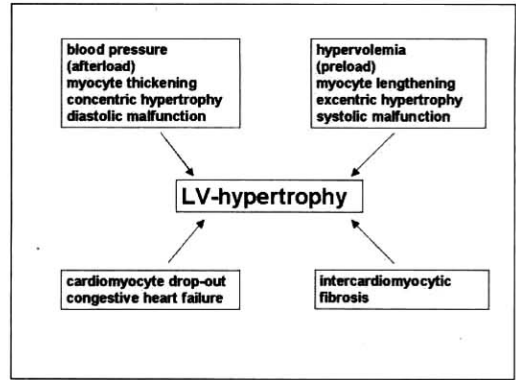
ELVA trial
 asymptomatic patients on statins
 metoprolol vs placebo
 progression of intima media thickness in 3 year follow up

- 0.08 vs + 0.03 (p<0.01)

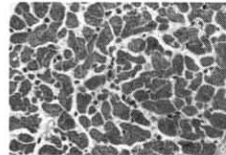
Wikstrand, Am. J. Cardiol. (2003)91:25H

The heart in uremia

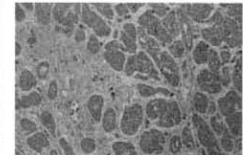
- LV hypertrophy
- Heart failure
- Cardiac fibrosis
- Ischemic heart disease
 - coronary atherosclerosis
 - ischemia intolerance



Morphology of the human myocardium in renal failure

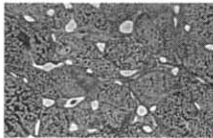


normal morphology

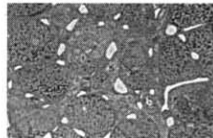


morphology of the myocardium of a patient with chronic renal failure

Morphology of the myocardium in experimental renal failure



sham operated control rat



subtotaly nephrectomized rat with renal failure of 14 months duration

Selective activation of interstitial, but not endothelial cells

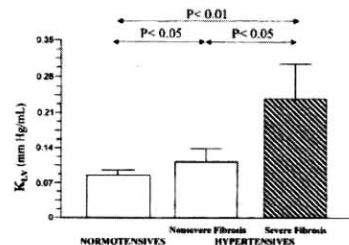
$V_v(\text{cm}^3/\text{cm}^3 \times 10^3)$	Subtotal NX	Sham op
endothelial cells		
nuclei	10.2 ± 0.7	10.6 ± 2.6
cytoplasm	12.2 ± 4.2	15.1 ± 5.6
Interstitial cells		
nuclei	20.9 ± 12.6	4.6 ± 3.4
cytoplasm	18.5 ± 5.7	10.3 ± 4.7

Mall, Kidn Intern (1988)33:804

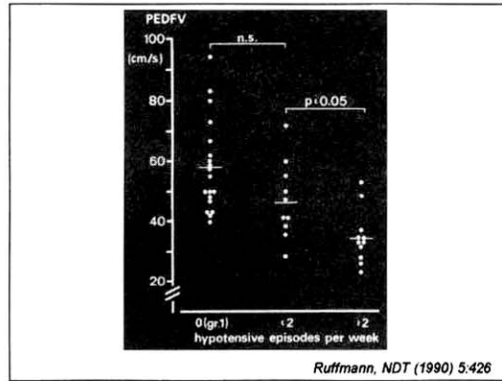
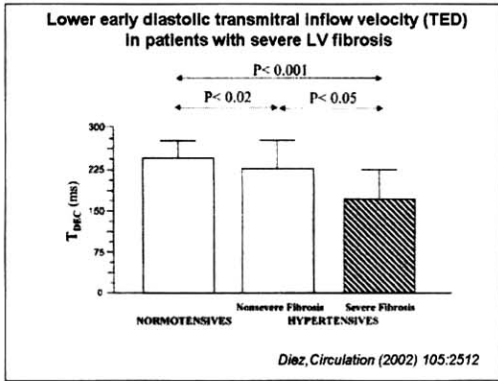
Functional consequences of cardiac fibrosis

- reduced LV compliance
 - ventricular filling requires higher filling pressures
- altered stress – strain relationship
- arrhythmia
 - interposition of fibrous tissue with high electrical resistance
 - local delay in spread of action potential
 - reentry type of arrhythmia

