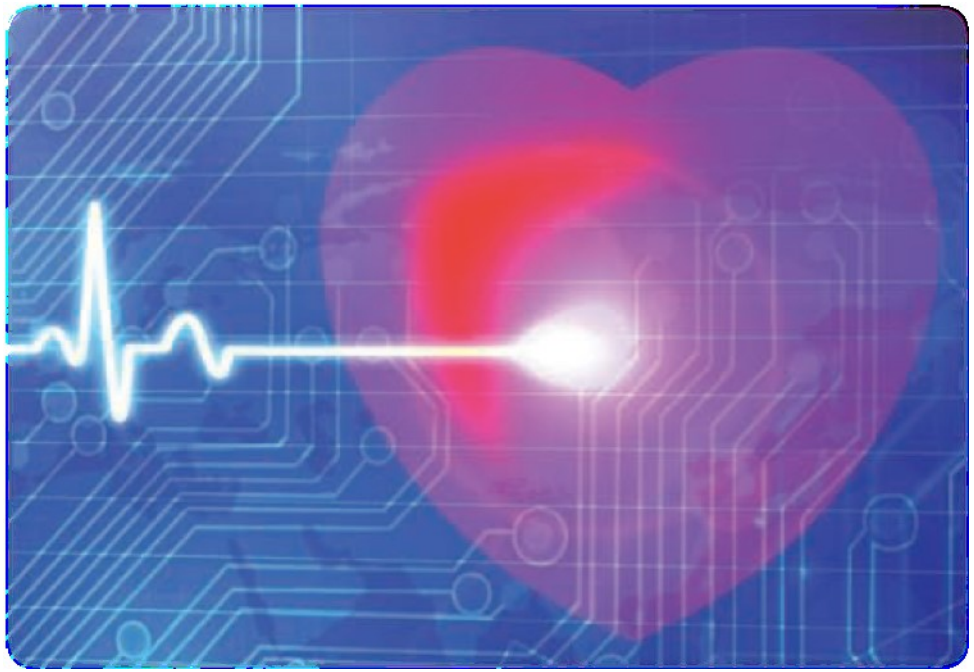

Cardiotossicità da anti-VEGF e TKI multitarget

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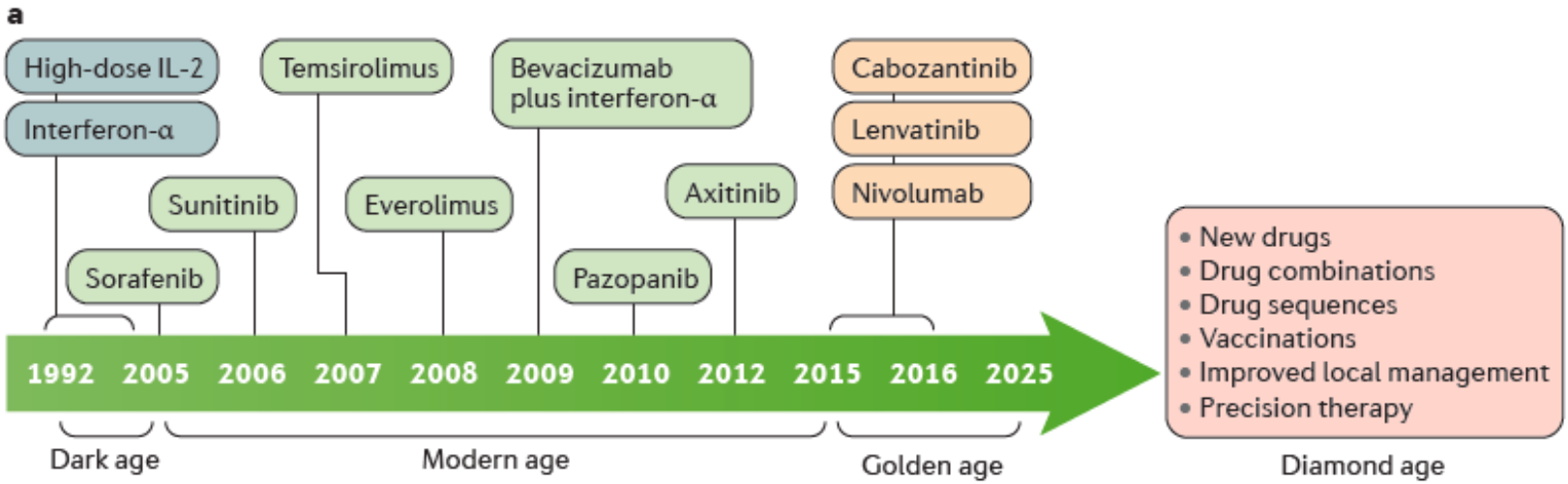
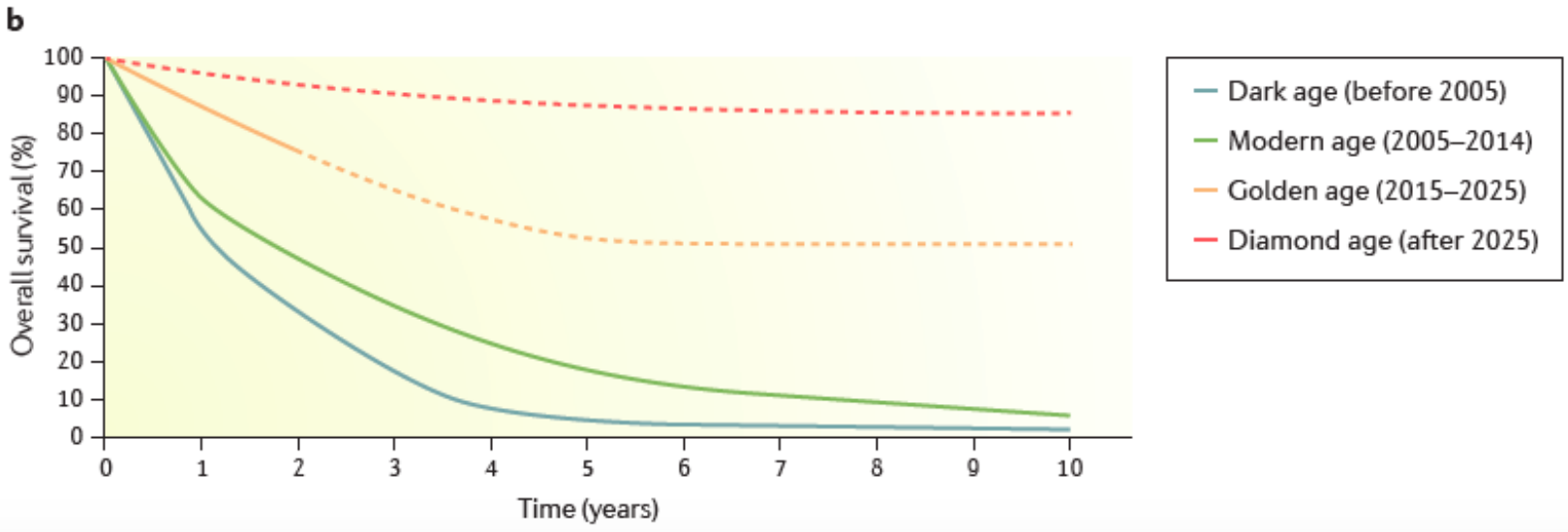
Disclosures

- No pertinent C.O.I. with this presentation
- Advisory Boards/Honoraria/Consultant for:
  - BMS
  - Janssen
  - Merk
  - Pfizer
  - Roche

What happens in mRCC?

