



The role of FGF23 beyond CKD-MBD: Is it important?



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Disclosures

✓ Scientific support

- ✓ AbbVie, Amgen, Dutch Kidney Foundation, FMC, Pfizer, Sanofi, Shire

✓ Consultant, lecture fees, other

- ✓ AbbVie, Alexion, Amgen, Astellas, VFMCRP, Otsuka

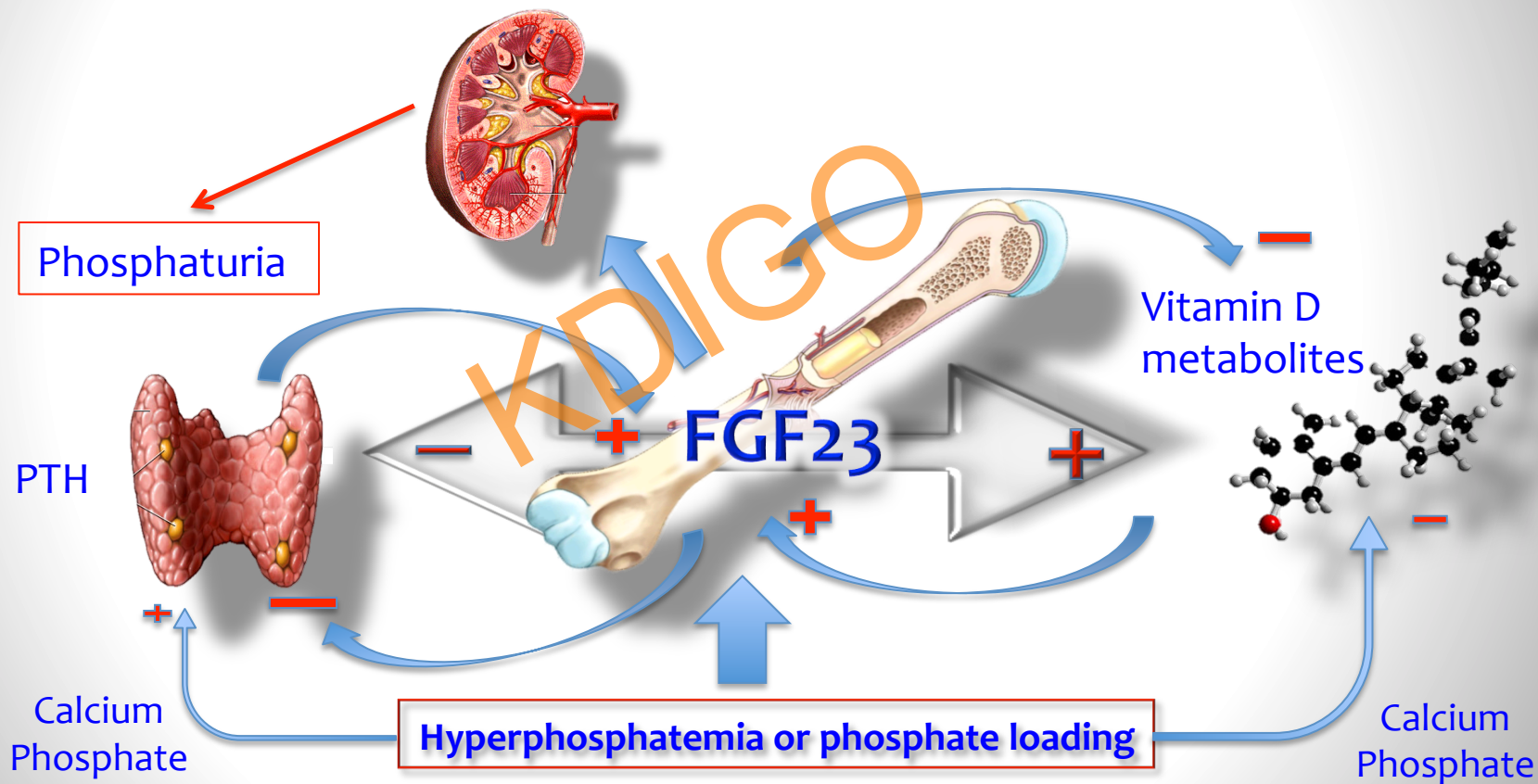
- ✓ (See DOI at www.era-edta.org)



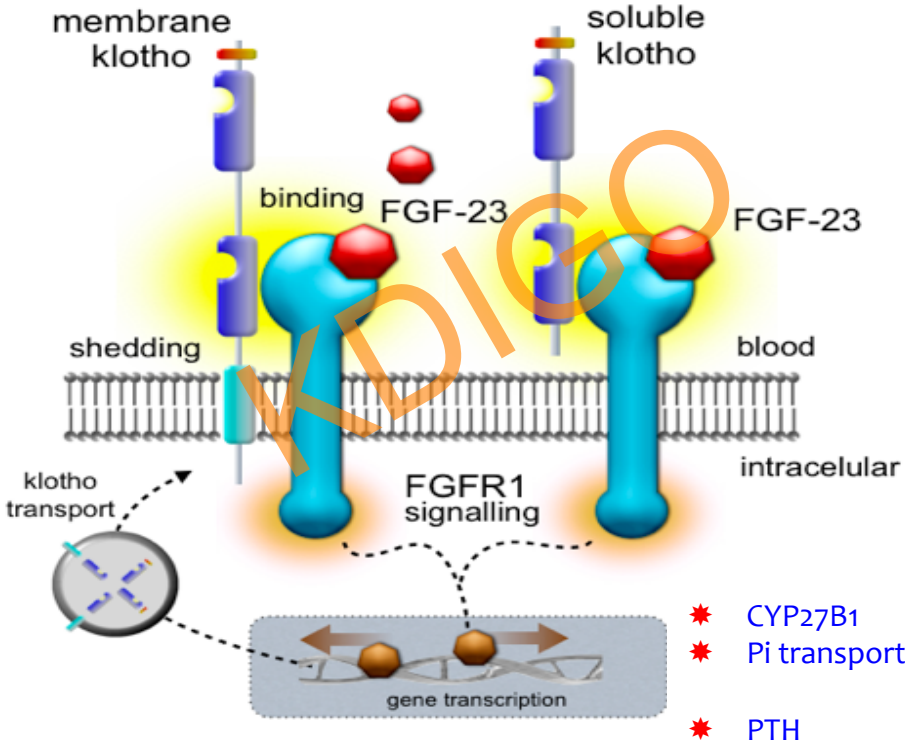


KDIGO

Role FGF23 in CKD-MBD



Classical FGF23 signaling



FGF23 actions outside MBD

- ✓ Heart
- ✓ Infection
- ✓ Inflammation
- ✓ Volume control
- ✓ Vessels: vasodilation



