# Cardiovascular Toxicity in Oncology Trials Workshop

FDA

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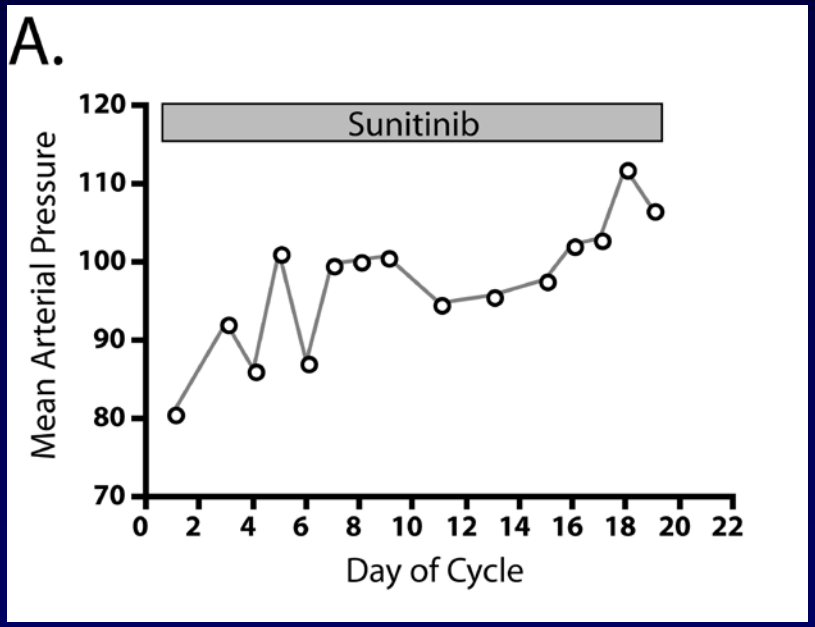
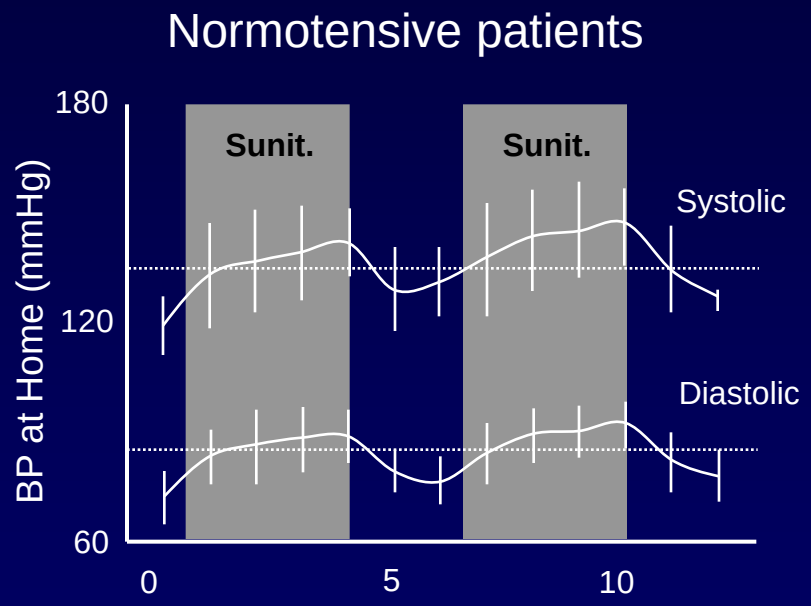
# Outline