Therapeutic evolution and survival outcome of metastatic clear cell renal cell carcinoma through the four different eras





Hsieh JJ et al., Nature Reviews 2017

Cardiovascular (CV) Toxicity

- Cumulative CV toxicities include
  - QT interval prolongation and torsade de pointes
  - Coronary insufficiency
  - Heart failure
  - Arterial thromboembolism

1. Sutent® Prescribing Information. New York, NY: Pfizer, Inc; May 2011.
2. Nexavar® Prescribing Information. Wayne, NJ:Bayer HeathCare Pharmaceuticals, Inc; Oct 2011.
3. Votrient® Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline; Oct 2009.
4. Sternberg CN et al. J Clin Oncol. 2010;28:1061-1068.
5. Inlyta® Prescribing Information. New York, NY: Pfizer, Inc; Jan 2012.
6. Schmidinger M et al. J Clin Oncol. 2008;26:5204-5212.

Cardiovascular (CV) Toxicity: Clinical Evidence

- Individual incidence of most events is <5%, but risk is still significant

- Meta-analysis (N = 10,255)[1]
  - Rate of arterial thromboembolism with sunitinib and sorafenib was 1.4%
  - 3-fold increase in risk over control

- Meta-analysis (N = 6,935)[2]
  - Rate of heart failure with sunitinib was 4.1%
  - 1.8-fold increase in risk over control

1. Choueiri TK et al. J Clin Oncol. 2010;28:2280-2285.
2. Richards CJ et al. J Clin Oncol. 2011;29:3450-3456.

Cardiovascular (CV) Toxicity: Risk Assessment

- Conduct a formal risk assessment at baseline
  - Evaluation and correction of any BP abnormalities at baseline
  - Standardised BP measurement
  - Thorough patient history and physical evaluation
  - ECG and LVEF assessment in patients with history of cardiac disease
  - Laboratory tests as indicated
- Educate patients on possible CV side effects and their symptoms
- Consult with a local CV specialist if indicated
- During treatment, monitor patients for development of CV complications

1. Maitland ML et al. J Natl Cancer Inst. 2010;102:596-604.
2. Izzedine H et al. Ann Oncol. 2009;20:807-815.
3. Ravaud A et al. Oncologist. 2011;16(suppl 2):32-44.
4. Bamias A et al. J Clin Oncol. 2009;27:2567-2569.

Incidence of Cardiac Toxicity with Inhibitors of VEGF-Signaling

	SUN[1]		SOR[2]		BEV[3,4]		PAZ[5]		AX[5]	
	all	3+4	all	3+4	all	3+4	all	3+4	all	3+4
CHF	13	nr	nr	nr	<1	<1	nr	nr	nr	nr
Ischemia	nr	nr	nr	3	<1	<1	nr	nr	nr	nr

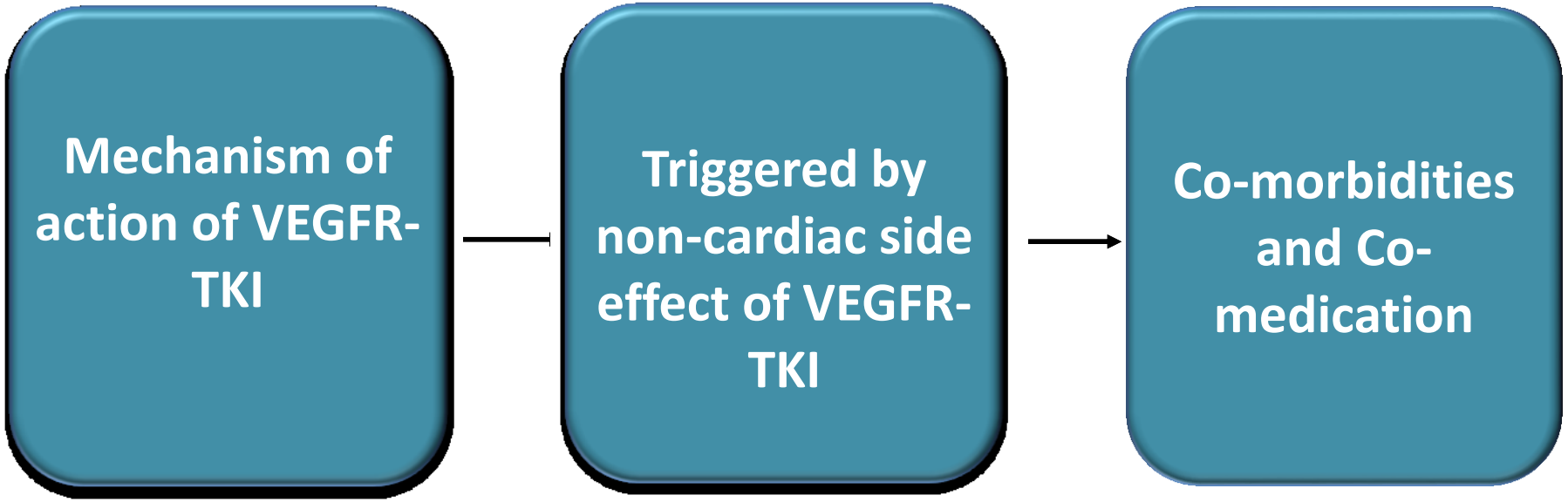
Cardiac toxicity is an under-reported phenomenon

- 74 patients on sunitinib and sorafenib:
- 33.8% with cardiac events (definition: cTNT increase, symptomatic arrhythmia, new left ventricular dysfunction, acute coronary syndrome)
- 40.5% ECG changes
- 18% typical clinical symptoms
- 9.4% seriously compromised

All considered eligible for TKI continuation after recovery

1.Motzer RJ et al., J Clin Oncol 2009; 2. Rini B et al., Lancet 2011; 3. Rini B et al., J Clin Oncol 2010; 4. Escudier B et al., Lancet 2007; 5.Motzer RJ New Engl J Med 2013; 5. Rini B et al., Lancet 2011; 6.Schmidinger M et al., J Clin Oncol 2008