Not about: non classical regulation

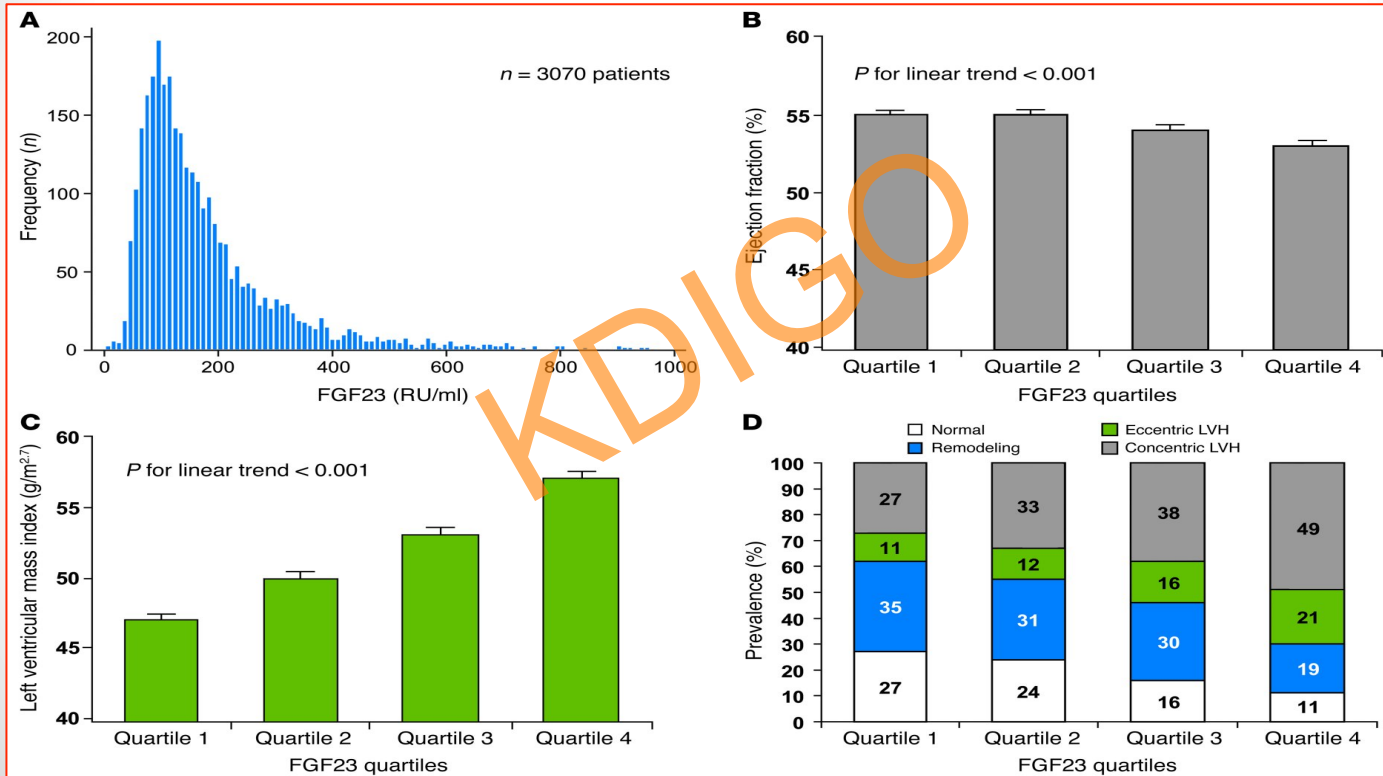
- ✓ Iron
- ✓ Inflammation
- ✓ Calcium



FGF23 and the heart

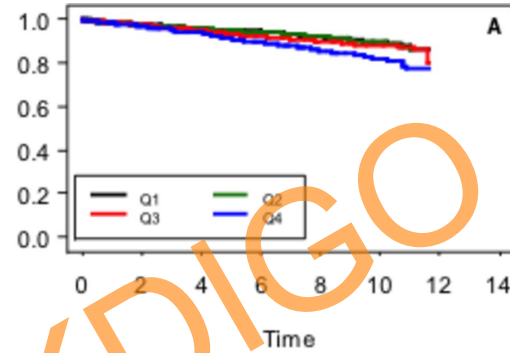
KDIGO

Causality for FGF23?