1. TKI-induced hypertension: Monitoring and Treatment
2. Proteinuria induced by TKIs
3. Considerations for trial design

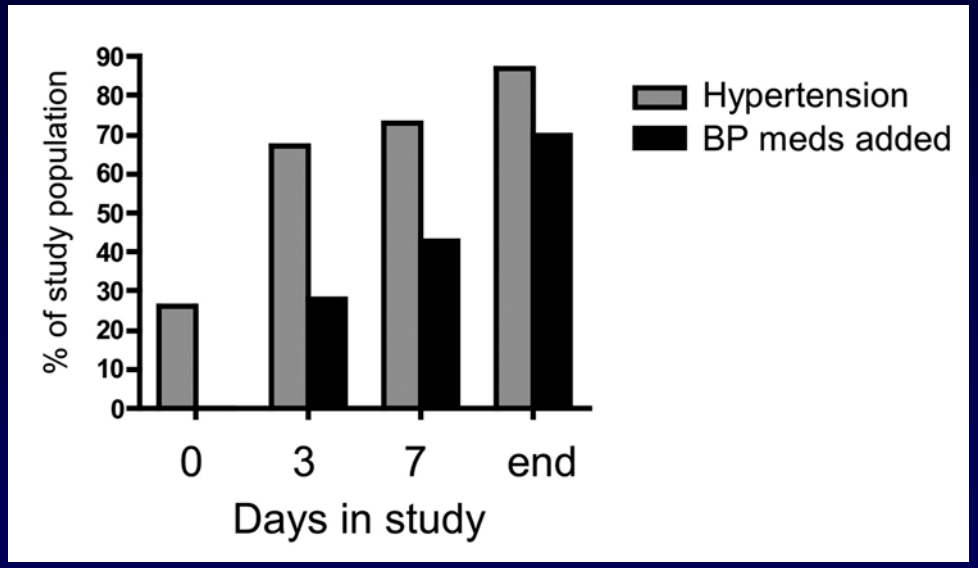
# Hypertension on Sutent



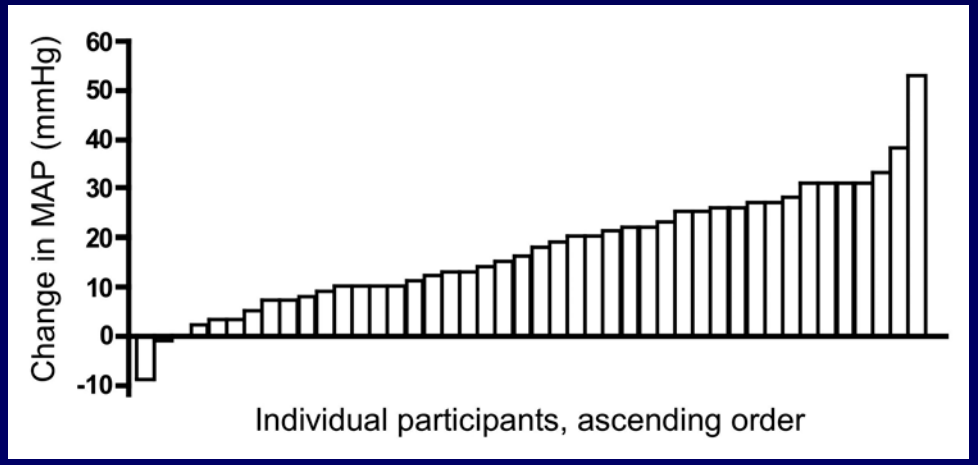




Azizi M et al. N Engl J Med 2008;358:95-97

# HTN: Rapid, Can be Severe

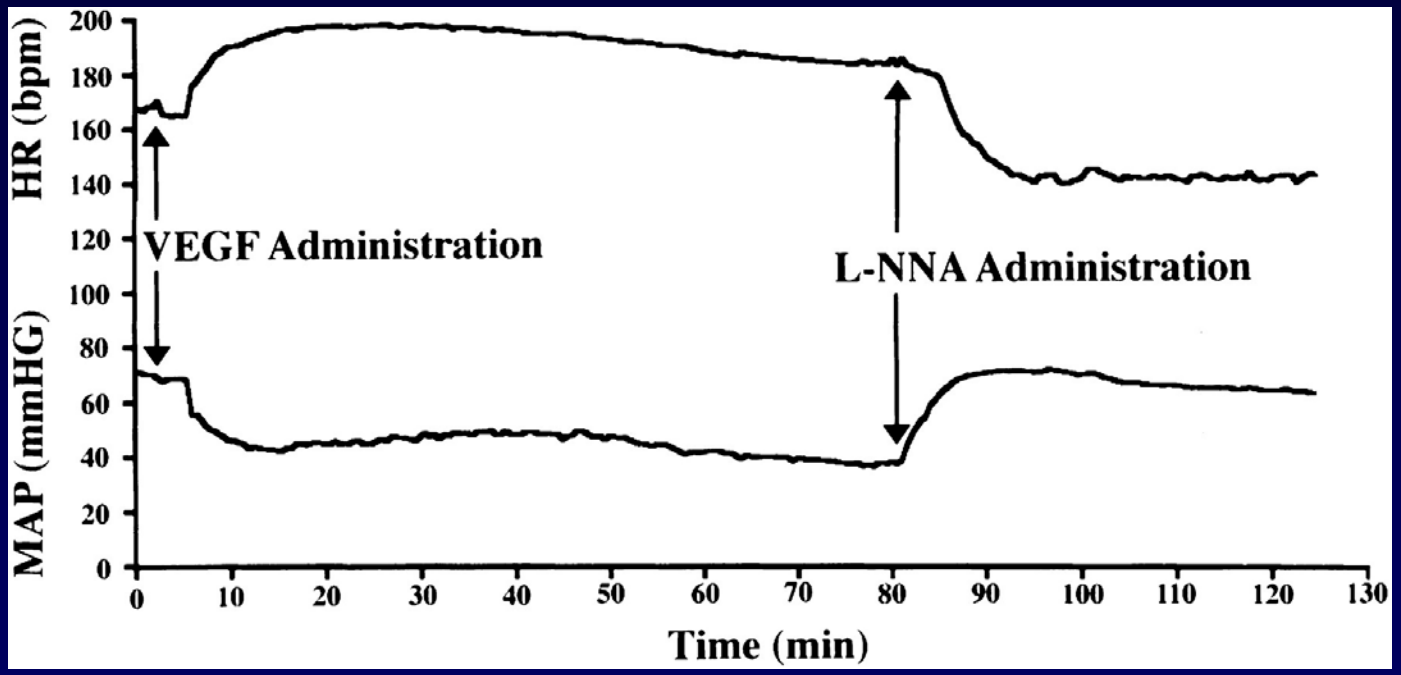



HTN:
26% to 87%




Robinson, Humphreys, CJASN 2010

