VANDERBILT UNIVERSITY
MEDICAL CENTER

Renal Cell Cancer and TKIs:

What is my target BP?
Should I use home monitoring?
What is my target BP in cancer patients?

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Presenter Disclosure Information

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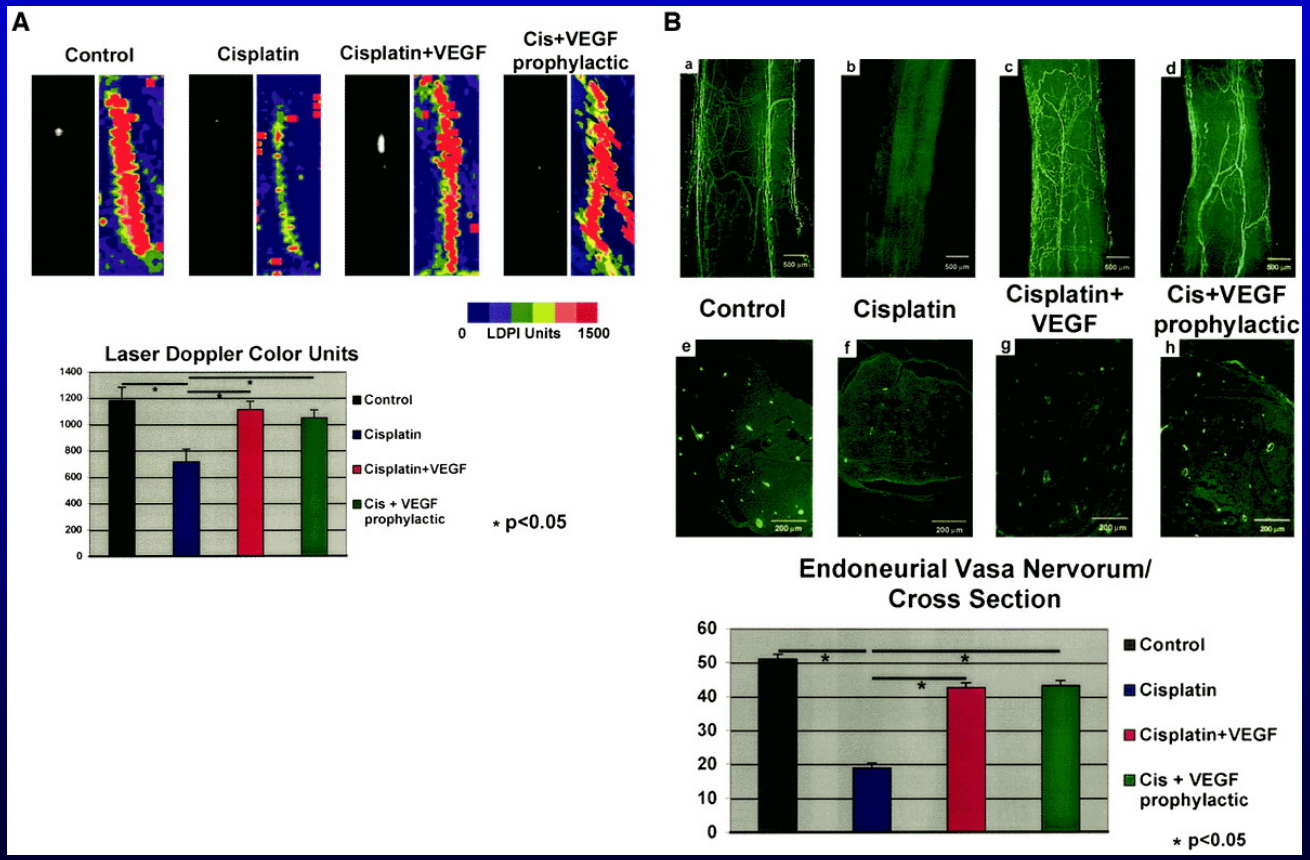
- I will not discuss off label use or investigational use in my presentation.
- I have financial relationships to disclose:
  - Research support from: Takeda, Inc.
  - Consultant (modest): Roche, Amgen, BMS, Prothena

Therapy for both Oncology and Cardiology are intimately intertwined at the vascular level



Kirchmair R. Circulation. 2005 May 24;111(20):2662-70.