Pathomechanism of Cardiac Toxicity: a Multifactorial Process



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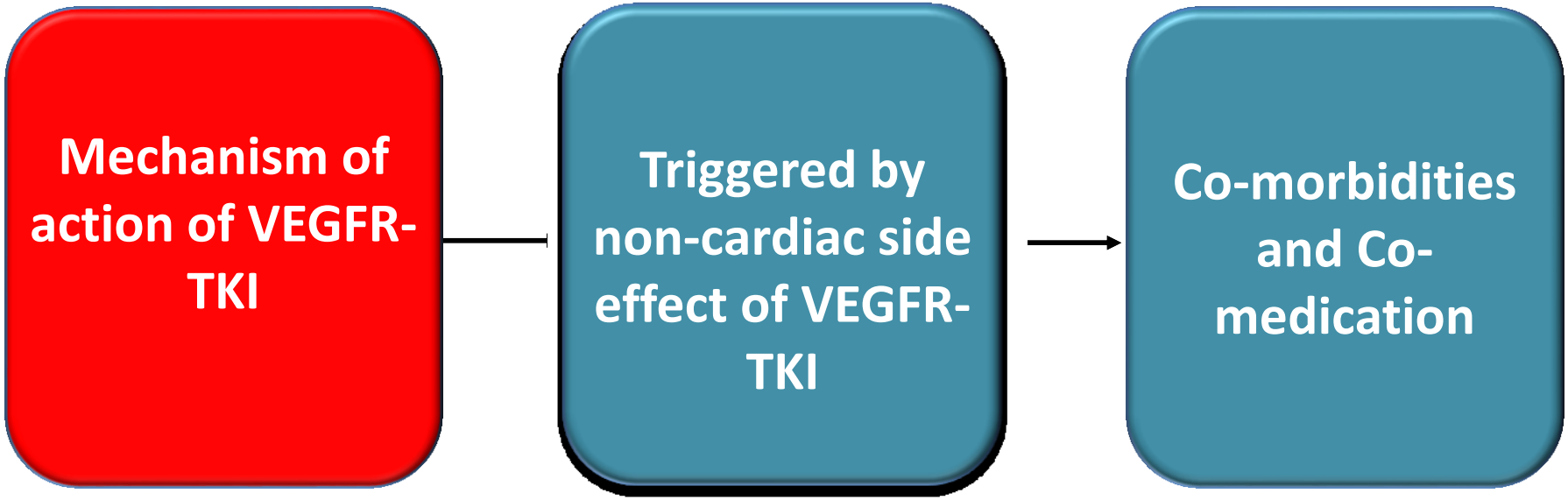

MKIs Impair Kinases that are Physiologically Highly Relevant for the Heart

Kinases and Drugs	Role of kinase in the Heart/Vasculature
C-KIT (sun, sor)	Homing of BM-derived cardiac stem cells to sites of post-MI-injury; stem cell differentiation, cardiomyocyte terminal differentiation
VEGFR (all RCC- agents)	Myocardial capillary density, stem cell differentiation into cardiac myocytes, vasodilation through nitric oxide activation; production of NO and PGI2 (anti-platelet activity)
PDGFR (sun, sor, paz)	PDGF mediates signaling between myocytes and adjacent EC Intramyocardial delivery of PDGF improved post-MI ventricular function
RAF (sor)	Conditional deletion led to LV dilatation and heart failure after pressure overload
mTOR (eve, tems)	Regulation of cardiac cell growth/hypertrophy, energy/metabolic status

Cheng H et al., Circulation Res 2010

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Inhibition of these kinases is not sufficient to induce cardiac toxicity → Second/third/forth hits required

Cheng H et al., Circulation Res 2010

Second/Third Hits...

1. Energy run down of cardiac myocyte
2. Failure of protective responses to restrict energy utilization
3. Failed adaptation with cardiac stress

Second/Third Hits...

1. Energy run down of cardiac myocyte
2. Failure of protective responses to restrict energy utilization
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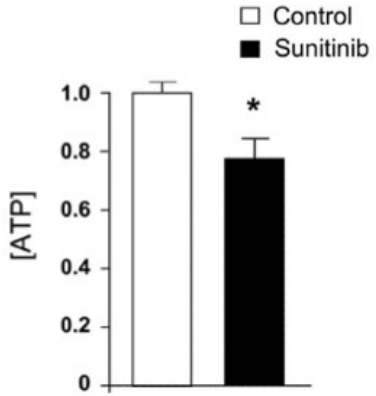
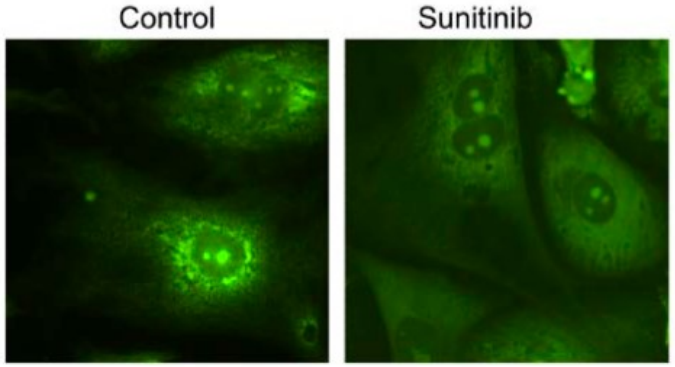
Biopsies from Patients with TKI-Induced CHF: Alterations in Cardiac Energy Transduction

- Transmission electron microscopy:
  - marked abnormalities in mitochondrial structure
  - collapse of mitochondrial membrane potential
  - significant decrease in intracellular ATP1