# VEGF mediates NO-dependent hypotension




Horowitz, J. R. et al. Arterioscler Thromb Vasc Biol 1997;17:2793-2800

Arteriosclerosis, Thrombosis, and Vascular Biology

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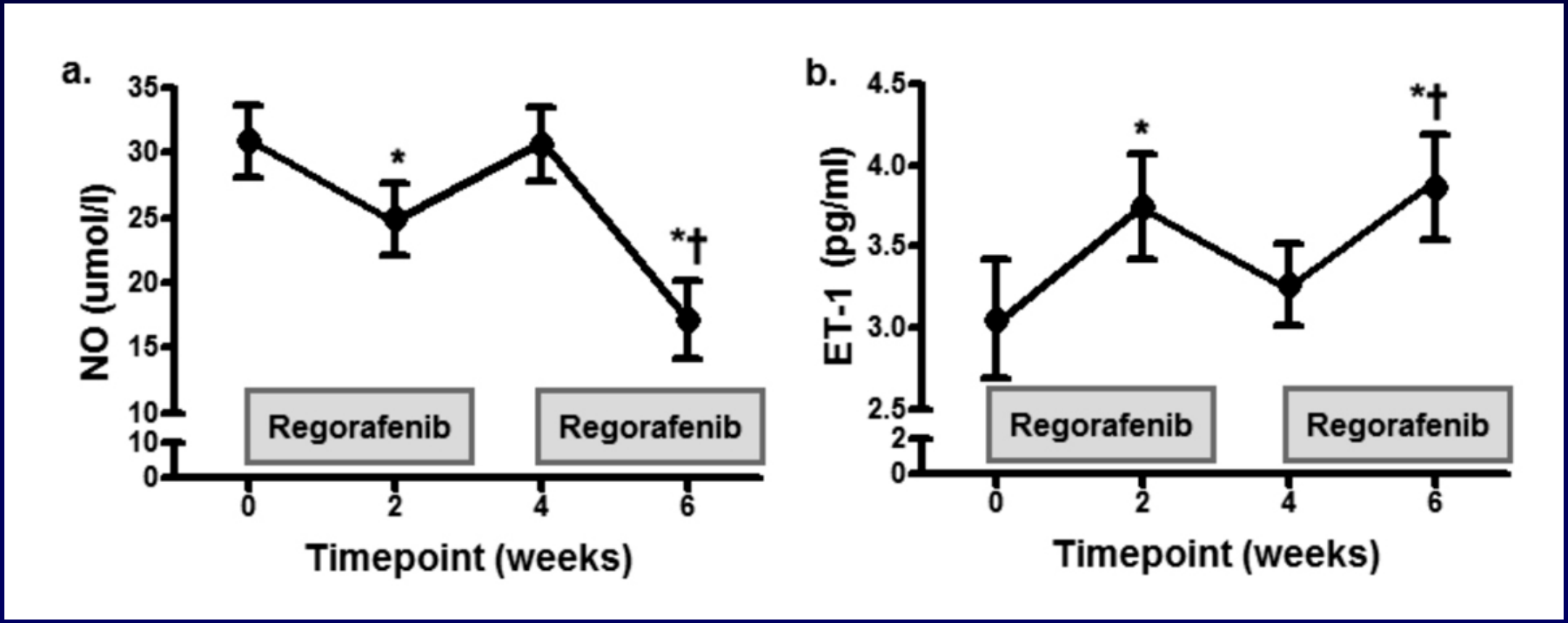
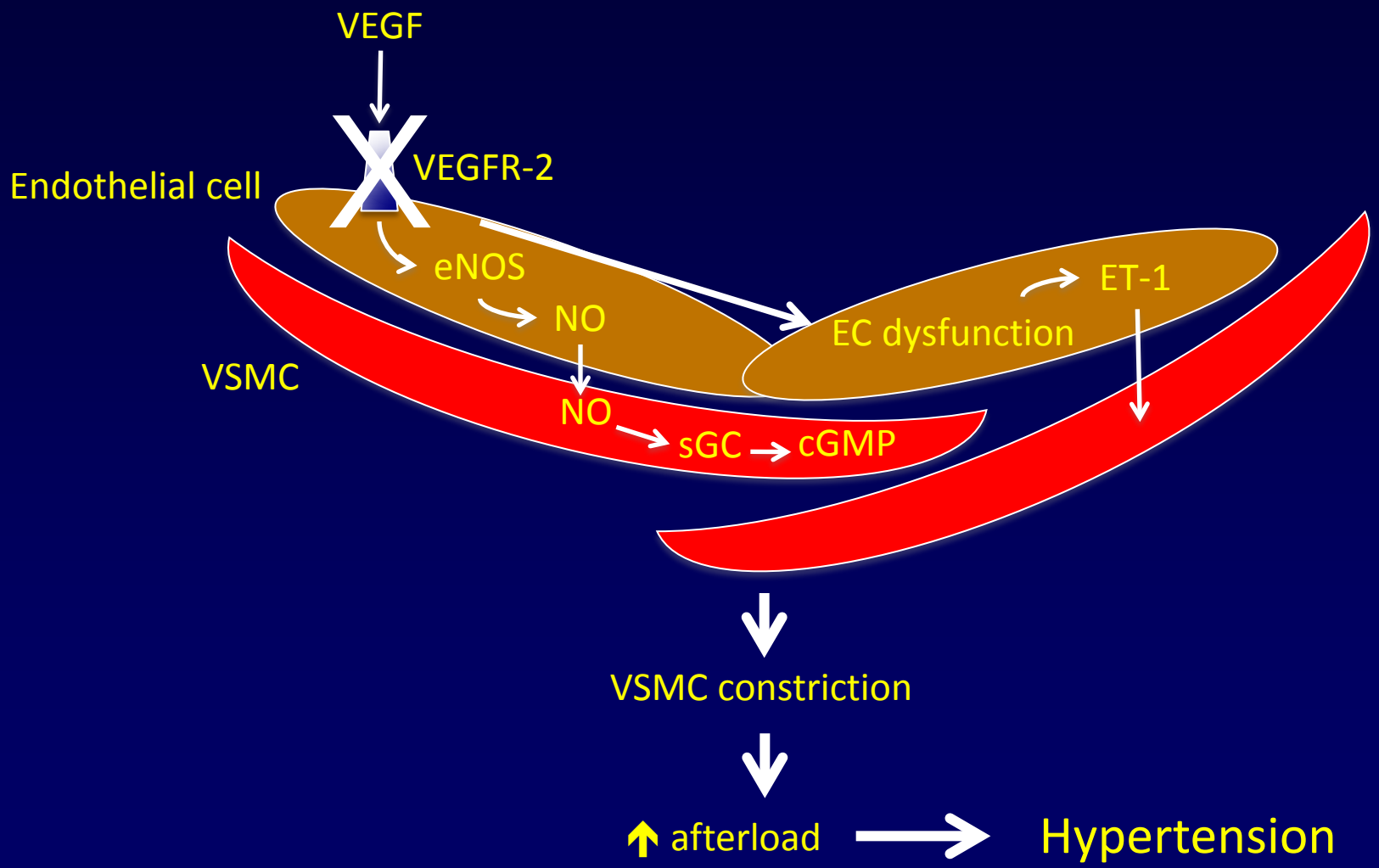
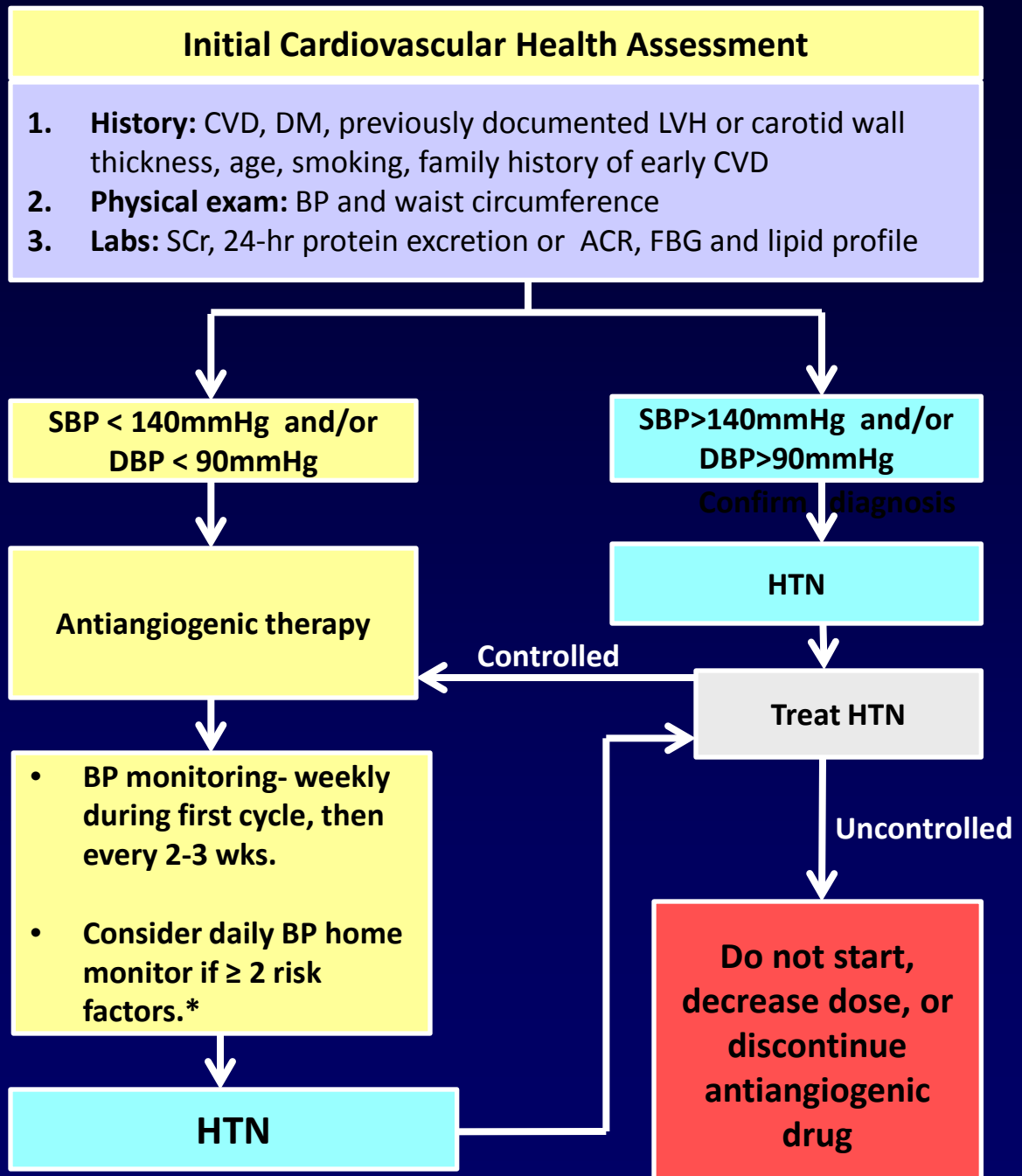
# anti-VEGF agents reduce urinary NO and increase ET-1