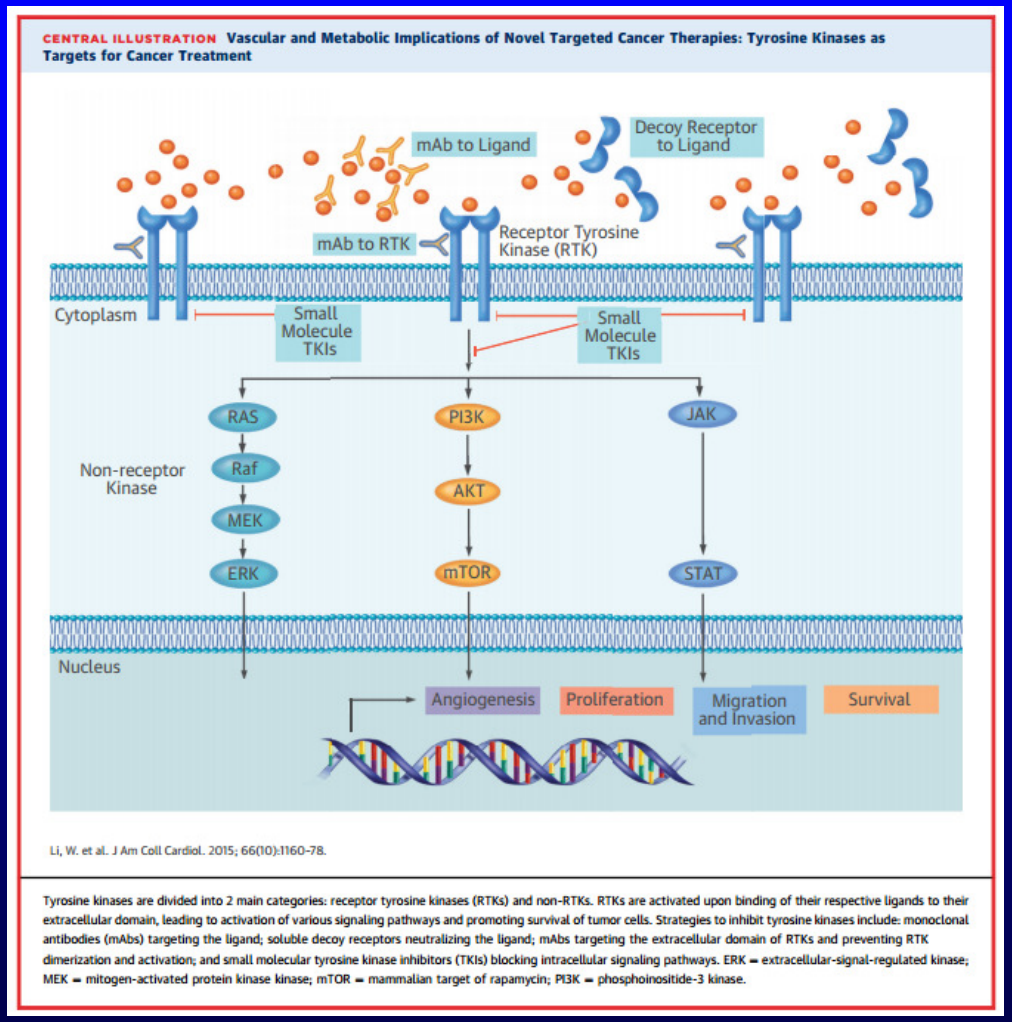
Definition of a “Kinase Inhibitor”:

- A drug that interferes with *cell communication and growth* and is sometimes used to treat cancer

Chemotherapeutic Agents in Use Known to Antagonize Vascular Endothelial Growth Factor (anti-VEGF) or have Anti-Angiogenic Properties

- Bevacizumab
- Sunitinib
- Sorafenib
- Vandetanib
- Pazopanib
- Axitinib
- Cabozantinib
- Ramucirumab
- Regorafenib

When considering CV toxicity of tyrosine kinase inhibitors (TKIs), the field is broad



Li, W et al, JACC 2015, p1160-78

Case study: Anti-VEGF therapy

- 60 y/o F, with HTN and DM, presents with metastatic renal cell cancer that led to L nephrectomy, radiation to pelvis and ribs, and resection of R femur tumor who was started on sunitinib 2 months ago.
- MEDS: triamterene, losartan, sunitininb 37.5 mg, Zofran
- PE: BP 168/92, P88, wt 178#, R16
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Case Study: What should be done?