punctate stain =mitochondrial localisation

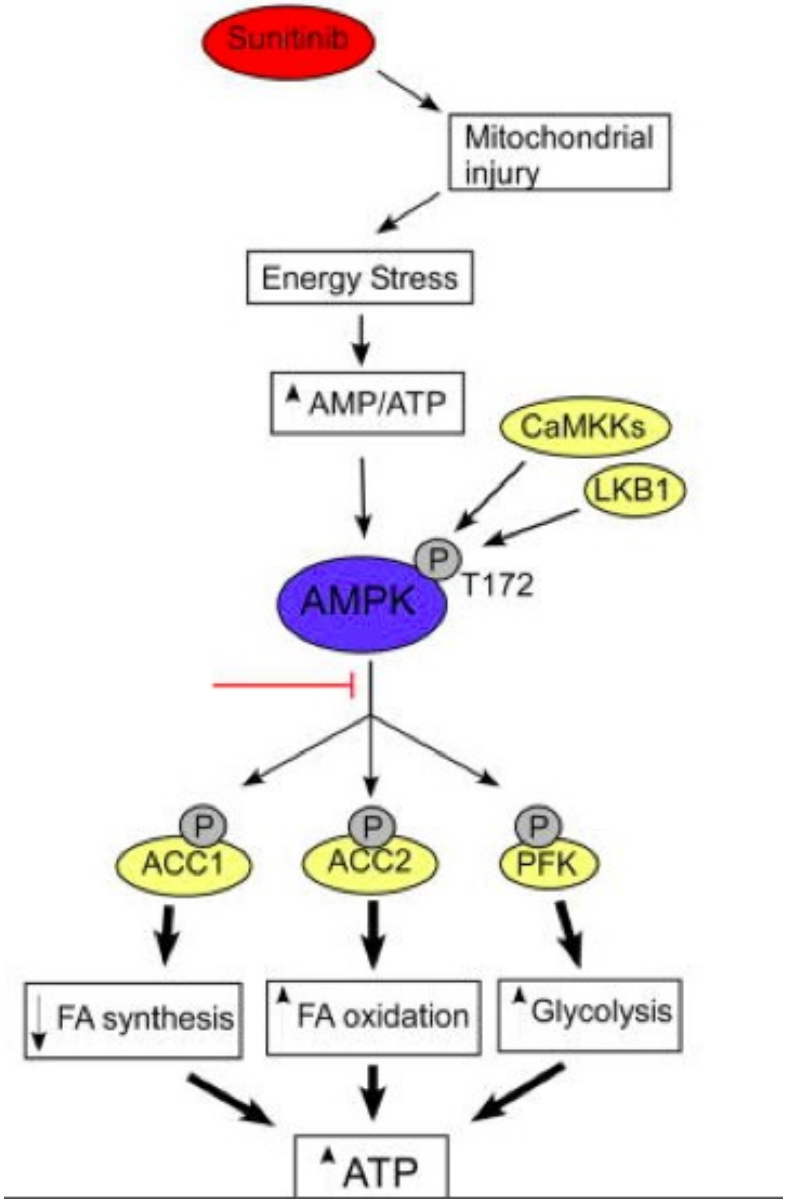
diffuse stain, consistent with loss in MMP

Kerkela R et al., *Clin Transl Sci* 2009

Second/Third Hits...

1. Energy run down of cardiac myocyte
2. Failure of protective responses to restrict energy utilization
3. Failed adaptation with cardiac stress

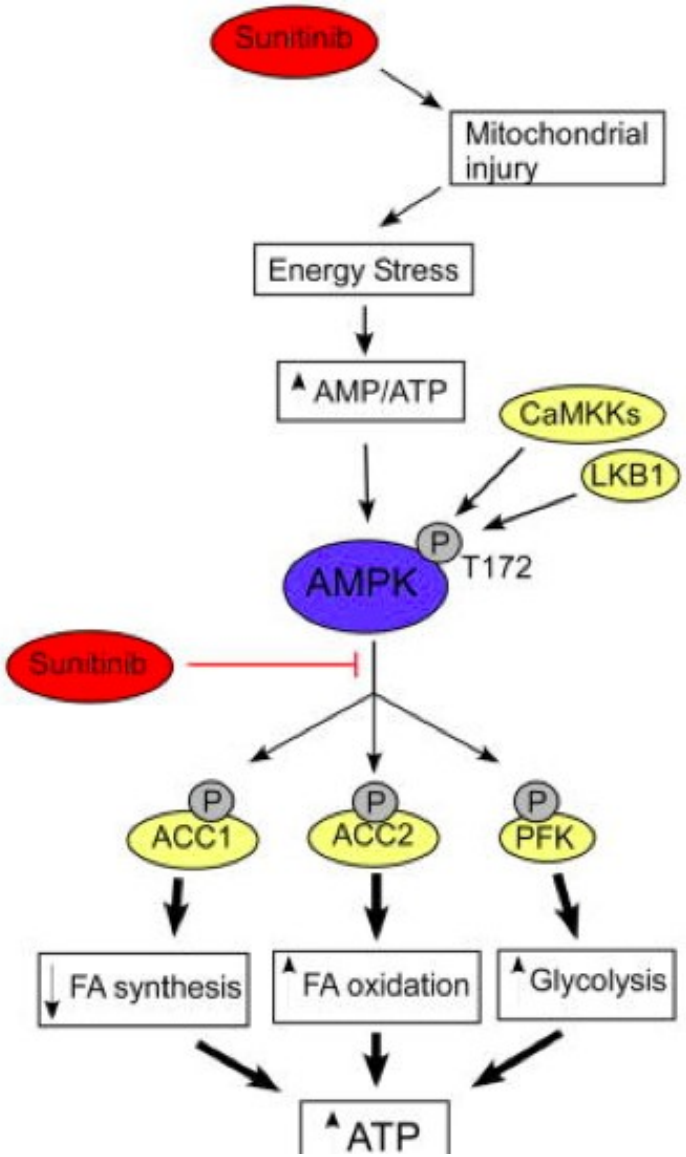
Failure of protective responses to restrict energy utilization



- Energy depletion → **activation** of 5‘adenosine monophosphate activated protein kinase **(AMPK)** in cardiomyocytes
  - AMPK: protects cells against ATP deficiency by turning off energy-consuming biosynthesis of cholesterol and fatty acids

Zhang P et al., Hypertension 2008

Failure of protective responses to restrict energy utilization



- ***However: AMPKisa direct target of e.g. sunitinib and is inhibited at biologically relevant concentrations***

Zhang P et al., Hypertension 2008

Second/Third Hits...

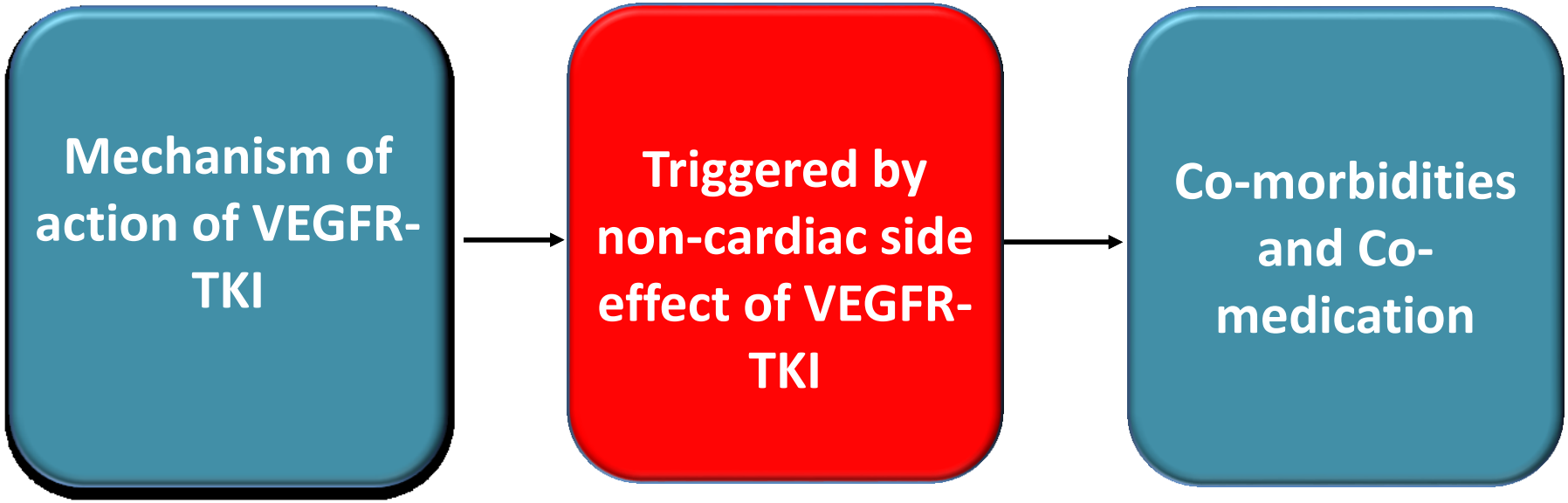
1. Energy run down of cardiac myocyte
2. Failure of protective responses to restrict energy utilization
3. Failed adaptation with cardiac stress