Humphreys 2010, 2012

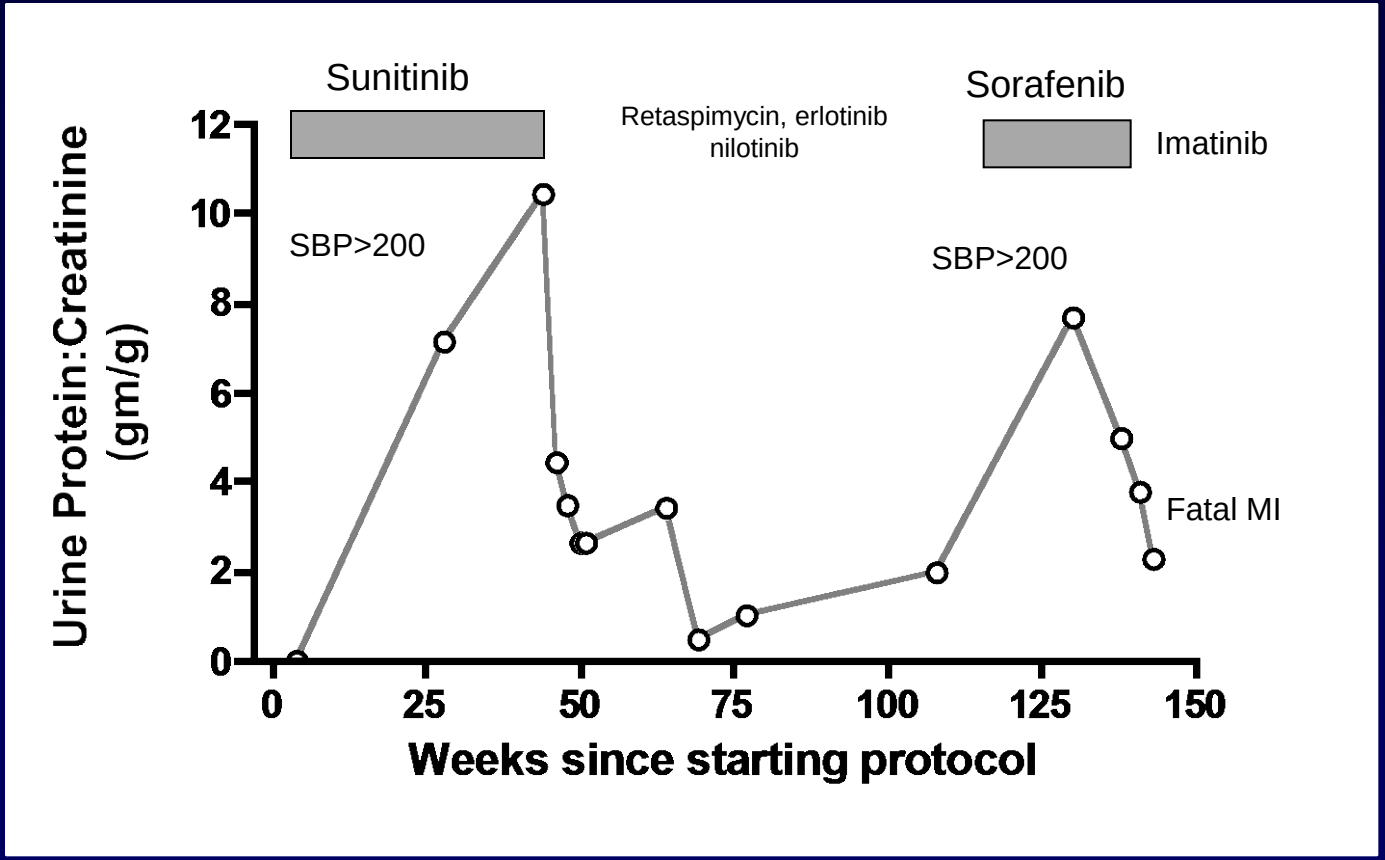
# Model


VEGF
VEGFR-2
Endothelial cell
eNOS
NO
ET-1
EC dysfunction
VSMC
NO
sGC
cGMP
VSMC constriction
afterload
Hypertension