- Control BP with what meds?
- How do we follow this patient going forward?
- Any other general recs?

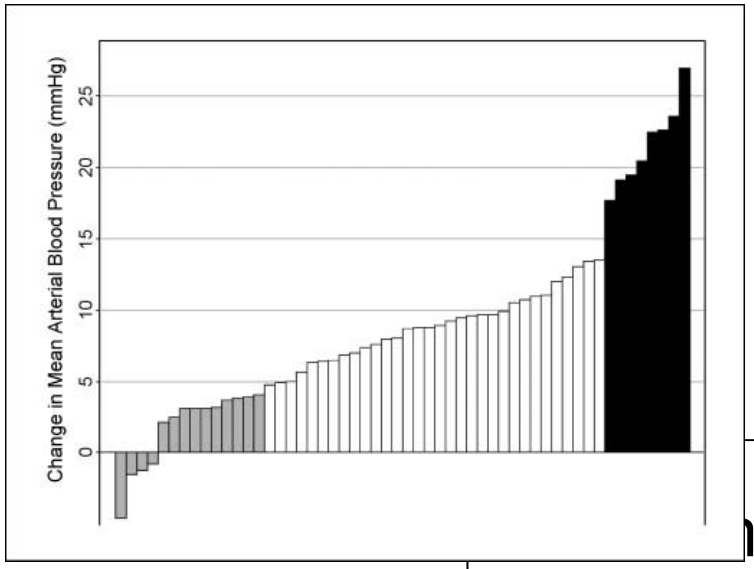
What about Hypertension as a precursor to HF?

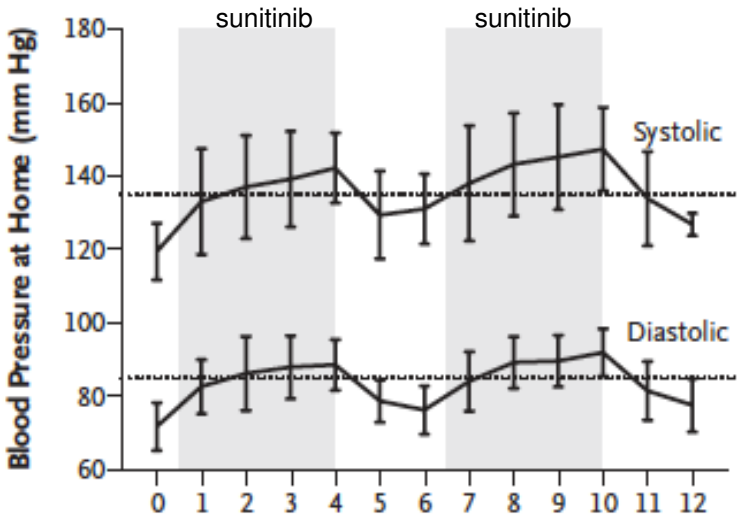
Sunitinib, a novel oral chemotherapeutic agent with anti-VEGF properties, is associated with hypertension and heart failure

Table 2. Nature of Cardiotoxicity, Severity of Heart Failure, and Short Term Outcomes

Pt #	BP at baseline	Dose	Duration of drug (days)	Worst NYHA Class	BNP (pg/ml; normal ≤ 100)	LVEF post-drug	HF Therapy	LVEF post Treatment with HF Therapy	Max BP on Drug	Outcome
1	150/72	50	44	4	558	25-30%	ACE-I, B-blocker	25-30%	155/85	Expired in 6 months
2	150/80	50	4	3	3338	30-35%	Nitrates, B-blocker	45-50%	184/110	Expired in 4 months
3	140/94	25	4	4	2110	25-30%	Increased ACE-I	30%	210/110	Expired in 1 month
4*	142/67	25	29	2	409	40-45%	Increased ACE-I	60-65%	174/85	LVEF improved then worsened to 35-40% on sunitinib
5	162/92	50	20	4	409	<20%	Added ACE-I, B-blocker	-	195/97	Expired in 1 month
6	146/75	50	29	3	356	50-55%	B-blocker	-	160/80	HF symptoms improved after sunitinib was discontinued and sinus rhythm was restored

Khakoo, et al, 2008; 112:2500-8





?