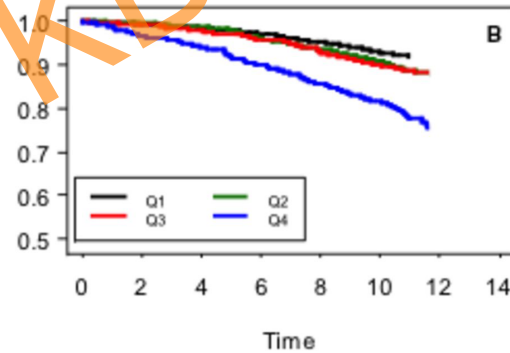


Framingham cohort

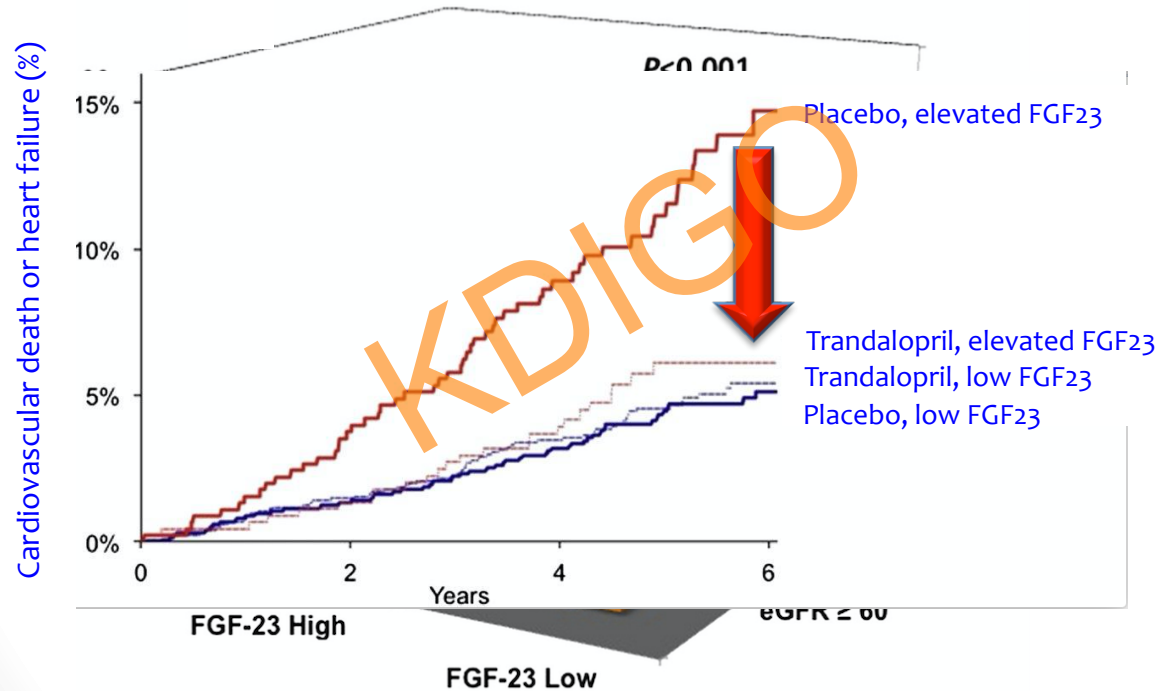
Cardiovascular
mortality



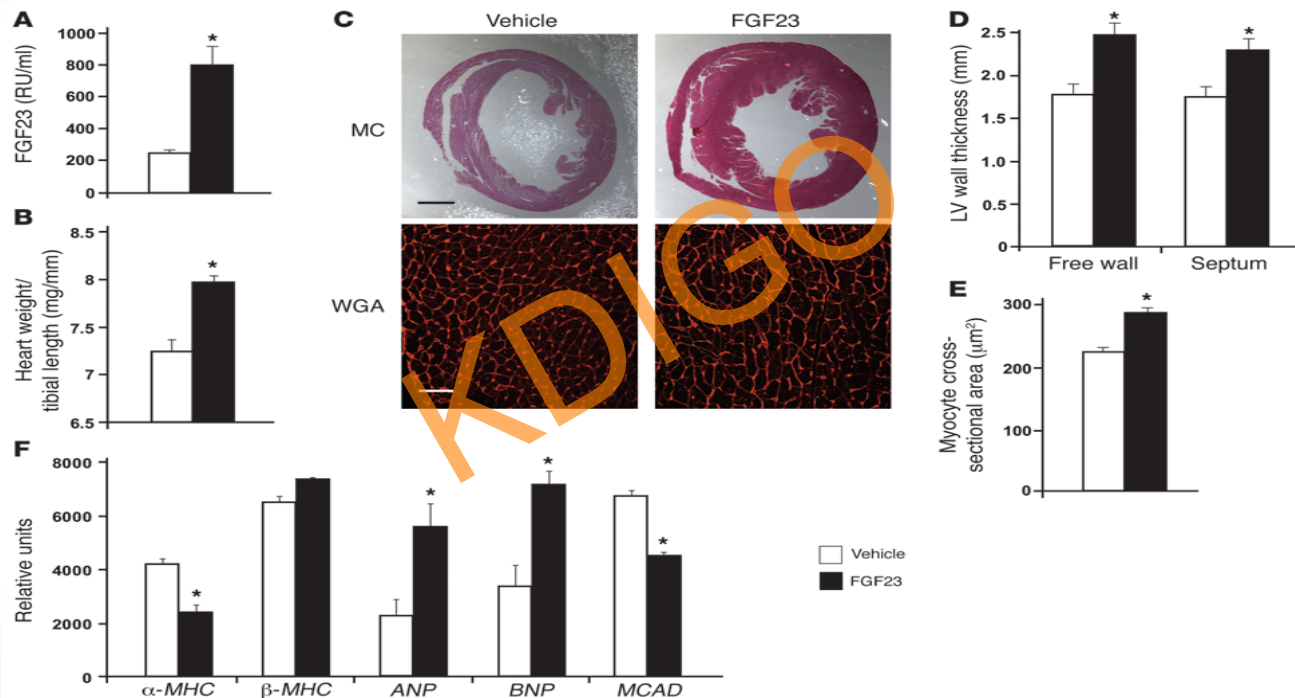
All cause
mortality

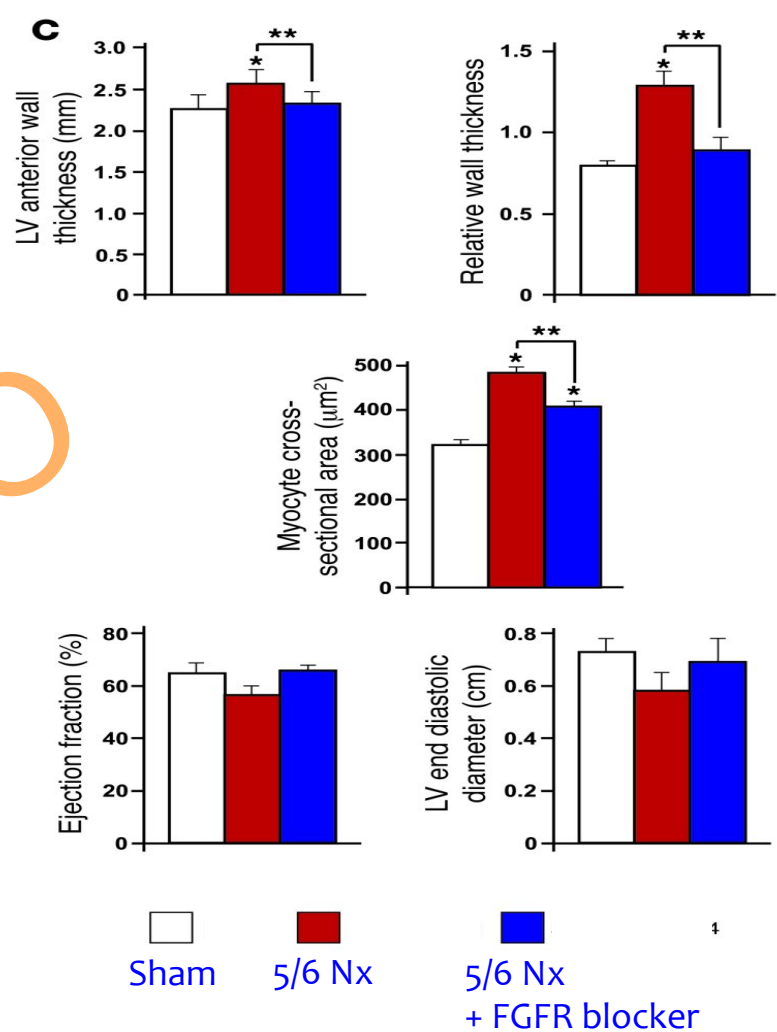
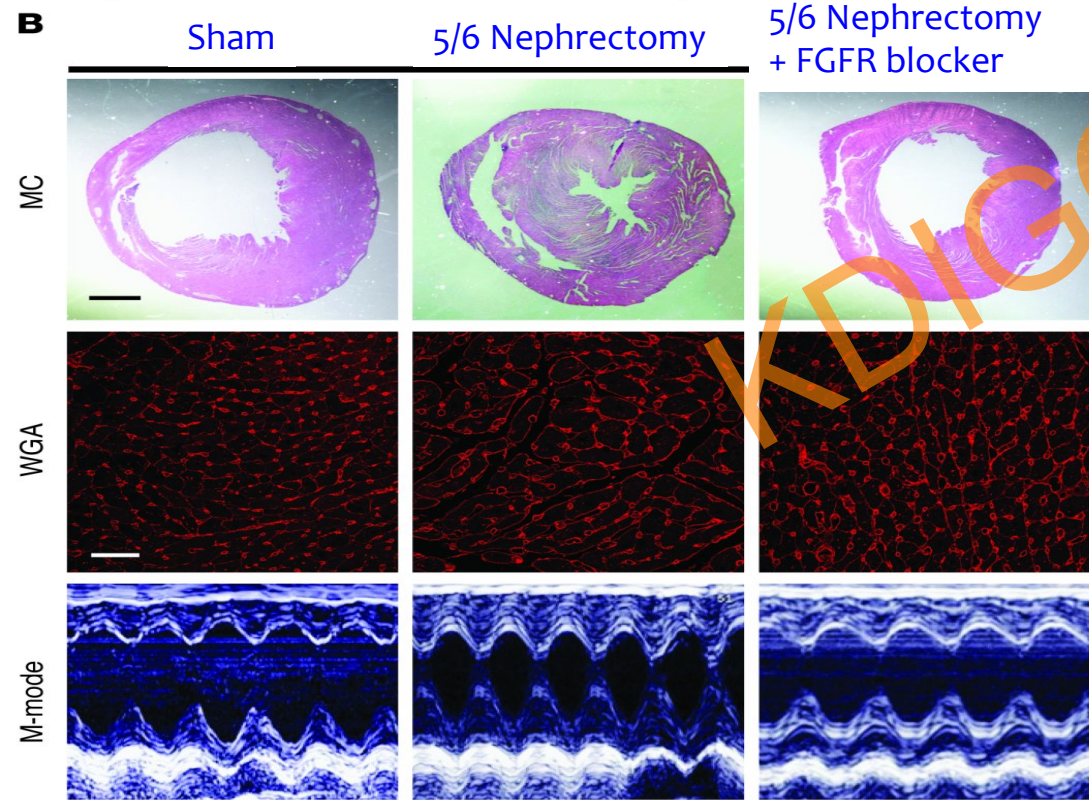
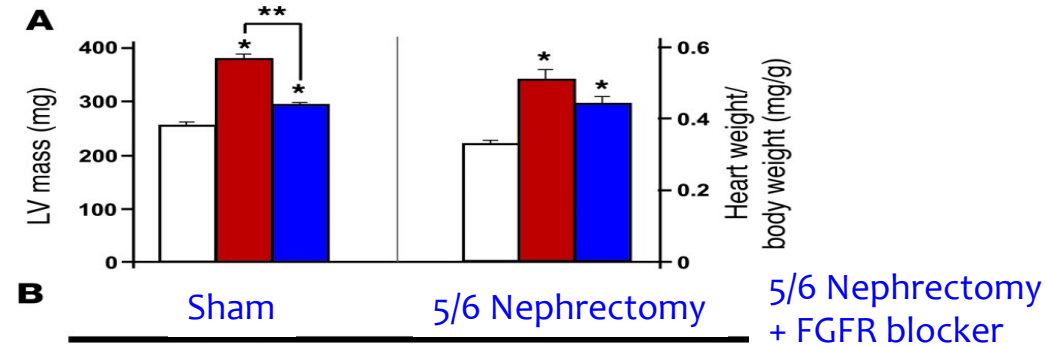