de Jesus-Gonzalez N et al. 2012

# Recurrent Proteinuria on anti-Angiogenic Therapies

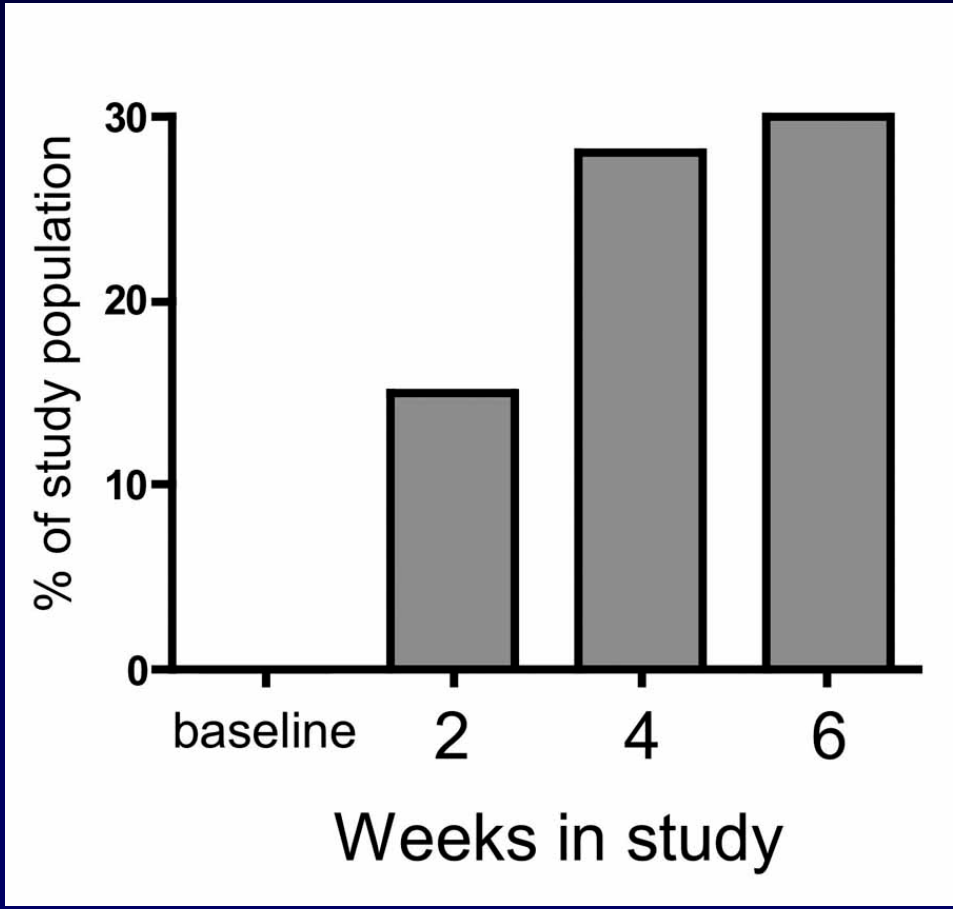


# Is Proteinuria Rare?

- ✓46 consecutive women enrolled in a Phase II trial of Cediranib for ovarian cancer
- ✓Age 41 – 77 years
- ✓25% had baseline HTN
- ✓BP recorded twice daily, UA every two weeks