Energy Depletion and AMPK-Inhibition

- May become relevant only in the setting of cardiac stress
  - ✓In the setting of pressure overload, AMPKα2 knockout mice had a greater loss of LV function following aortic constriction

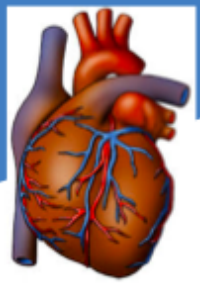
Zhang P et al., Hypertension 2008

Pathomechanism of Cardiac Toxicity: a Multifactorial Process



Cardiotoxicity Triggered by Non-Cardiac Side Effects

Hypothyroidism and heart



T3 effect on nuclear level	• On cardiac myocyte, T3 regulates transcription of genes that encode for Ca2+ATPase exchanger, voltage-gated potassium channels[1]
T3 function on non-nuclear level	• Involved in ion channels for sodium, potassium and calcium[1]
T3 effect on muscle cell	• T3 directly affects vascular smooth muscle cells and promotes relaxation[2]
T3 and CV-system	• Hypothyroidism: increased vascular resistance and endothelial dysfunction due to reduced nitric oxide availability[4,5]

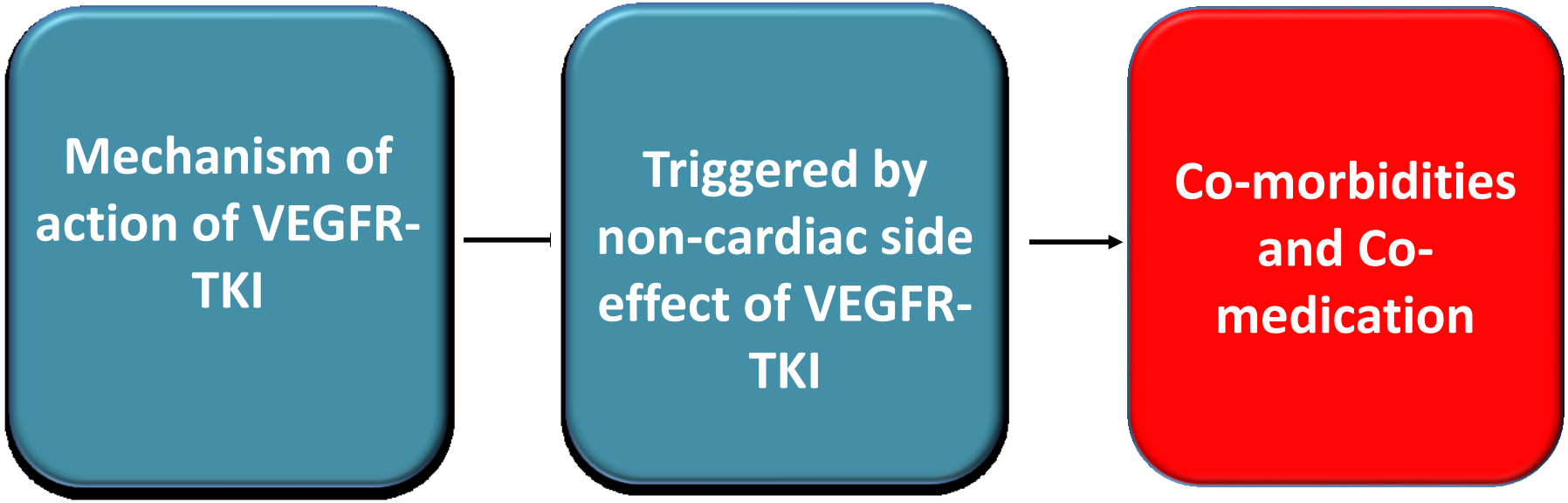
1.Klein I et al., N Engl J Med 2001; 2.Ripoli A et al., J Am Coll Cardiol 2005; 3.Faber J et al., Thyroid 2002; 4.Lekakis J et al., Thyroid 1997; 5.Taddei S et al., J Endocrinol Metab 2003

T3 Depletion Causes Cardiac Toxicity

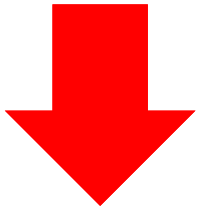
- Impaired relaxation and ventricular filling
- Increase in peripheral vascular resistance and dBP
- Reduced EF at exercise

Biondi et al. J Clin Endocrinol Metab. 1999;84:2064.

Pathomechanism of Cardiac Toxicity: a Multifactorial Process



The Median Age at Diagnosis of mRCC is 65 years



The risk of a patient with mRCC to have concomitant (overt or subclinical) CVD is high (73%)