HYPERTENSION

Maitland et al. *Clinical Cancer Research*, 2009.
Azizi et al. *NEJM*, 2009.

Emerging model for VSP inhibitor Associated Cardiomyopathy

Inhibition of VEFGR or PDGFR

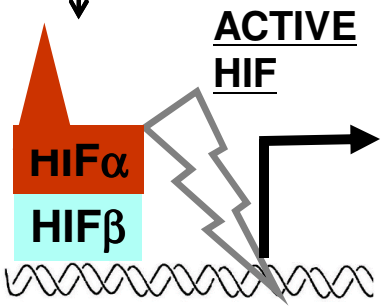
↓

Microvascular Dysfunction

↓

Chronic Myocyte Hypoxia

↓

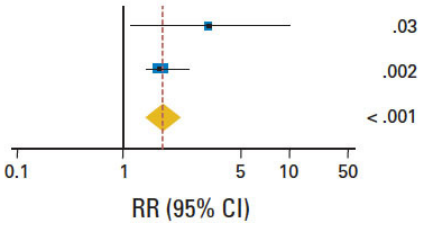


VSP-Inhibitor Associated Cardiomyopathy

Meta-analysis of clinical heart failure in sunitinib trials

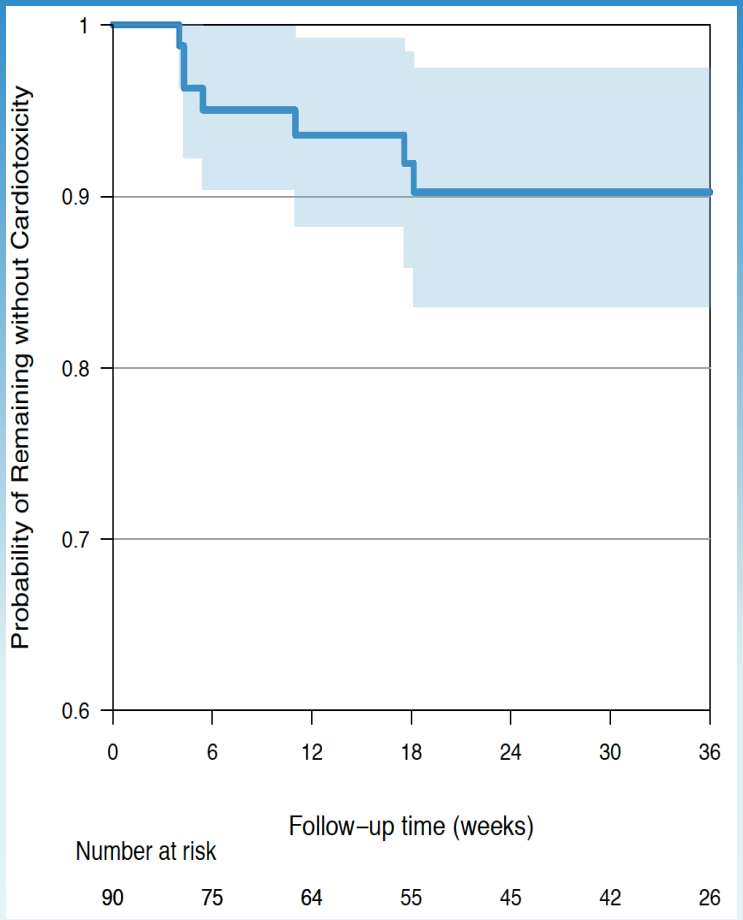
Trial	Year	Phase	No. of Events	Sample Size	CHF Incidence	CHF 95% CI
All-grade CHF (n = 12)						
Demetri et al[2]	2006	III	22	202	10.9	7.3 to 16.0
Motzer et al[3]	2007	III	78	375	20.8	17.0 to 25.2
Motzer et al[37]	2006	II	7	63	11.1	5.4 to 21.5
Motzer et al[38]	2006	II	8	105	7.6	3.9 to 14.5
Saltz et al[44]	2007	II	0	82	0.0	
Kulke et al[43]	2008	II	1	107	0.9	0.1 to 6.3
Gore et al[35]	2009	EAP	11	4,371	0.3	0.1 to 0.5
Hensley et al[45]	2009	II	1	23	4.4	0.6 to 25.2
Kontovinis et al[36]	2009	II	3	42	7.1	2.3 to 19.9
MacKay et al[41]	2010	II	1	19	5.3	0.7 to 29.4
Tomita et al[39]	2010	II	2	51	3.9	1.0 to 14.4
Matsumoto et al[40]	2011	II	0	18	0.0	
Combined			134	5,458	4.1%	1.5% to 10.6%
					Test for heterogeneity: Q = 218.48; $P < .001$; $I^2 = 95.0\%$	