Schopick …Humphreys, CJASN 2010

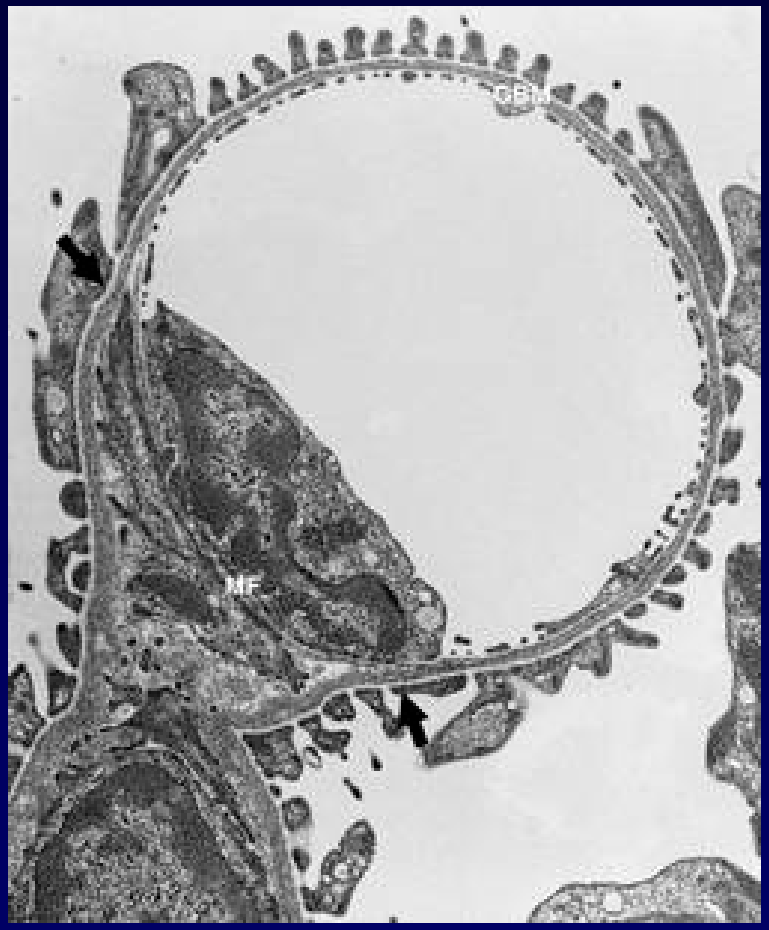
# New Proteinuria in 30% within 6 Weeks

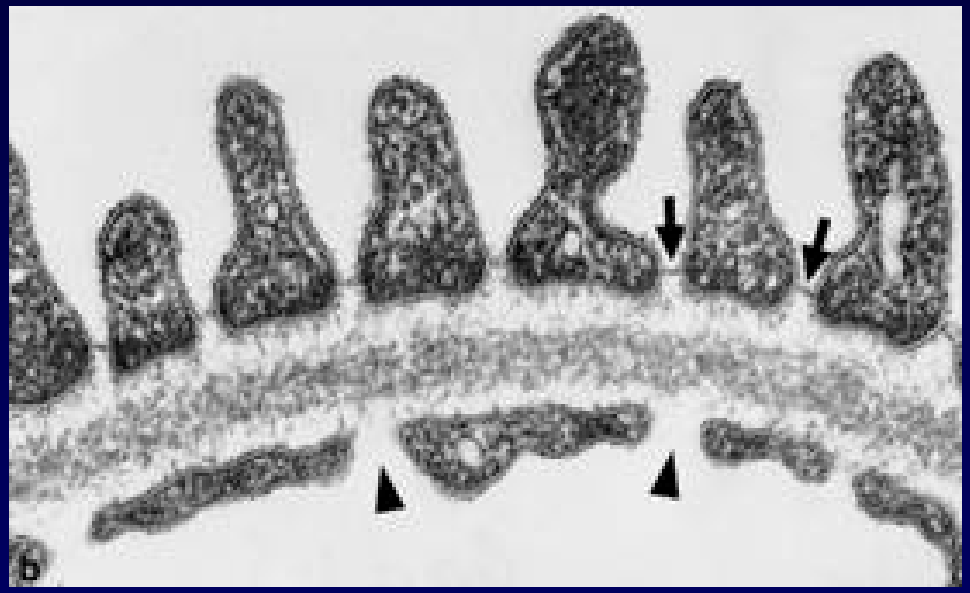


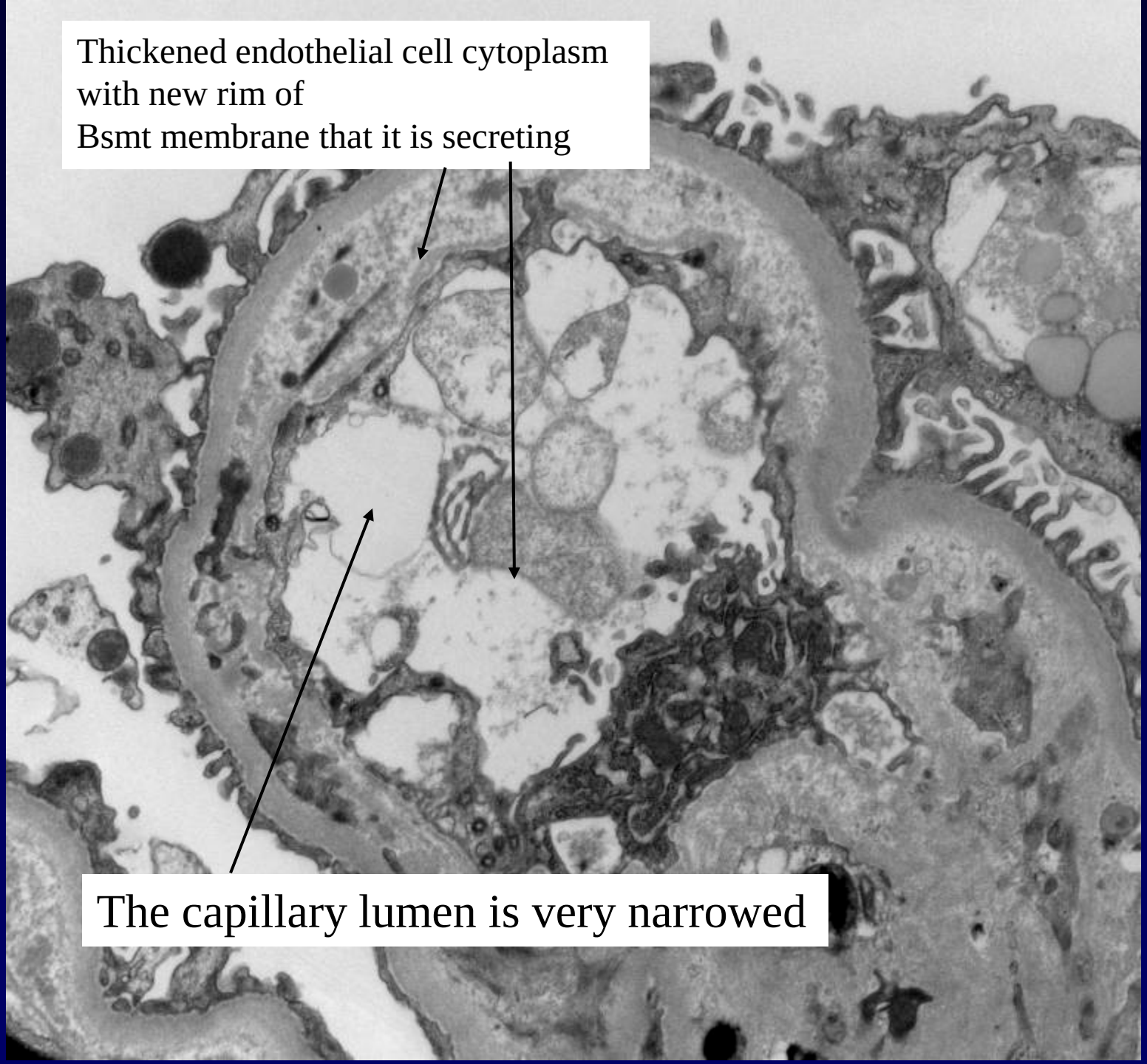

Proteinuria = UA≥ 1+

Schopick et al, CJASN 2010

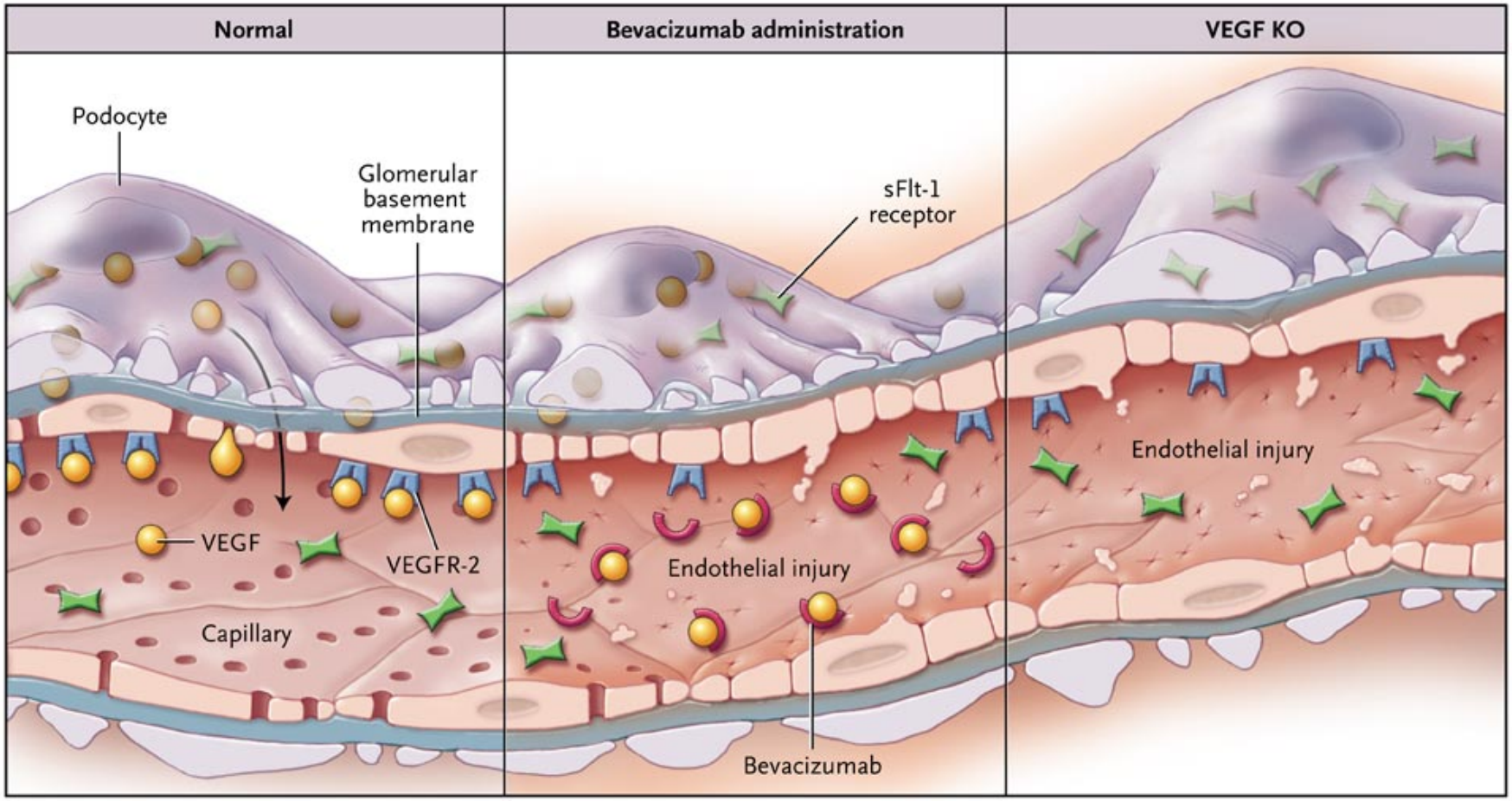
# Normal glomerular capillary loop cross section




Thickened endothelial cell cytoplasm