Increased left chamber stiffness in patients with severe LV fibrosis



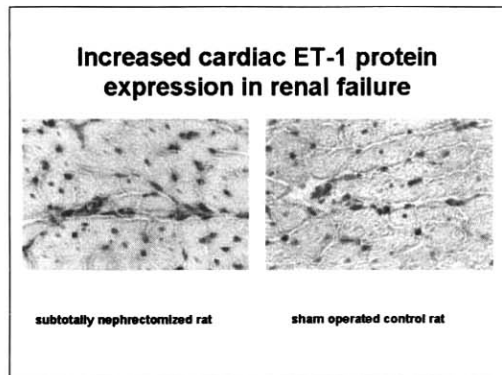
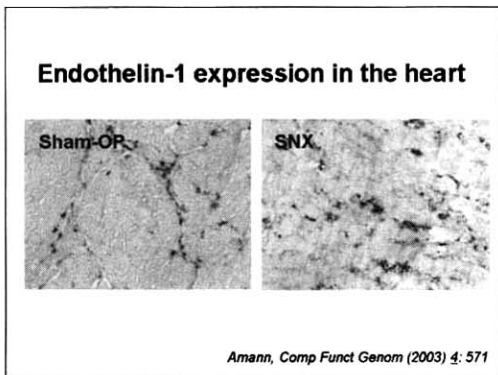
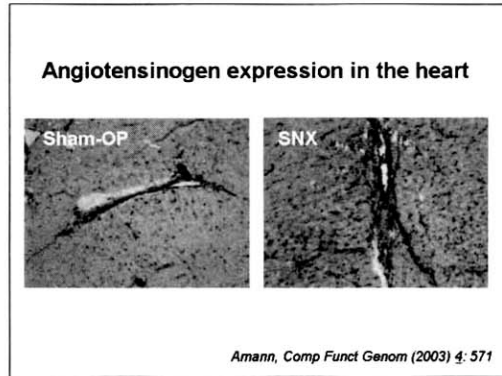
Diaz, Circulation (2002) 105:2512



- ACE inhibitors reduce cardiac fibrosis
Amann, J.Clin.Bas.Cardiol (2001)4:109
- Endothelin receptor blockers reduce cardiac fibrosis
Nabokov, Kidn.Intern. (1999) 55:512

suggested pathway :

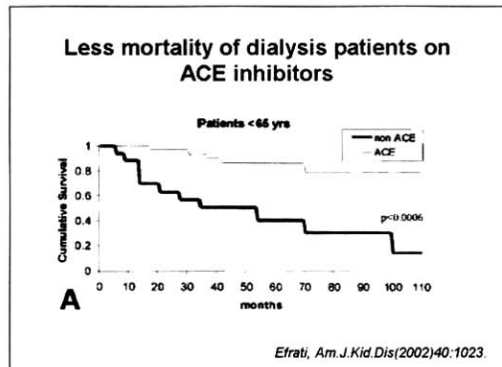
ANG II
endothelin
fibrosis



in subtotally NX rats administration of ACE inhibitors
⇒ less LV hypertrophy, cardiac fibrosis and cardiomyocyte drop out
Amann, Kidn Intern(2000) 58:153
Amann, Kidn.Intern(2003) 63:1708

in the IDNT and RENAAL trials
⇒ trend for less CV events with angiotensin receptor blockers
Lewis, NEJM(2001)345:851
Brenner, NEJM(2001)345:861

in a retrospective study
⇒ less mortality of dialysis patients on ACE inhibitors
Efrati, AJKD(2002) 40:1023



- ACE inhibitors reduce cardiac fibrosis
Amann, J.Clin.Bas.Cardiol (2001)4:109
- Endothelin receptor blockers reduce cardiac fibrosis
Nabokov, Kldn.Intern. (1999) 55:512

suggested pathway :

ANG II
endothelin
fibrosis

PTH and phosphate permissive factors

In vivo

In vitro

Amann, JASN (1994)4:1814
Amann, Kid.Intern. (2003) 63:1296

The heart in uremia

- LV hypertrophy
- Heart failure
- Cardiac fibrosis
- Ischemic heart disease
 - coronary atherosclerosis
 - ischemia intolerance

Lindner A, Charra B, Sherrard DJ, Scribner BH

Accelerated atherosclerosis in prolonged maintenance hemodialysis

New Engl J Med (1974) **290**: 697-701

Prevalence of coronary heart disease in dialysed patients

⇒ 30 – 40 %

- Coronary angiography

Ikram, Kldn.Intern. (1983) 24: 371

- Autopsy

Clyne, Scand.J.Urol.Nephrol(1986) 24:371

The Apolipoprotein E Knockout Mouse: A Model Documenting Accelerated Atherogenesis In Uremia

MORIZ BUZELLO,¹ JOHANNES TÖRNIG,¹ JÖRG FAULHABER,² HEIMO EHMKE,¹ EBERHARD RITZ,¹ and KERSTIN AMANN^{3*}

¹Department of Pathology, University of Erlangen-Nürnberg, Erlangen, Germany; ²Departments of Pathology and Translational Medicine, University of Heidelberg, Heidelberg, Germany; and ³Department of Physiology, Universitätsklinikum Lippendorf, Homburg, Germany.