	Sunitinib		Control			
	No. of Events/ Total No.	Incidence, % (95% CI)	No. of Events/ Total No.	Incidence, % (95% CI)	Relative Risk (95% CI)	*P*
All-grade						
Demetri (2006)	22/202	10.9 (7.3 to 16.0)	3/102	2.9 (1.0 to 8.7)	3.70 (1.14 to 12.1)	.03
Motzer (2009)	78/375	20.8 (17.0 to 25.2)	44/360	12.2 (9.2 to 16.0)	1.70 (1.21 to 2.39)	.002
Overall	100/577	15.5 (8.0 to 27.9)	47/462	6.7 (1.6 to 24.1)	1.81 (1.30 to 2.50)	< .001
Heterogeneity test, Q		8.71		6.30	1.53	
P		.003		.012	.216	
I^2		88.5%		84.1%	34.8%	



Richards,…Moslehi and Choueiri. *Journal of Clinical Oncology*, 2011.

Sunitinib Associated with LV Dysfunction



- 90 patients with metastatic renal cell cancer, treated with sunitinib
- On population level, significant but small decline in LVEF of 1.9% with sunitinib
- Overall, 9.7% developed LV dysfunction and all events occurred by cycle 3 (majority in first cycle)

Narayan, et al. Clin Cancer . 2017.

From: The Frequency and Severity of Cardiovascular Toxicity From Targeted Therapy in Advanced Renal Cell Carcinoma Patients

JCHF. 2013;1(1):72-78. doi:10.