with new rim of
Bsmt membrane that it is secreting
The capillary lumen is very narrowed

# Hypothetical Model of Disruption of VEGF Signaling in Renal Thrombotic Microangiopathy




Eremina V et al. N Engl J Med 2008;358:1129-1136

# Are On-Target Toxicities Desirable If They Can Be Managed?

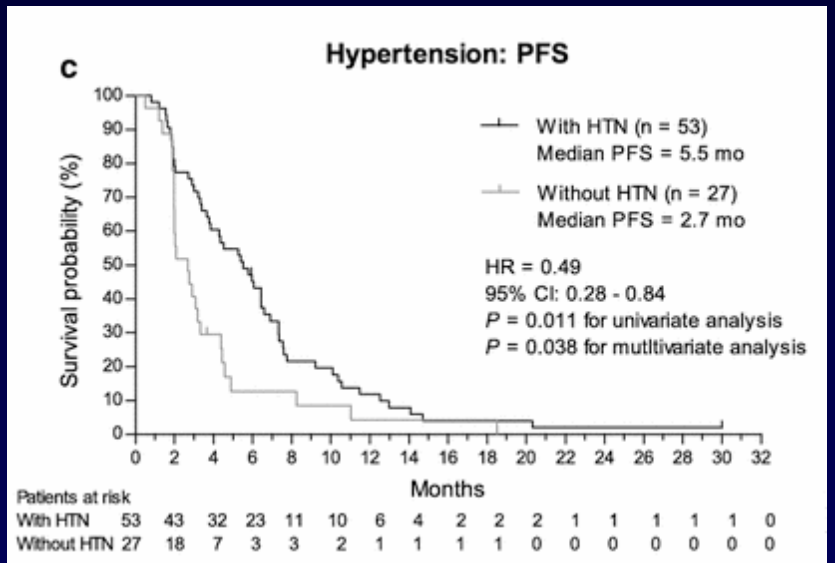
On target toxicity

vs.