Uninephrectomy aggravates atherogenesis in the apo E -/- mouse

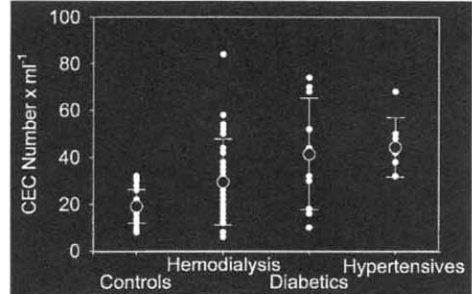
	maximal plaque diameter (μ)	plaque area per aortic circumference (μ ² ×10 ⁻³)
sham op	191 ± 90	5.15 ± 1.21
uninephrectomy	322 ± 65.5	36.9 ± 15.5
subtotal NX	473 ± 165	70.2 ± 30.1

Buzello, JASN (2003) 14:311

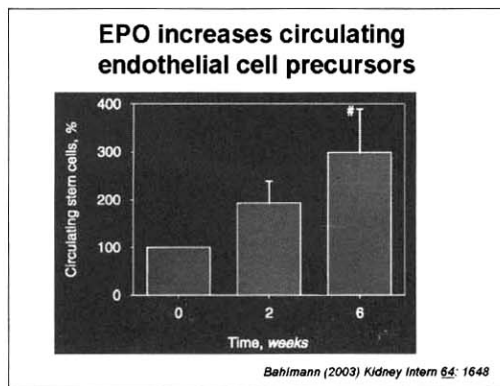
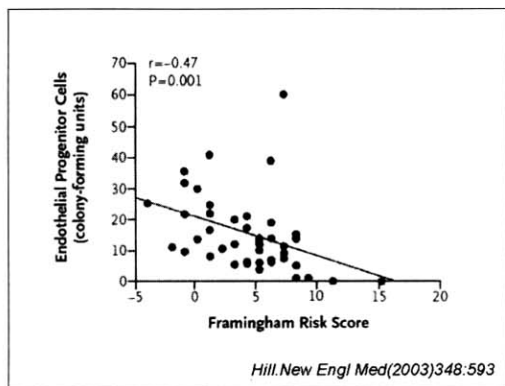
Circulating endothelial cells



Koç (2003), Am J Kidney Dis 42: 704



Koç (2003), Am J Kidney Dis 42: 704

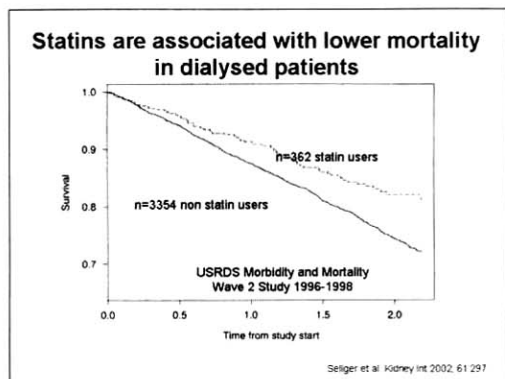


Statins in dialysed patients – DOPPS data

	hazard ratio	p
all cause mortality		
all patients	0.69	0.001
CAD	0.7	0.001
hypertension	0.7	0.001
cardiovascular mortality		
all patients	0.78	0.03
CAD	0.83	0.14
hypertension	0.72	0.01

Bailey, Puerto Rico, 2004

- ### Evidence for efficacy of statins in (subgroups) of patients with impaired renal function in controlled trials
- Alert study
Holdaas, Lancet (2003) 361 : 2024
 - Ascot study
Sever, Lancet (2003) 361:1149
 - CARE study
Tonelli, Ann.Int.Med. (2003) 138:98



Lipid lowering and carotid IMT – nonrenal CAD vs CKD patients

	baseline		2 years	
	CAD	renal	CAD	renal
LDL-cholesterol (mg/dl)	101 ± 27	108 ± 31	62 ± 19	70 ± 27
maximum intima-media thick. (mm)	0.81 ± 0.17	0.73 ± 0.14	0.7 ± 0.13	0.73 ± 0.13
p			0.001	N.S.