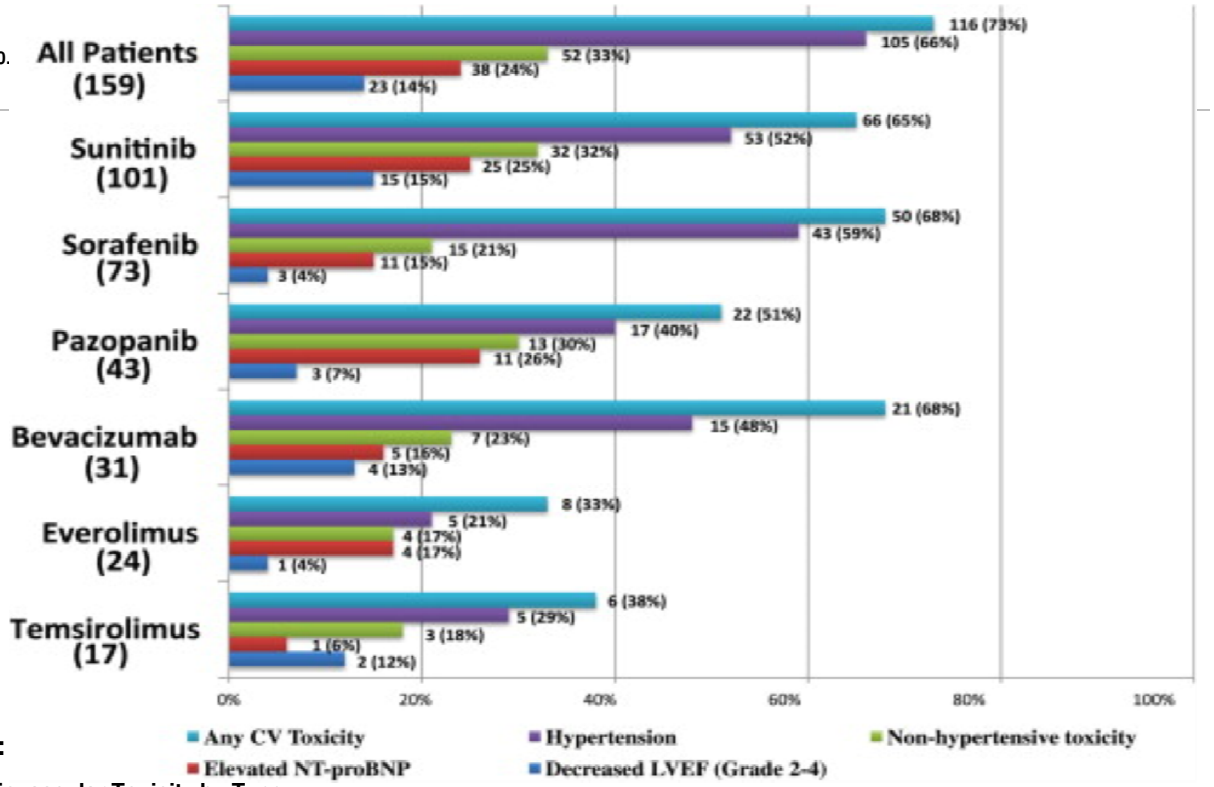


Figure Legend:

Incidence of Cardiovascular Toxicity by Type

The incidence of cardiovascular toxicity varied by type of toxicity and by chemotherapy agent received. Many patients received multiple therapies in succession and are included only once in "All Patients." CV = cardiovascular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal B-type natriuretic peptide.

From: The Frequency and Severity of Cardiovascular Toxicity From Targeted Therapy in Advanced Renal Cell Carcinoma Patients

JCHF. 2013;1(1):72-78. doi:10.1016/j.jcl

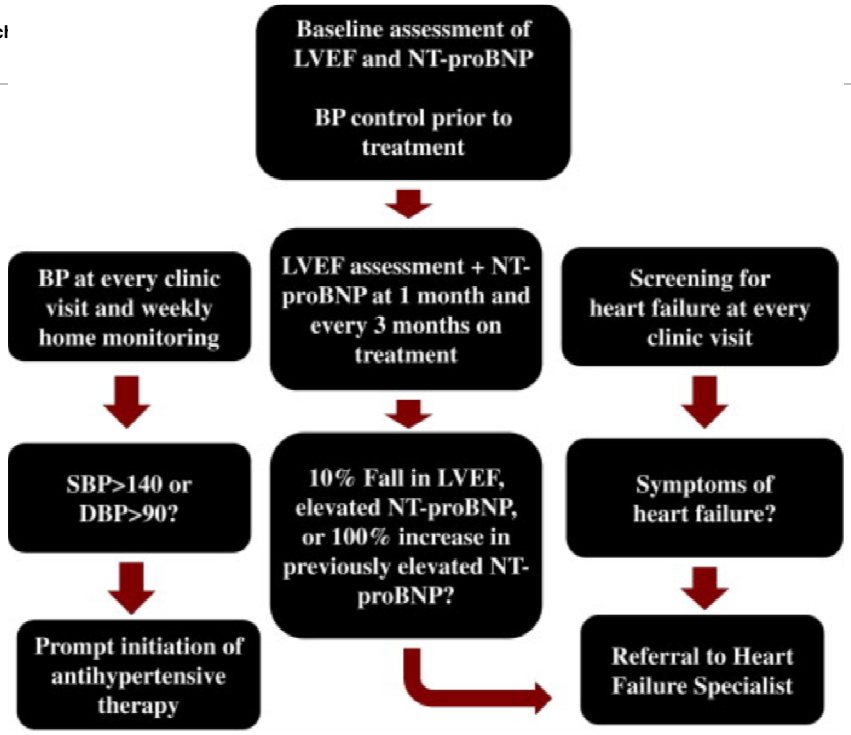


Figure Legend:

The Stanford Monitoring Algorithm for Targeted Therapies

Cardiovascular monitoring algorithm for patients with renal cell carcinoma receiving targeted chemotherapy. BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure; other abbreviations as in Figure 1.