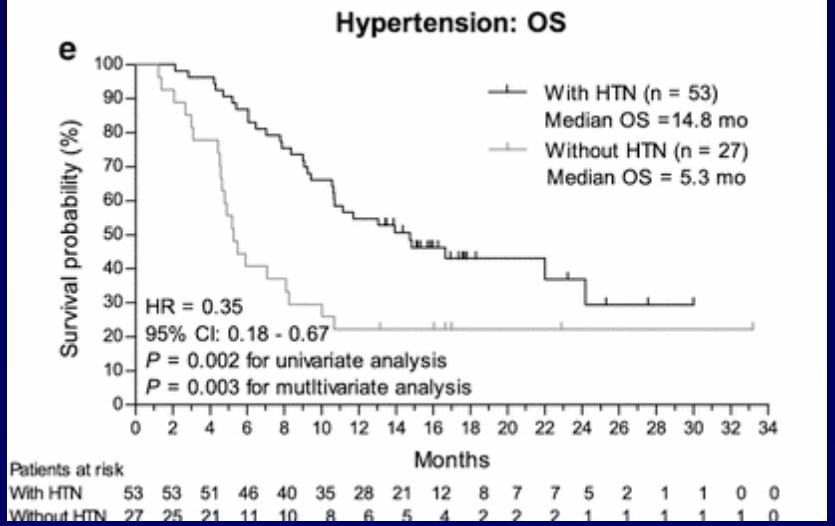
Off target toxicity

# Apatanib-treated breast CA

PFS = 5.5 vs. 2.7 mo
(P = 0.011)



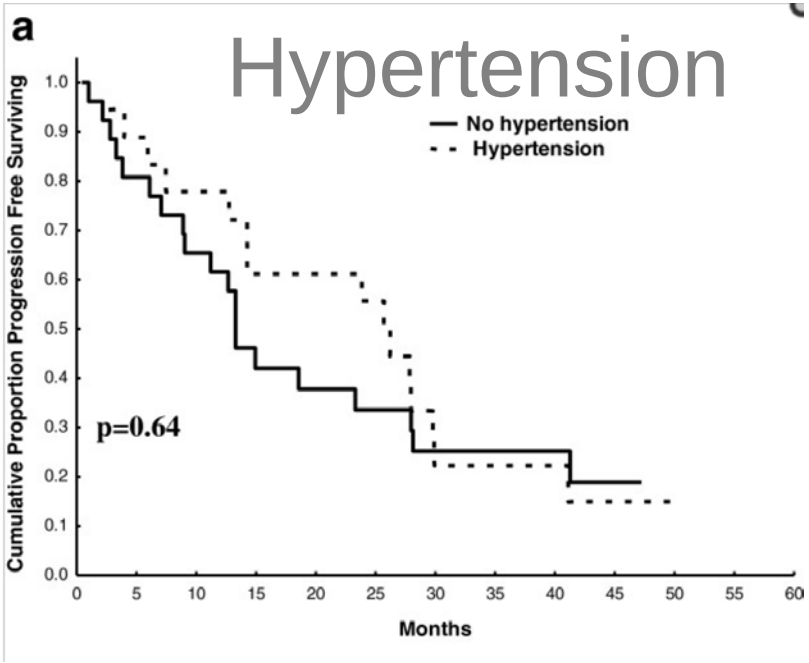

OS = 14.8 vs. 5.3 mo
(P = 0.002)

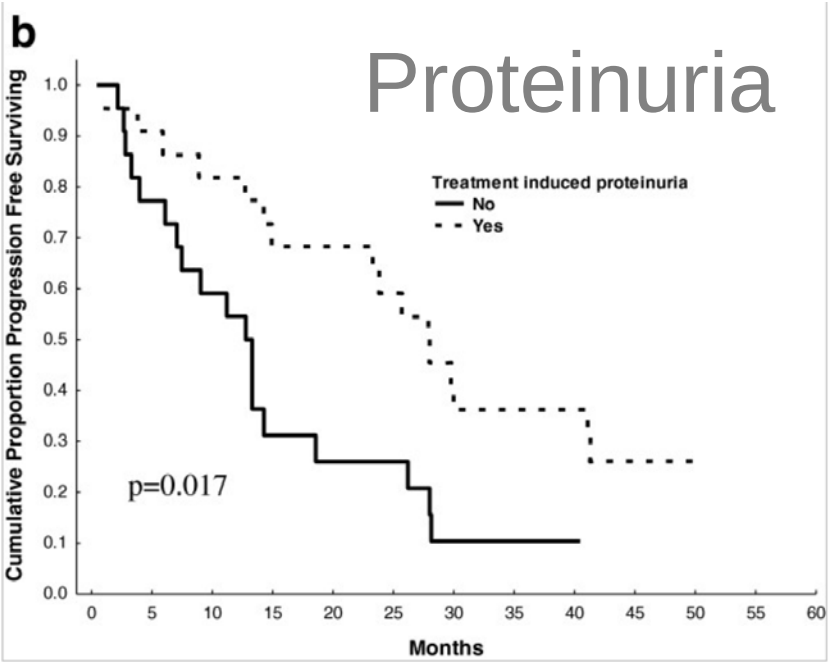



HTN =
SBP>140
or
DBP>90

Fan et al., Breast Cancer Res Treat (2014)

# On-target toxicities as a pharmacodynamic biomarker: Neuroendocrine CA




Berutti et al., BMC Cancer, 2015

# Managing anti-VEGF renal toxiciteis

Control BP, use ACE/ARB first, followed by diuretics and CCB

Monitor urine protein and kidney function monthly

If sub-nephrotic proteinuria, may continue therapy with aggressive BP and ACE/ARB

If renal failure, nephrotic proteinuria or hypertensive emergency occurs, need dose reduction, washout or discontinuation (in consultation with oncology)

# Considerations for future trial design

Example: Apatanib for refractory gastric CA

- Blinded RCT, 800 pts, “positive” results:
- PFS 2.6 vs. 1.8 mo, OS 6.5 vs. 4.7 mo
- Objective response in only 1.7%

Biomarker needed to enrich study population!

- Most common gr ¾ AEs: HTN, Proteinuria, hand-foot in 2-8%
- Analyze outcomes based on AEs, those that correlate study biology for candidate predictive biomarkers pre-Rx

# Thank You