FGF23 as effect modifier for ACE inhibition

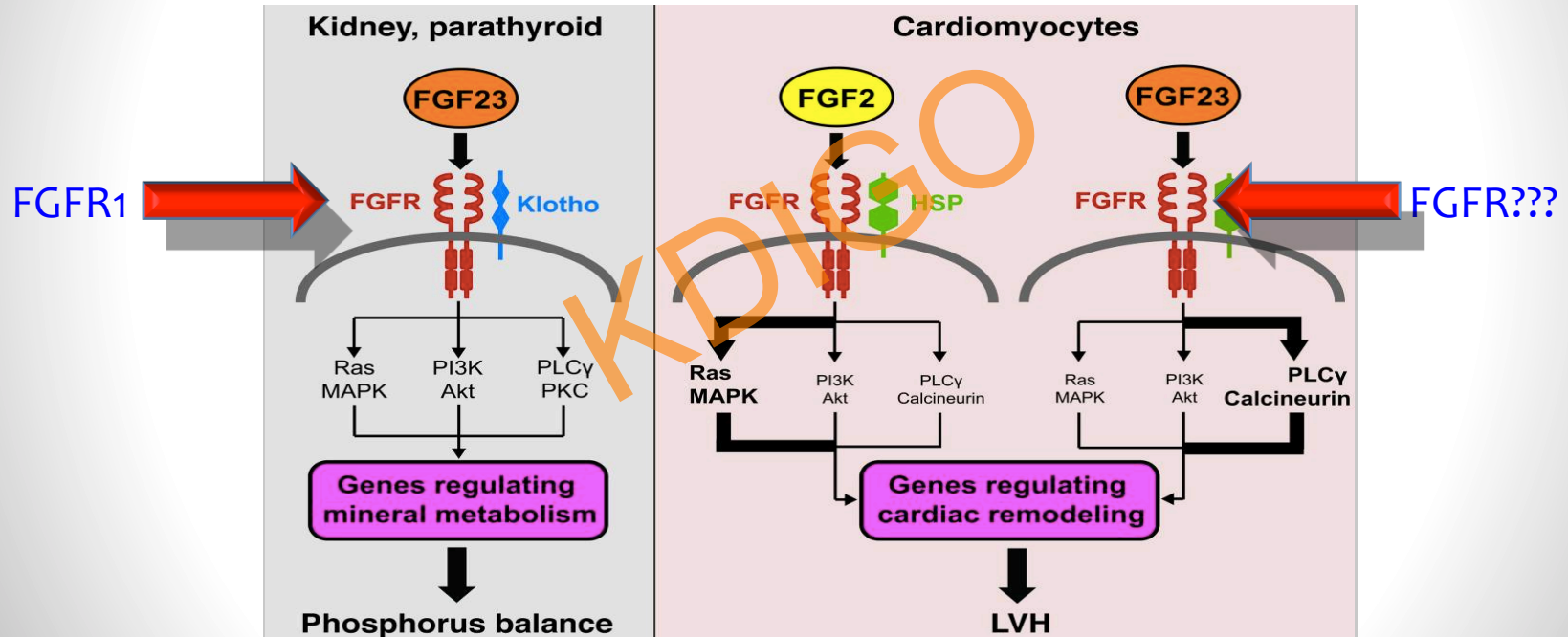


The role of FGF23



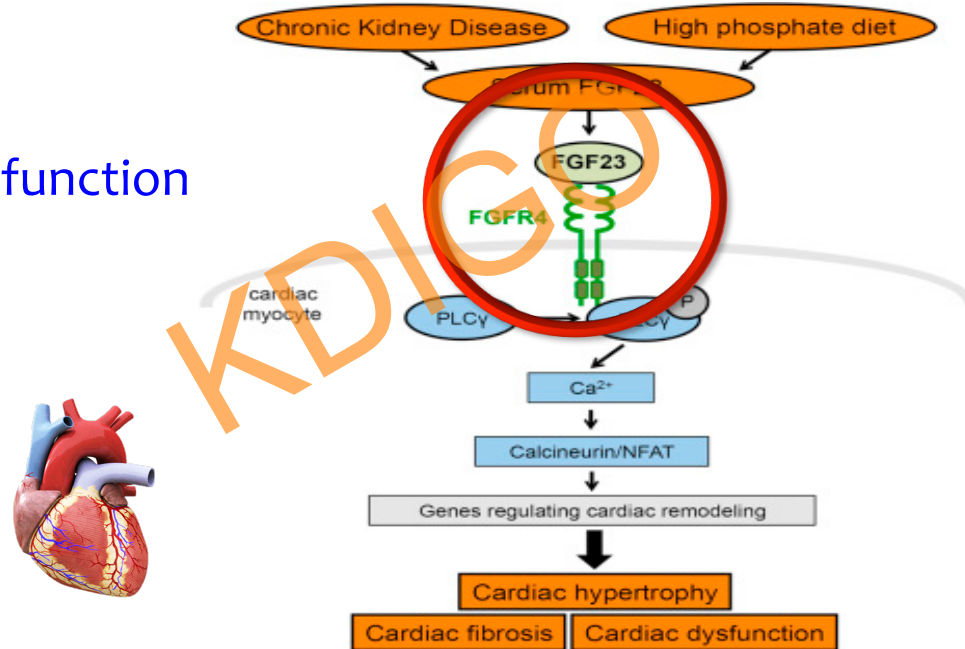


Klotho independency of FGF23: Heart

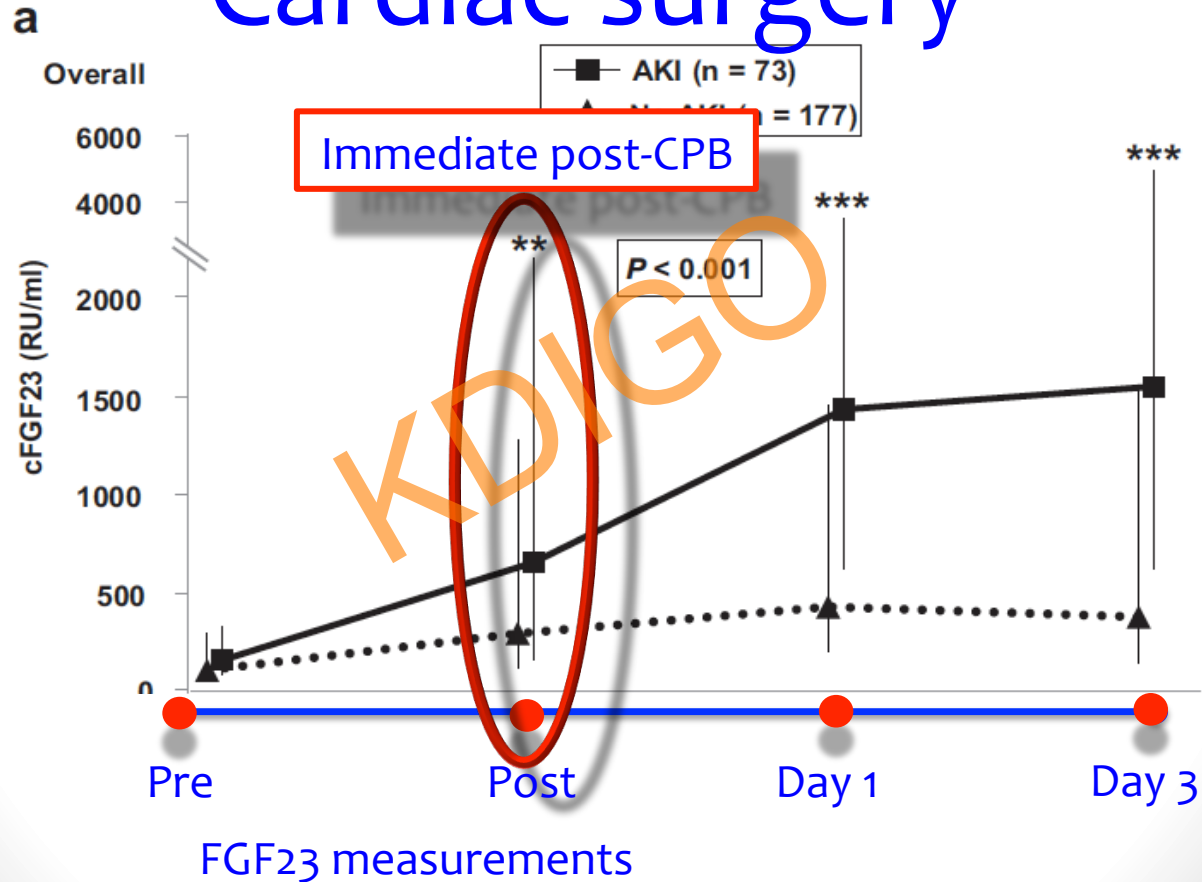


FGF23 receptor in the heart

✓ Specific FGFR4 function



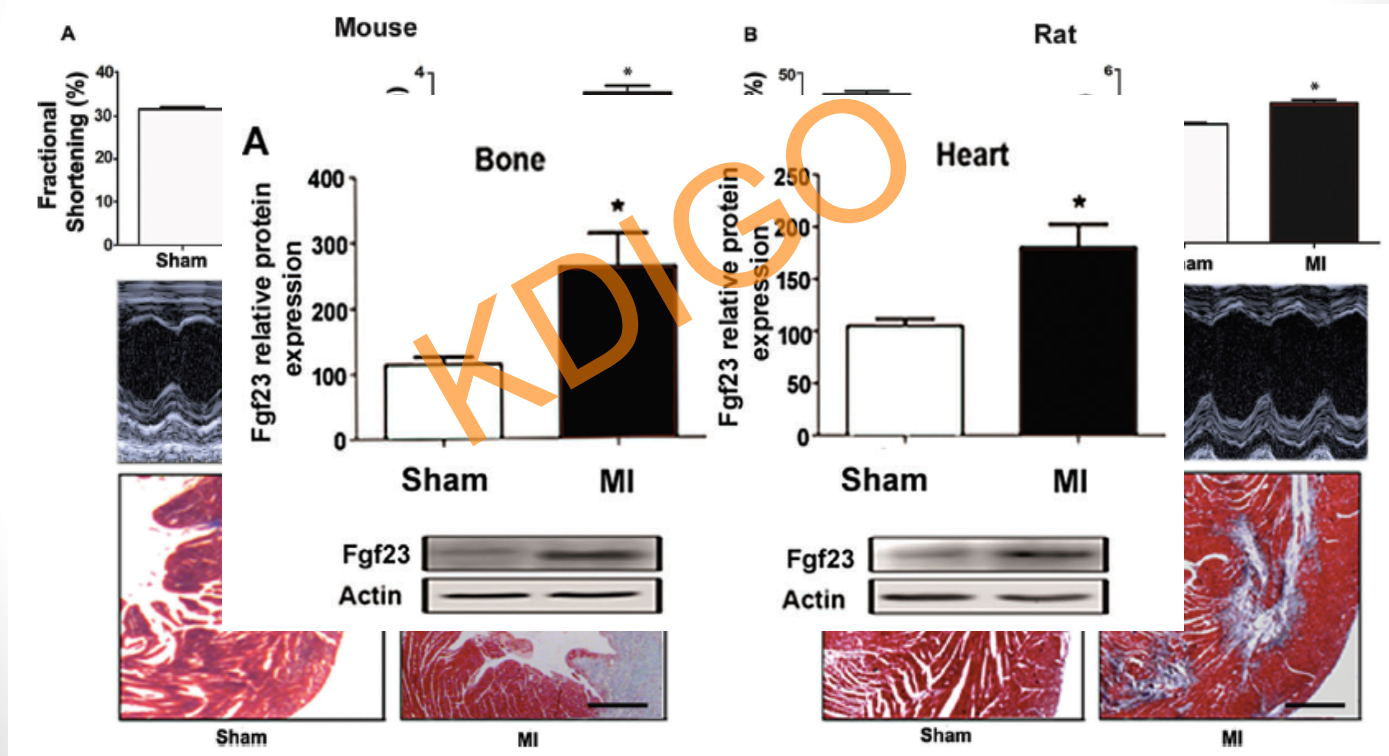
Cardiac surgery



CPB *induces* FGF23?