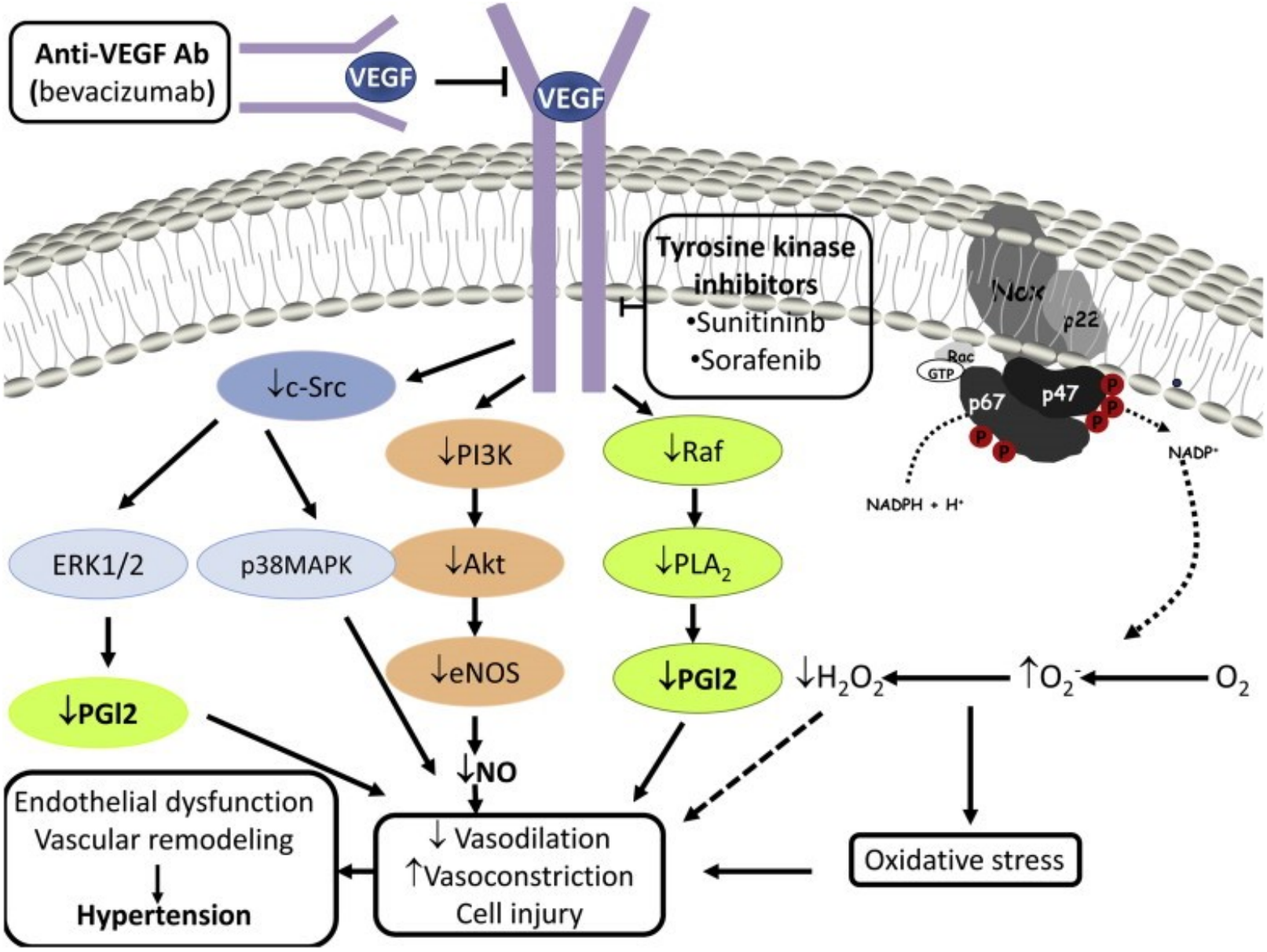
Jemal A et al., Cancer Statistics 2008

Concomitant Drugs Given for CVD may Cause Additive Toxicities

- Example: Arhythmias
- Some CVD Patients may use drugs that prolong QT interval
  - Amiodarone
- Amiodarone has a *known risk* of Torsades de Pointes
- TKIs are agents with *possible risk of* Torsades de Pointes

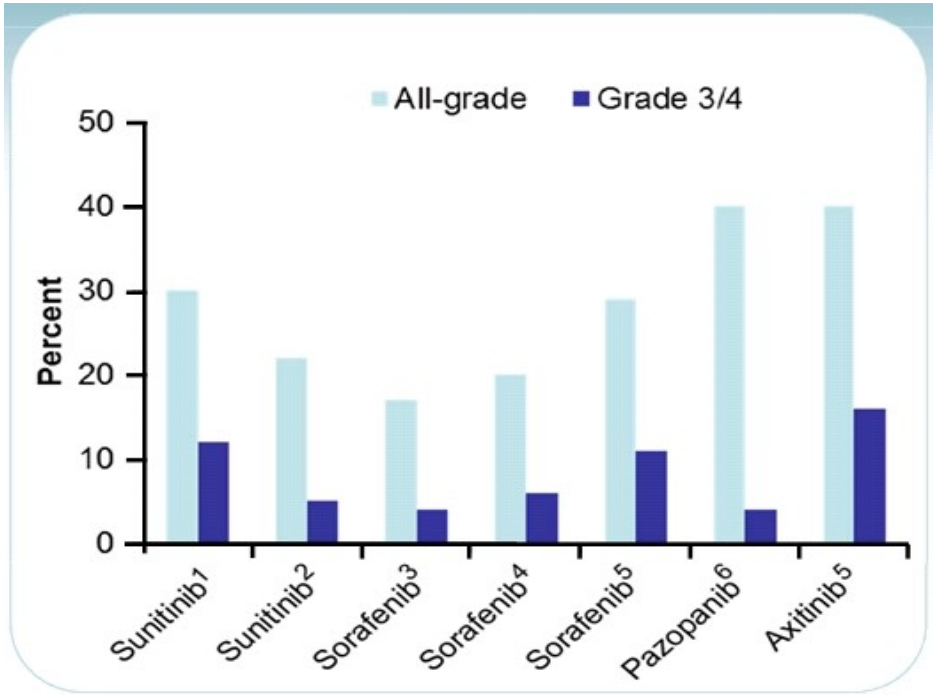
…and what about hypertension?

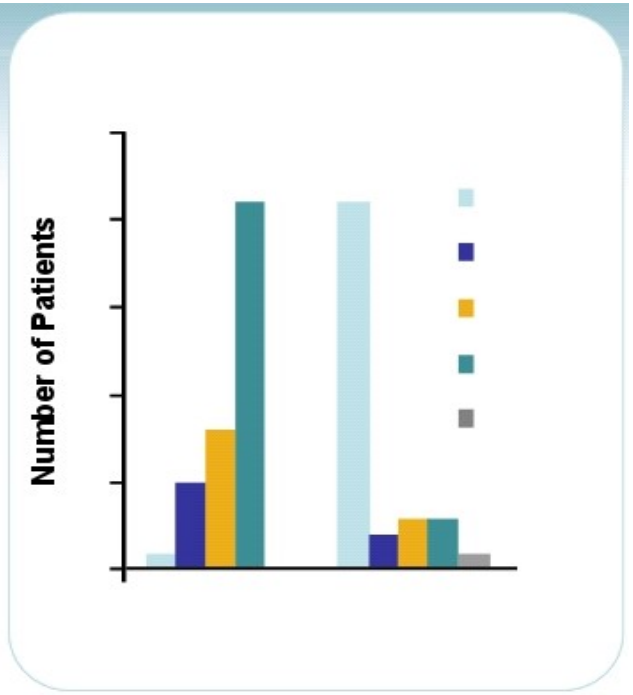
Hypertension and antiangiogenic drugs in mRCC



Hypertension

- Hypertension is common with anti-angiogenic therapy
- Seen with all TKIs[1-7]
  - ✓ Typically emerge within the first 4 weeks of therapy