Fahti, Am.J.Kid.Dis(2004), 43:45

Atorvastatin and Cardiovascular Complications in Type 2 Diabetics on Dialysis

- ### High coronary mortality of uremic patients
- fully explained by
- high prevalence of coronary lesions
 - or in addition
 - ischemia intolerance ?

백재원

Ischemia intolerance of the heart in uremia

- cardiomyocyte metabolism
- coronary artery remodelling ("secondary stenosis")
- microvessel disease
 - arterioles
 - capillaries

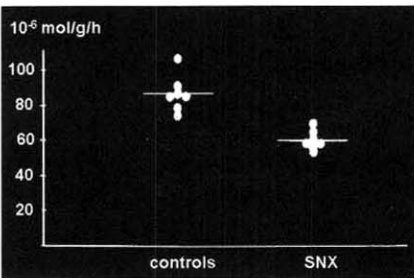
Infarcted area after ligation of left coronary artery sham-op vs subtotal nephrectomy



infarcted area (as % LV) :
30.6 ± 6.65 % vs 18.8 ± 6.58 %

Dikow, JASN (in press)

Insulin dependent glucose uptake in the isolated perfused Langendorff heart of uremic rats



Ritz AJKD (1993) 21: 113

Administration of insulin + glucose causes dramatic reduction of MI mortality in diabetic patients

620 patients
MI <24h
S-glucose >11mmol/l ± known diabetes
insulin + glucose for 24h
4x daily insulin for 4 months
3 y follow up
mortality 33% vs 44% in controls

Malmberg, BMJ (1997)314:1512
Malmberg, BMJ(2000)320:1148

Ischemia intolerance of the heart in renal failure

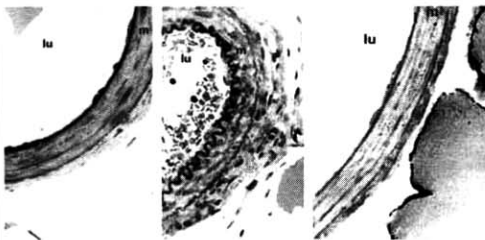
- cardiomyocyte metabolism
- coronary artery remodelling ("secondary stenosis")
- microvessel disease
 - arterioles
 - capillaries

Abnormal vascular remodelling in response to low flow

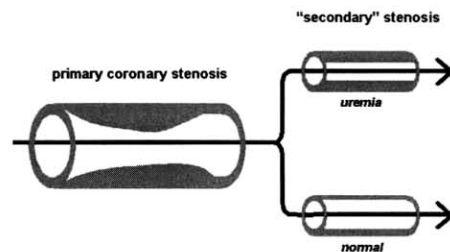
	SNX	SNX low flow	SNX low flow ET-RB
intimal thickness (µm)	2.06±0.61	4.21±1.39	1.2±0.71

SNX subtotal nephrectomy
ET-RB endothelin receptor blocker

Amann, JASN (2001) 12:2040



Amann, JASN (2001) 12: 2040



Excessive intimal proliferation in uremia – potential consequences

- high reocclusion rate after PTCA

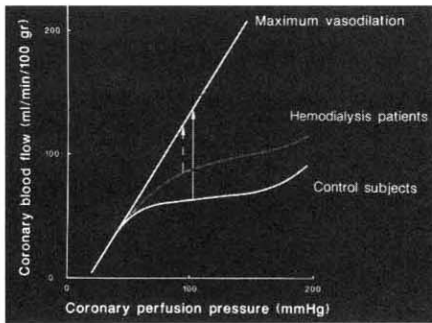
*Kahn, Am.Heart J. (1990) 119:484
Herzog, Circulation (2002)106:2207*

- excessive narrowing of postcoronary intramyocardial arteries

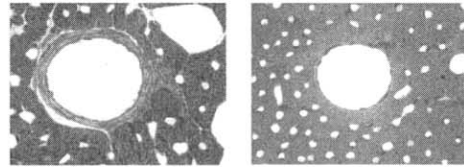
Mall, unpublished

Ischemia intolerance of the heart in renal failure

- cardiomyocyte metabolism
- coronary artery remodelling (“secondary stenosis”)
- microvessel disease
 - arterioles
 - capillaries