Experimental myocardial infarction increases FGF23



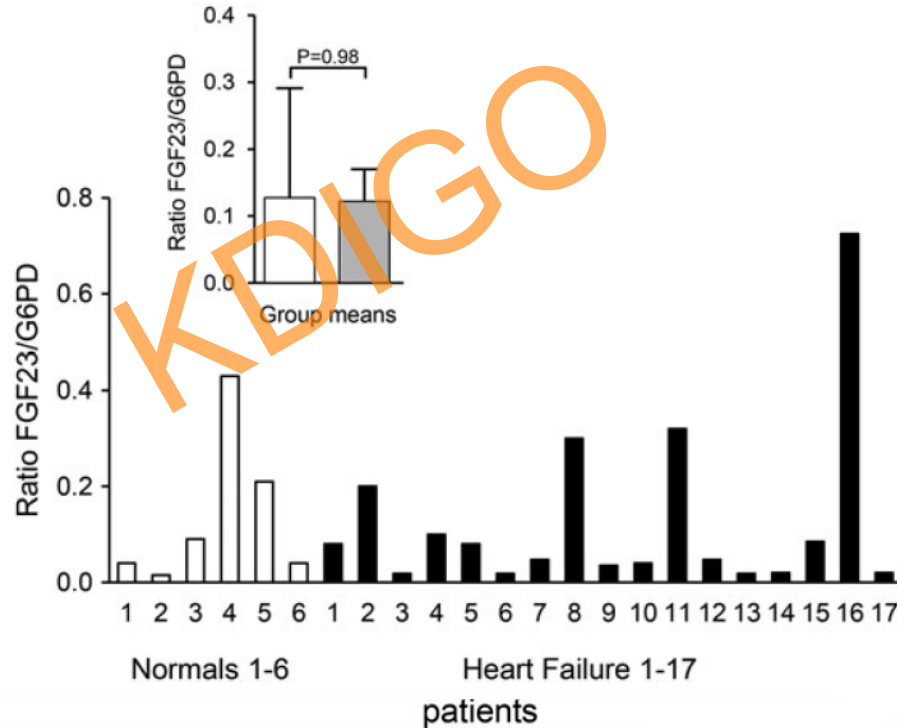
Heart failure increases FGF23

Human data

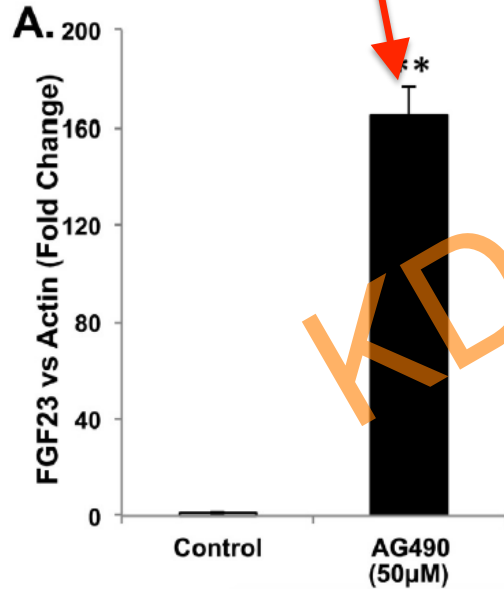
Acute
decompensated HF

versus

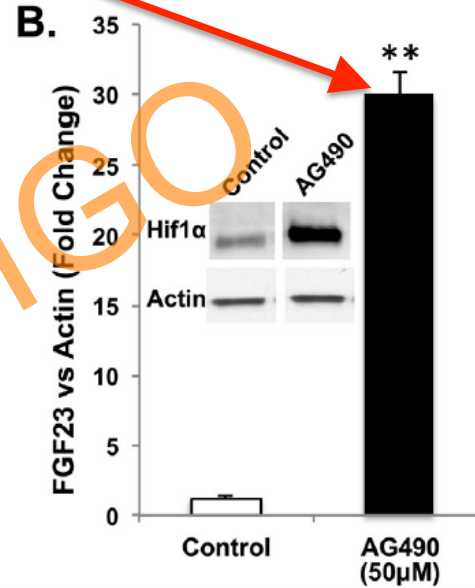
Control



HIF1 α activation in bone cells



Primary osteocyte cell culture



Osteoblastic cell line

Hypoxia induces FGF23!

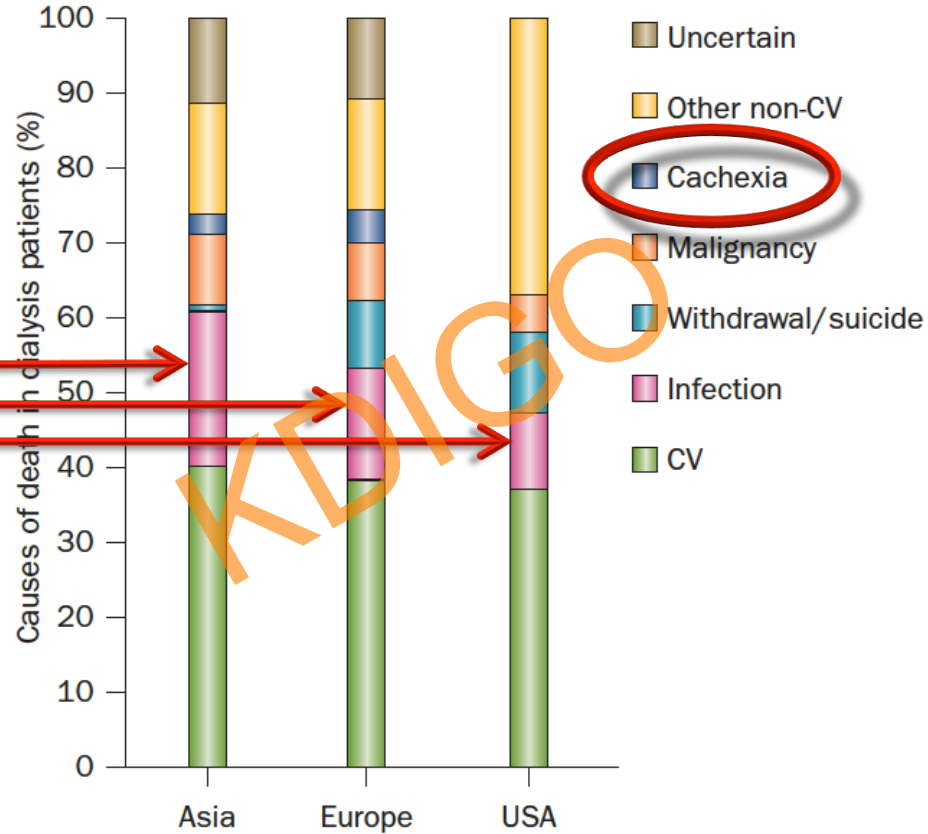


FGF23 actions outside MBD

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- ✓ Infection
- ✓ Inflammation
- ✓ Volume control
- ✓ Vessels: vasodilation



Infections



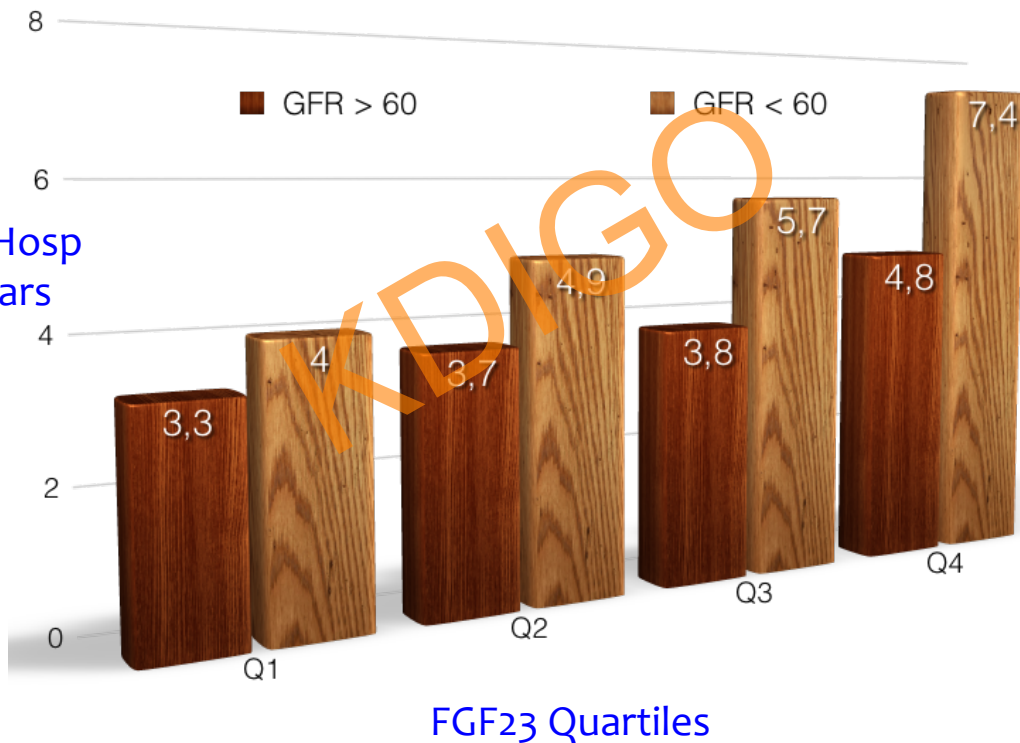
FGF23 and Infections

- ✓ Cardiovascular Health Study
- ✓ N=3141, age 78 ± 5 years (!)
- ✓ eGFR 71 ± 17 (ml/min/1.73 m²)