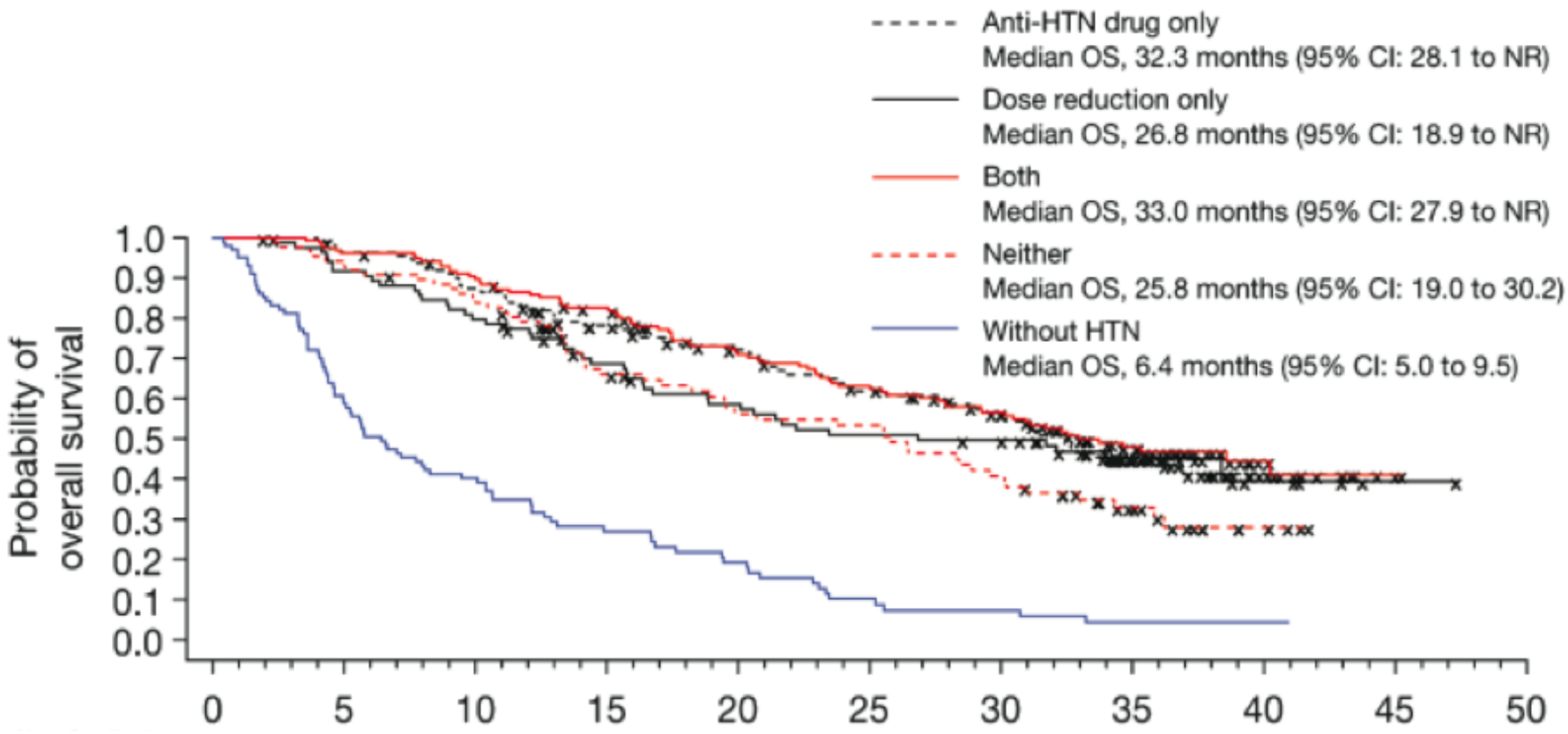
1. Motzer RJ et al. J Clin Oncol. 2009;27:3584-3590.
2. Gore ME et al. Lancet Oncol. 2009;10:757-763.
3. Escudier B et al. J Clin Oncol. 2009;27:3312-3318.
4. Beck J et al. Ann Oncol. 2011;22:1812-1823
5. Rini BI et al. Lancet. 2011;378:1931-1939
6. Sternberg CN. J Clin Oncol. 2010;28:1061-1068
7. Bamias A et al. Eur J Cancer. 2011;47:1660-1668.

Association of Side Effects and Outcome

Agent	Side effect	Correlation with outcome
BEV[1]	Hypertension>2	DCR: 91% vs 48% and TTP: 8.1 vs 4.2
BEV+IFN[2]	Hypertension>2	RR: 13 vs 9; OS:41.6 vs 16.2
SUN[3]	Hypertension SBP>140, DBP>90	RR: systolic: 55 vs 10; diastolic 57 vs 25%
SOR[4]	Hypertension all	Shrinkage: 90 vs 33
AX[5]	Diastol BP	PFS
SUN[6]	Hypothyroidism	PFS: 10.3 vs 3.6 OS: 18.2 vs 6.6
SUN[7]	Hypothyroidism	PFS: 575 vs 481 days
SUN[8]	Hypothyroidism	PFS: 8.55 vs 7.03 mo
SUN+SOR[9]	Hypothyroidism	PFS: 17 vs 10.8; OS: nr vs 13.9
SUN[10]	Hypertension	ORR: 54.8 vs 8.7% PFS: 12.5 vs 3.8; OS: 30.9 vs 7.2

1.Bono P et al., Ann Oncol 2009; 2. Rini B et al., J Clin Oncol 2010; Rini B et al., ASCO GU 2010;
4.Nozawa M et al., ASCO GU 2009; 5.Rixe O et al., ASCO 2009; 6.Wolter P et al., Br J Cancer 2008;
7.Bladou F et al., ASCO 2010; 8 Baldazzi V et al., UrologicOncol 2010 ; 9.Schmidinger M et al., Cancer 2011;
10.Rini B et al., J Natl Cancer Inst. 2011