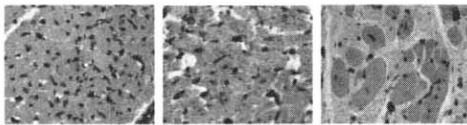
Intramyocardial arteries in experimental renal failure



subtotally nephrectomized rat

sham operated control rat

Less myocardial capillaries in uremic patients

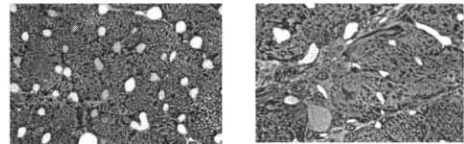


myocardium of a normotensive control patient

myocardium of a patient with essential hypertension

myocardium of a patient with chronic renal failure

Less myocardial capillaries in uremic rats



myocardium of a sham-operated control rat with normal number of capillary profiles

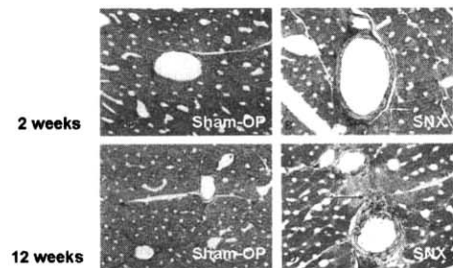
myocardium of a subtotally nephrectomized rat with markedly less capillary profiles

The heart in uremia

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 - coronary atherosclerosis
 - Ischemia intolerance

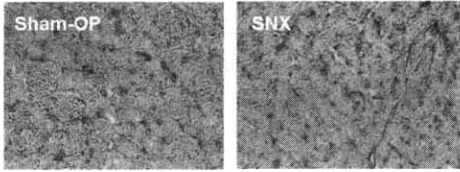
⇒ unlikely that one golden bullet will eliminate excess cardiac mortality in the renal patient

Changes of myocardium in renal failure



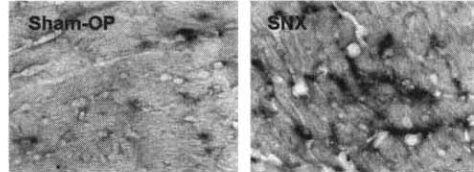
Amann, Comp Funct Genom (2003) 4: 571

Integrin-β1 expression in the heart



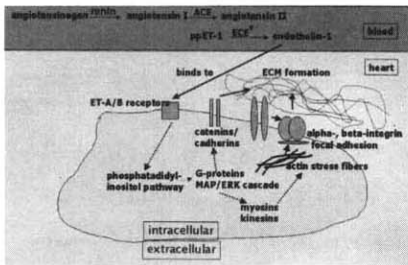
Amann, *Comp Funct Genom* (2003) 4: 571

TGF-β1 expression in the heart



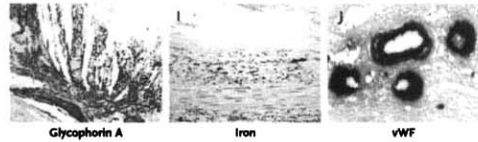
Amann, *Comp Funct Genom* (2003) 4: 571

Pathways postulated in cardiac remodelling of renal failure



Amann, *Comp Funct Genom* (2003) 4: 571

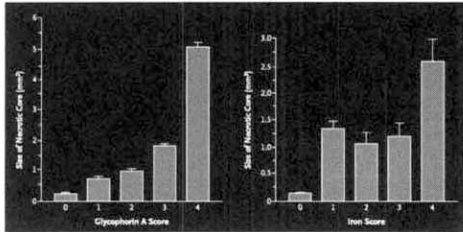
Thin-cap fibroatheroma



400x

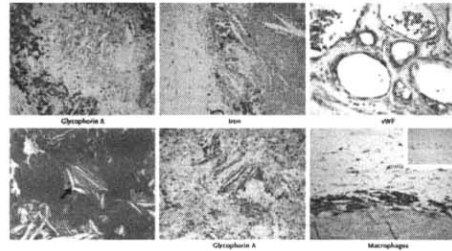
Kolodgie, *New Engl J Med* (2003) 349: 2319

Relation of Glycophorin A and Iron scores to necrotic score size



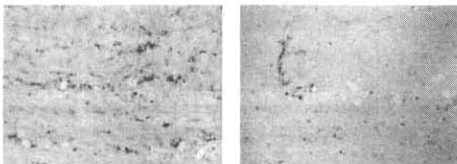
Kolodgie, *New Engl J Med* (2003) 349: 2319

Atherogenic changes associated with extravasated erythrocytes



Kolodgie, *New Engl J Med* (2003) 349: 2319

Increased cardiac ET-1 mRNA expression in renal failure



subtotally nephrectomized rat

sham operated control rat