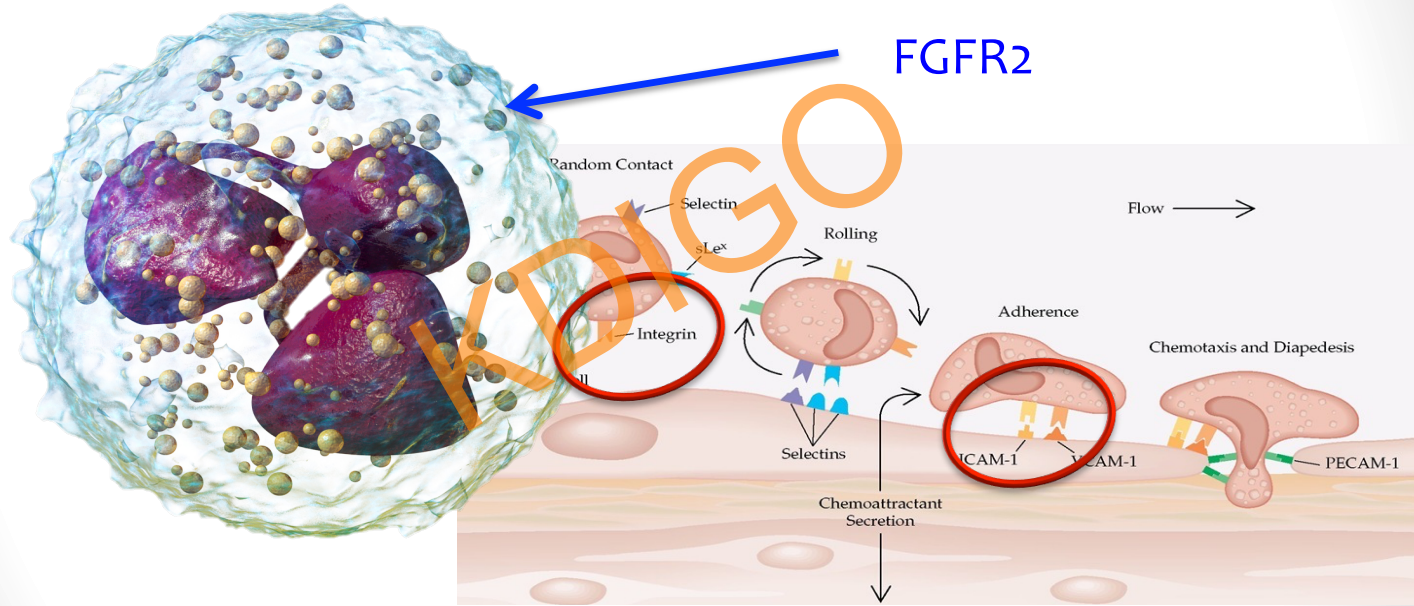
KIDIGO

FGF23 and Infections

- Incidence Rate
- Infection-related Hosp
- Per 100 person-years



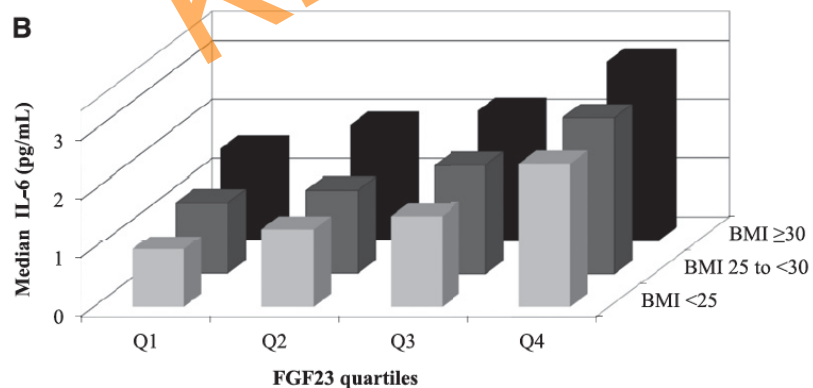
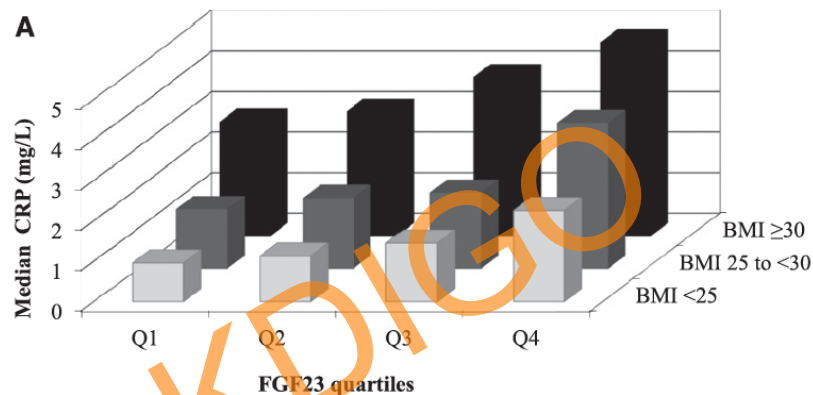
Klotho independent effect FGF23: neutrophils