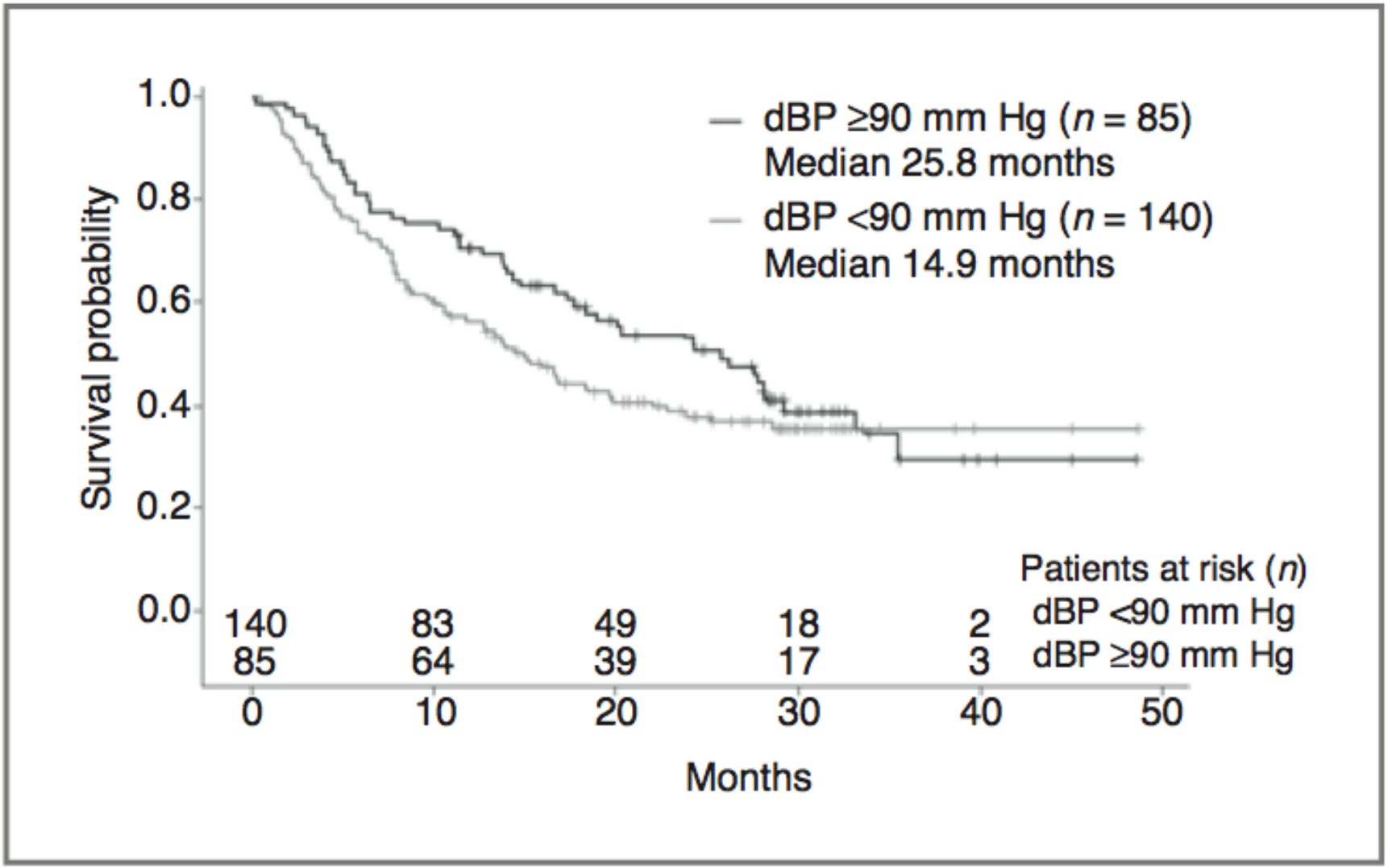
Hypertension as a potential biomarker of sunitinib-related efficacy



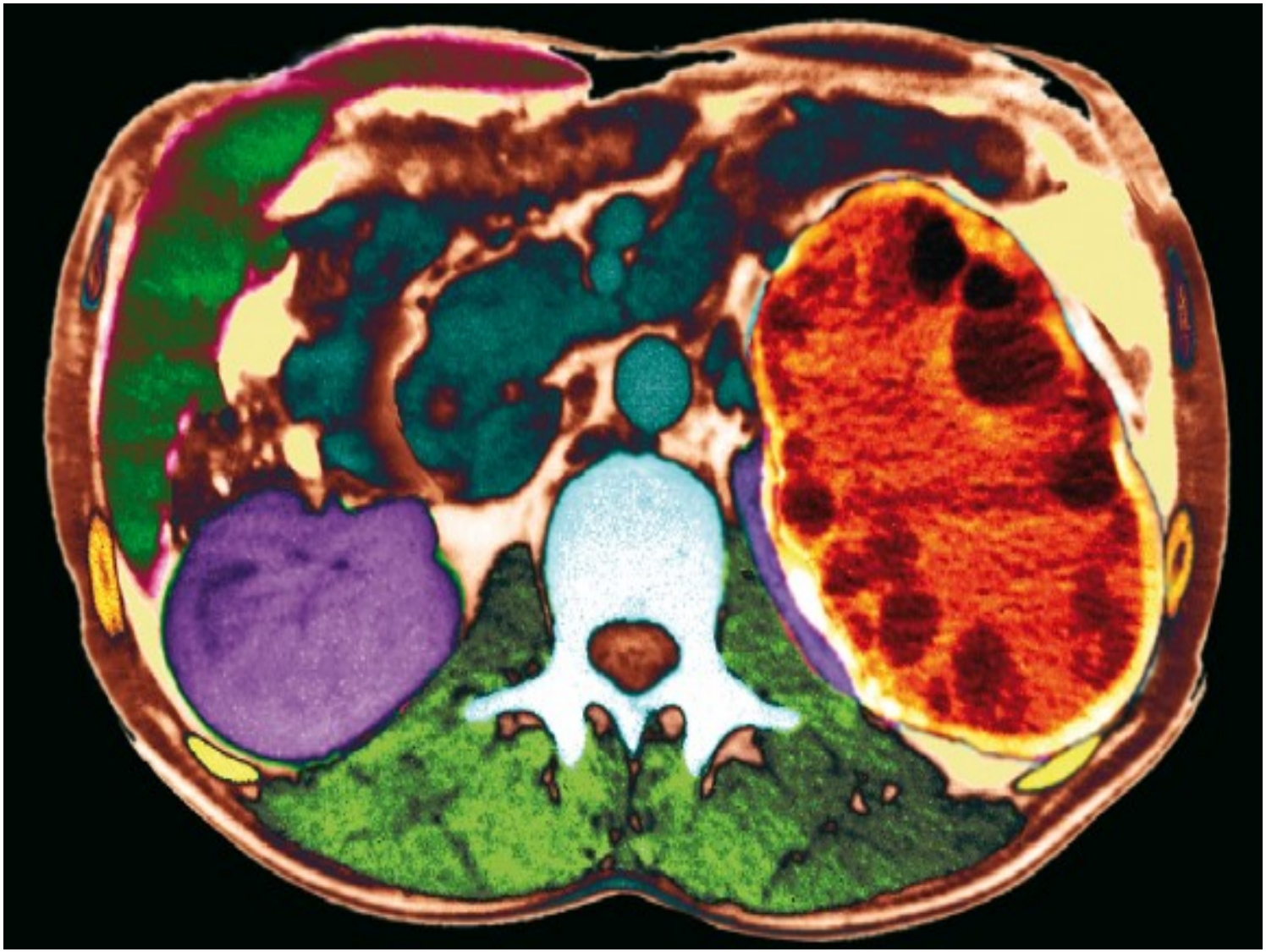
PFS was longer in patients with HTN, independent of use of anti hypertensive drugs and HTN-induced dose reduction

Rini B I et al. JNCI J Natl Cancer Inst 2011;103:763-773

Diastolic Blood Pressure as a Biomarker of Axitinib Efficacy



Rini B I et al. Clin Cancer Res 2011;17:3841-3849



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