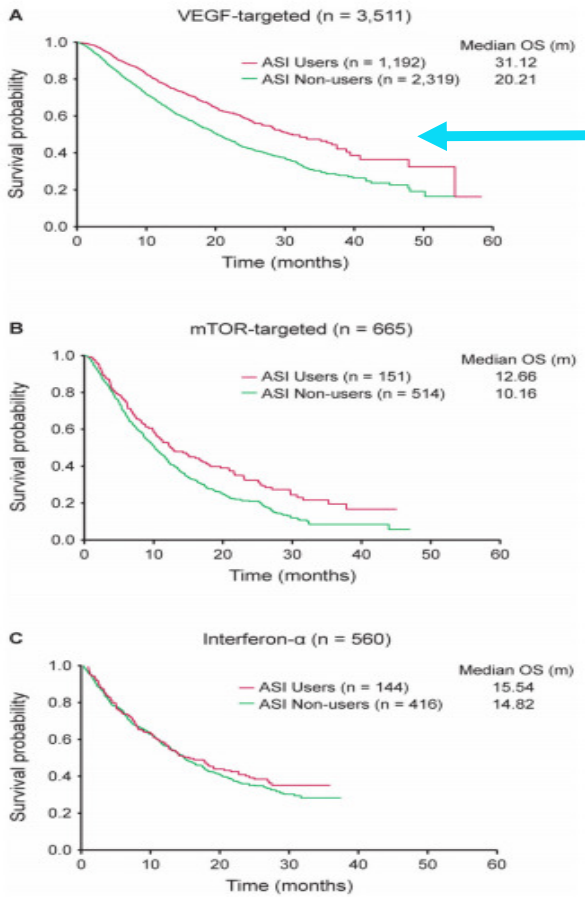


Figure 2.
Kaplan–Meier estimates of A) OS for patients receiving VEGF-targeted therapy, B) OS for patients receiving mTOR-targeted therapy, and C) OS for patients receiving IFN-a therapy stratified by ASI users versus non-users.

In Renal Cell Cancer, renin-angiotensin inhibitors are critical therapies especially with VSP inhibitors

R McKay et al, Clin Cancer Res. 2015 Jun 1; 21(11): 2471–2479.