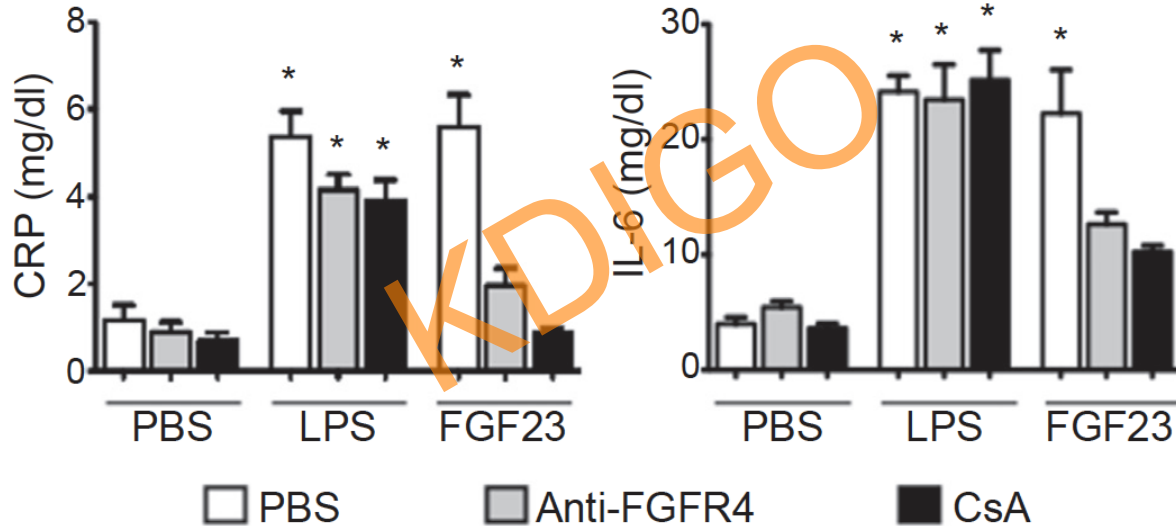
FGF23 and inflammation

- ✓ Cross-sectional
- ✓ Age $58 \pm$
- ✓ eGFR 43

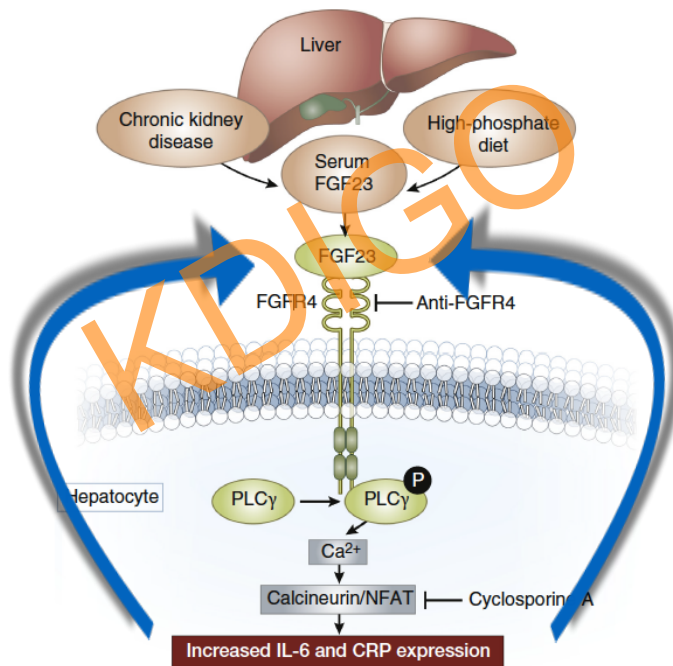
IL-6



Hepatocytes express FGFR4



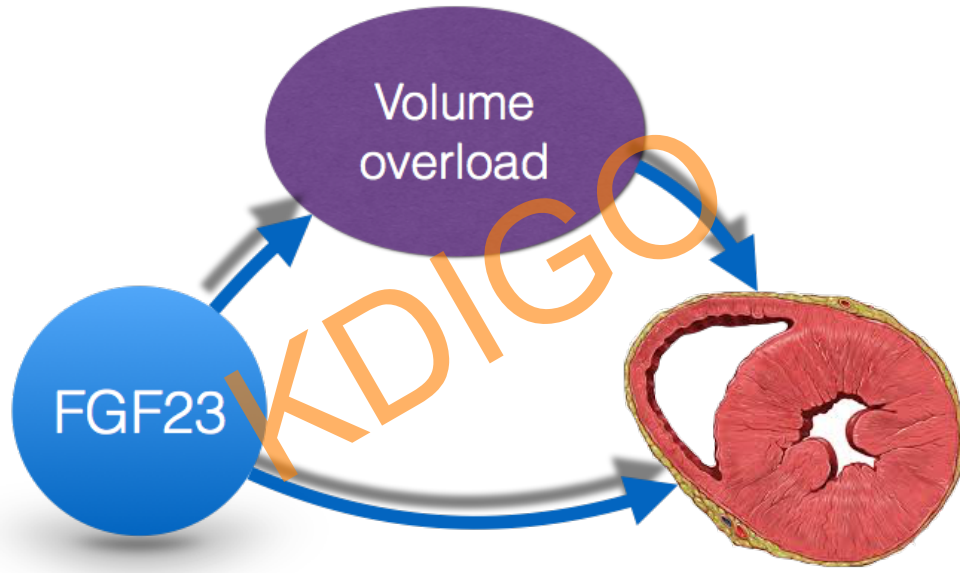
FGF23 and inflammation



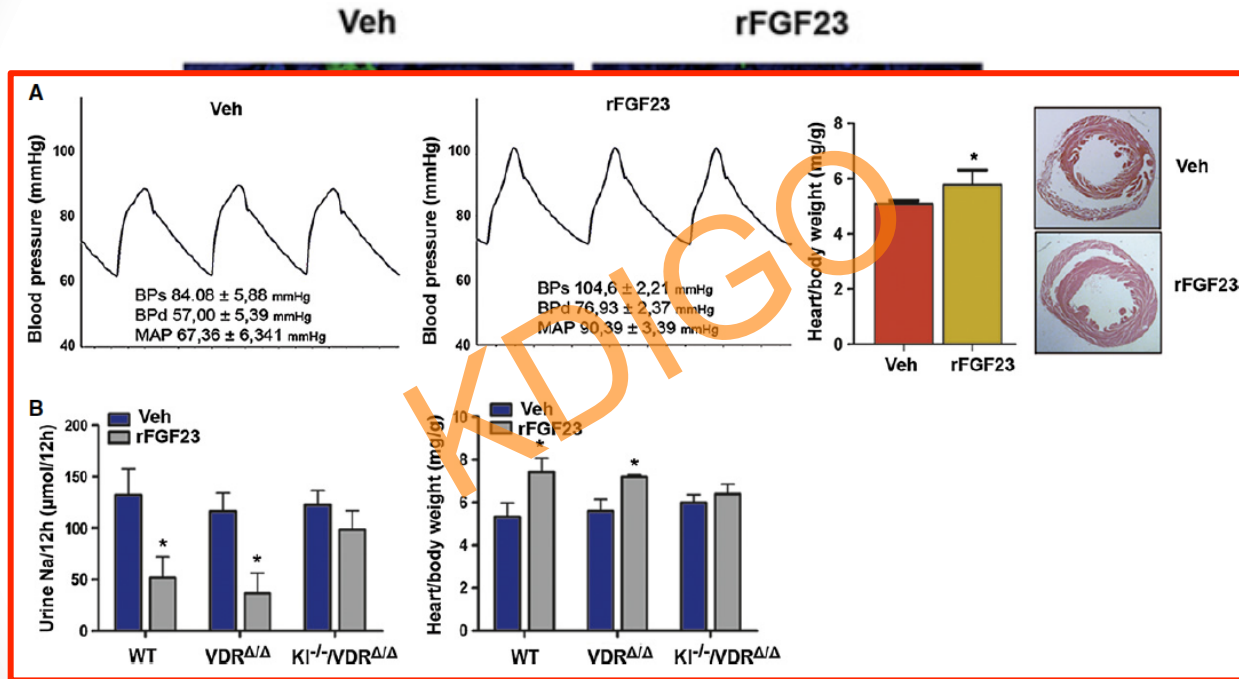
FGF23 actions outside MBD

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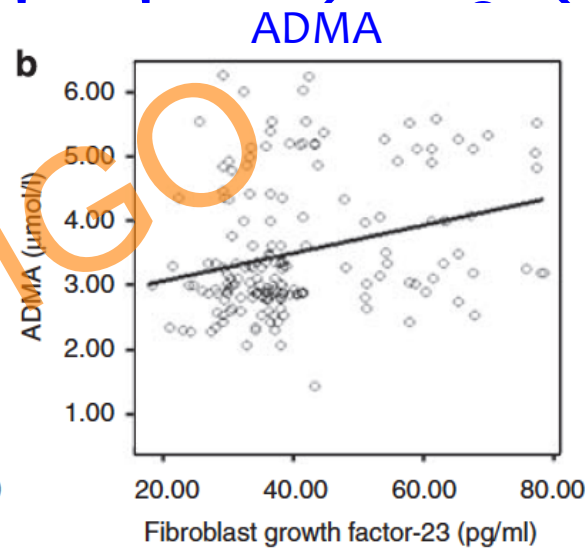
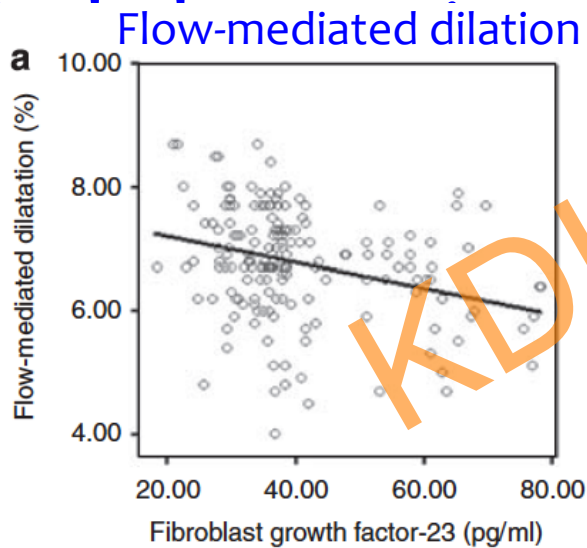
Rec. FGF23 in mouse model



FGF23 and vasodilation

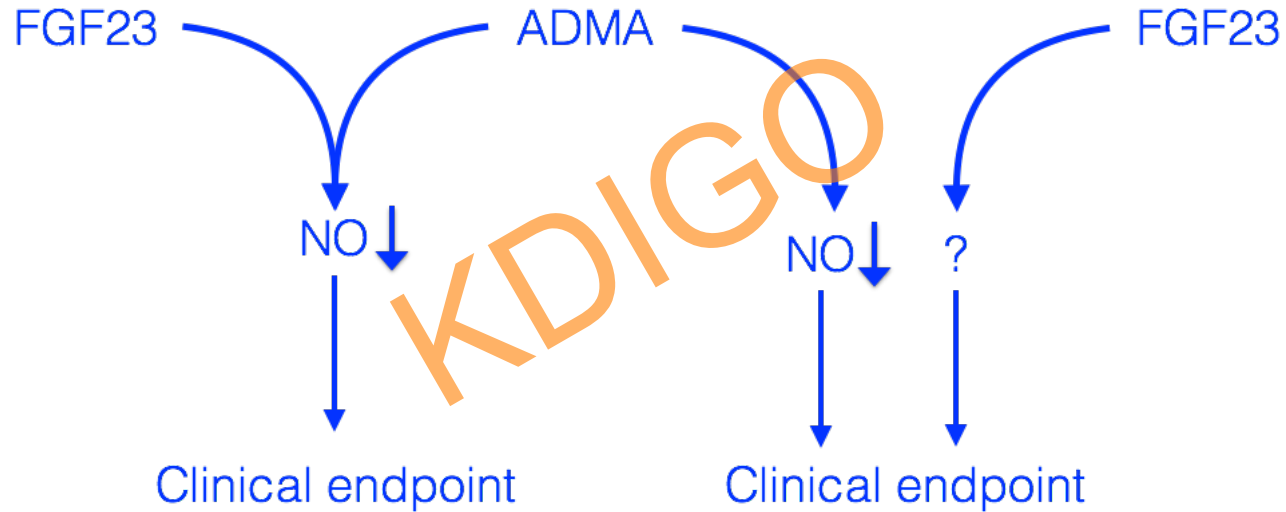
- ✓ Clin
- ✓ FGF
- fact
- ✓ Exc

- ✓ Pr
- ✓ Sr
- ✓ Diabetes
- ✓ Users of ACE inhibitors, ARB, vit D or statins



risk

Effect modification analysis

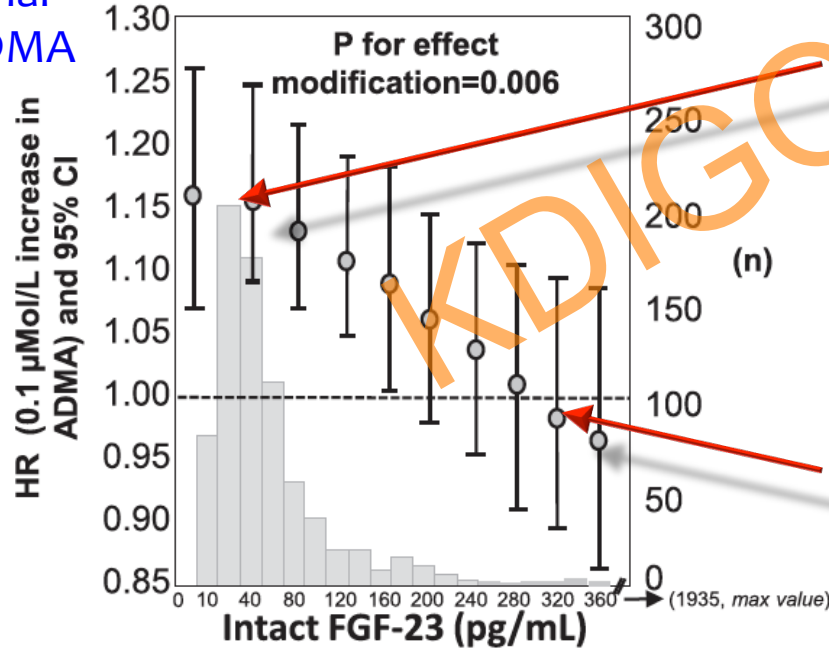


Epidemiology is:



FGF23 may interfere with NO production

Risk for renal event by ADMA

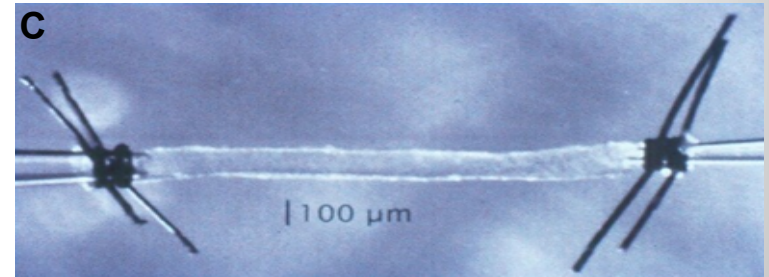
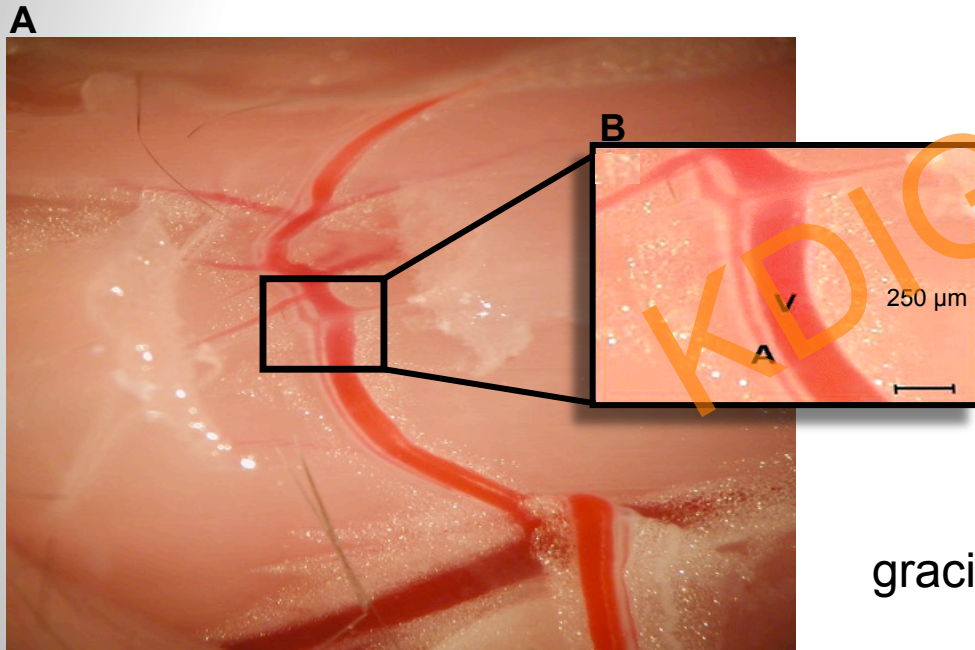


ADMA increases risk for renal event

- ADMA interferes with NO production and renal vasodilation

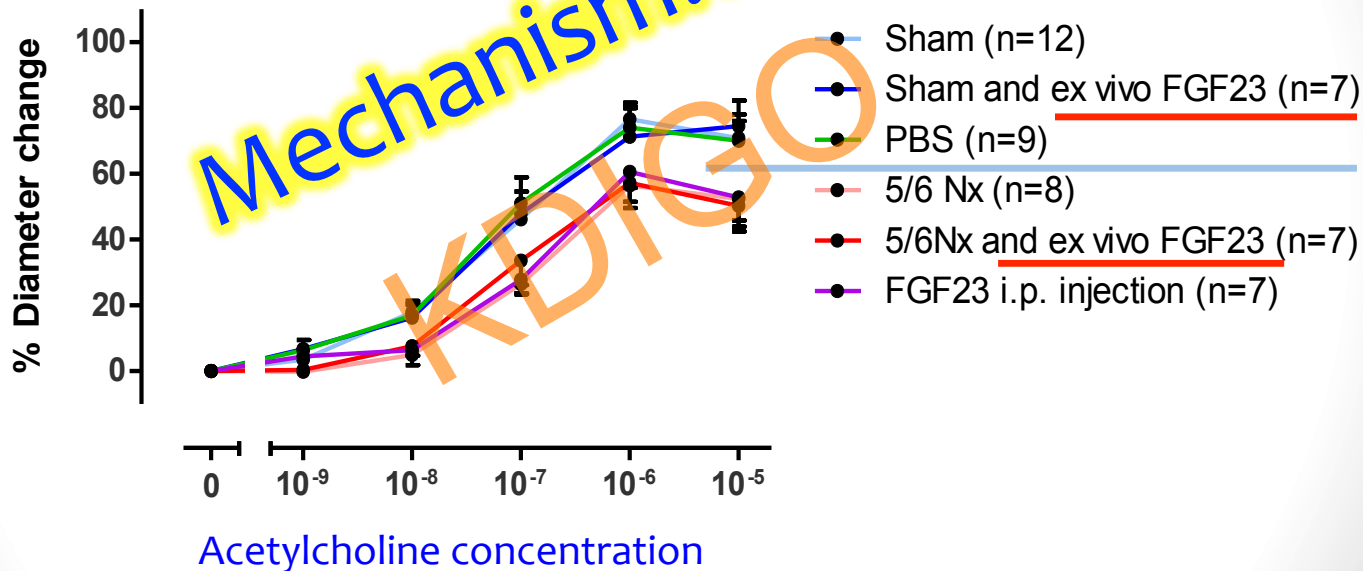
- High FGF23 overrides this effect

Examine vascular function on exogenous FGF23

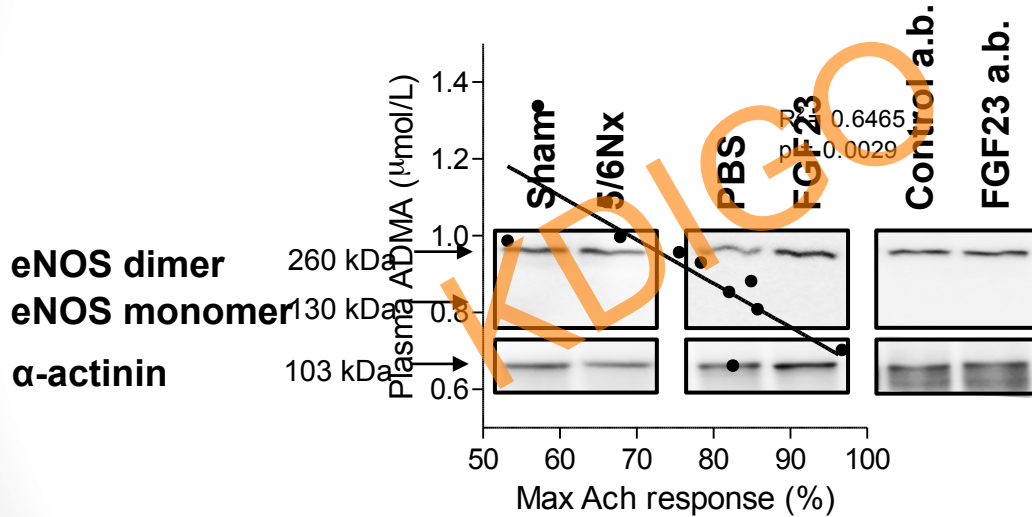


gracilis artery of a mouse

FGF23 impairs vasodilation in the absence of vascular klotho



Mechanism of NO decline



Normal coupling eNOS....

But increasing ADMA

Conclusions

- ✓ FGF23 has several effects beyond CKD-MBD
 - Direct induction of LVH
 - Heart failure in turn seems to amplify FGF23
 - FGF23 increases risk for (bacterial) infection
 - FGF23 directly induces inflammation
 - FGF23 *may* induce sodium retention (unconfirmed)
 - FGF23 limits vasodilation, probably *via* ADMA and/or NO↓

Thank you