RAS inhibitors seem to be very important for overall survival

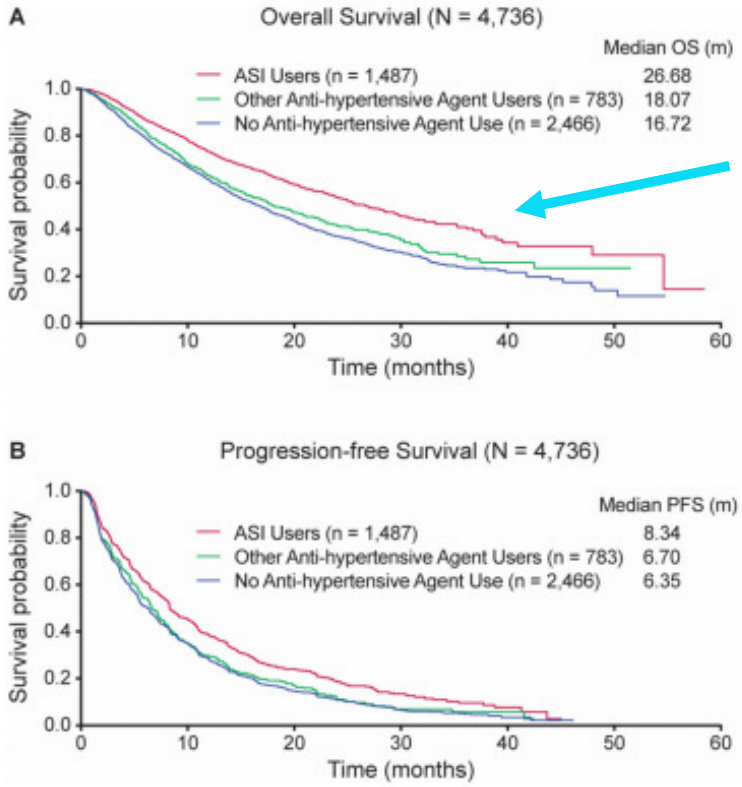


Figure 1.
Kaplan–Meier estimates of A) OS for the overall cohort, and B) PFS for the overall cohort stratified by ASI users, other anti-hypertensive agent(s) users, versus no anti-hypertensive agent use.

R McKay et al, Clin Cancer Res. 2015 Jun 1; 21(11): 2471–2479.

The problems are not always LV dysfunction

TABLE 4 Incidences and Risks of Arterial and Venous Thromboembolism Associated With VSP Inhibitors

Agent	Study (Ref. #)	Overall Incidence of VTE (%)	High-Grade VTE (Grade 3-5) (%)	RR of VTE		Study	Overall Incidence of ATE (%)	High-Grade ATE (Grade 3-5) (%)	RR of ATE	
				All-Grade	High-Grade				All-Grade	High-Grade
Bevacizumab (VEGF mAb)	Meta-analysis, 7,956 patients, 15 trials (120)	11.9	6.3	1.33	1.38	Meta-analysis, 12,617 patients, 20 trials (121)	3.3	2.0	1.44	2.14 (high-grade cardiac ischemia)
Pazopanib (TKI)	Meta-analysis, 7,441 patients, 17 trials (sunitinib: 3 trials; sorafenib: 4 trials; pazopanib: 3 trials; vandetanib: 5 trials; axitinib: 2 trials) (122)	2.76	1.92	1.10	0.85	Meta-analysis, 844 patients, 2 trials (123)	1.2	NA	4.61	NA
Sunitinib (TKI)						Meta-analysis, 4,628 patients, 4 trials (124)	1.3	NA	3.1	NA
Sorafenib (TKI)						Meta-analysis, 4,759 patients, 6 trials (124)	1.7	NA	2.39	NA
Axitinib (TKI)						Meta-analysis, 572 patients, 3 trials (123)	1.2	NA	1.17	NA
Vandetanib (TKIs)						Phase III RCT, 623 patients (123)	0	NA	0.13	NA
Regorafenib (TKI)	Phase III RCT in mCRC, 760 patients (125)	2	NA	NA	NA	NA	NA	NA	NA	NA
	Phase III RCT in advanced GIST, 199 patients (126)	No VTE or ATE events reported, but 1 patient in regorafenib arm died from cardiac arrest during treatment								
Cabozantinib (TKI)	Phase III RCT in MTC, 330 patients (112)	5.6	3.7	NA	NA	Phase III RCT in MTC (112)	2.3	0.9	NA	NA
Aflibercept (VEGF trap)	Phase III RCT in mCRC, 1,226 patients (127)	9.3	7.8	NA	NA	Phase III RCT in mCRC, 1,226 patients (127)	2.6	1.8	NA	NA
Ramucirumab (VEGFR2 mAb)	Phase III RCT in advanced gastric or GEJ adenocarcinoma, 665 patients (128)	3.98	2.45	NA	NA	Phase III RCT in advanced gastric or GEJ adenocarcinoma, 655 patients (128)	1.83	0.92	NA	NA
Lenvatinib (TKI)	Phase III trial, 261 patients (116)	5.4	3.8	NA	NA	Phase III trial, 261 patients (116)	5.4	2.7	NA	NA

ATE = arterial thromboembolic event; GEJ = gastroesophageal junction; mAb = monoclonal antibody; mCRC = metastatic colorectal cancer; MTC = medullary thyroid cancer; RCT = randomized controlled trial; TKI = tyrosine kinase inhibitor; VTE = venous thromboembolic event; other abbreviations as in Table 3.

Li, W et al, JACC 2015, p1160-78

Statins are helpful in renal cell cancer especially with anti-VEGF directed therapy

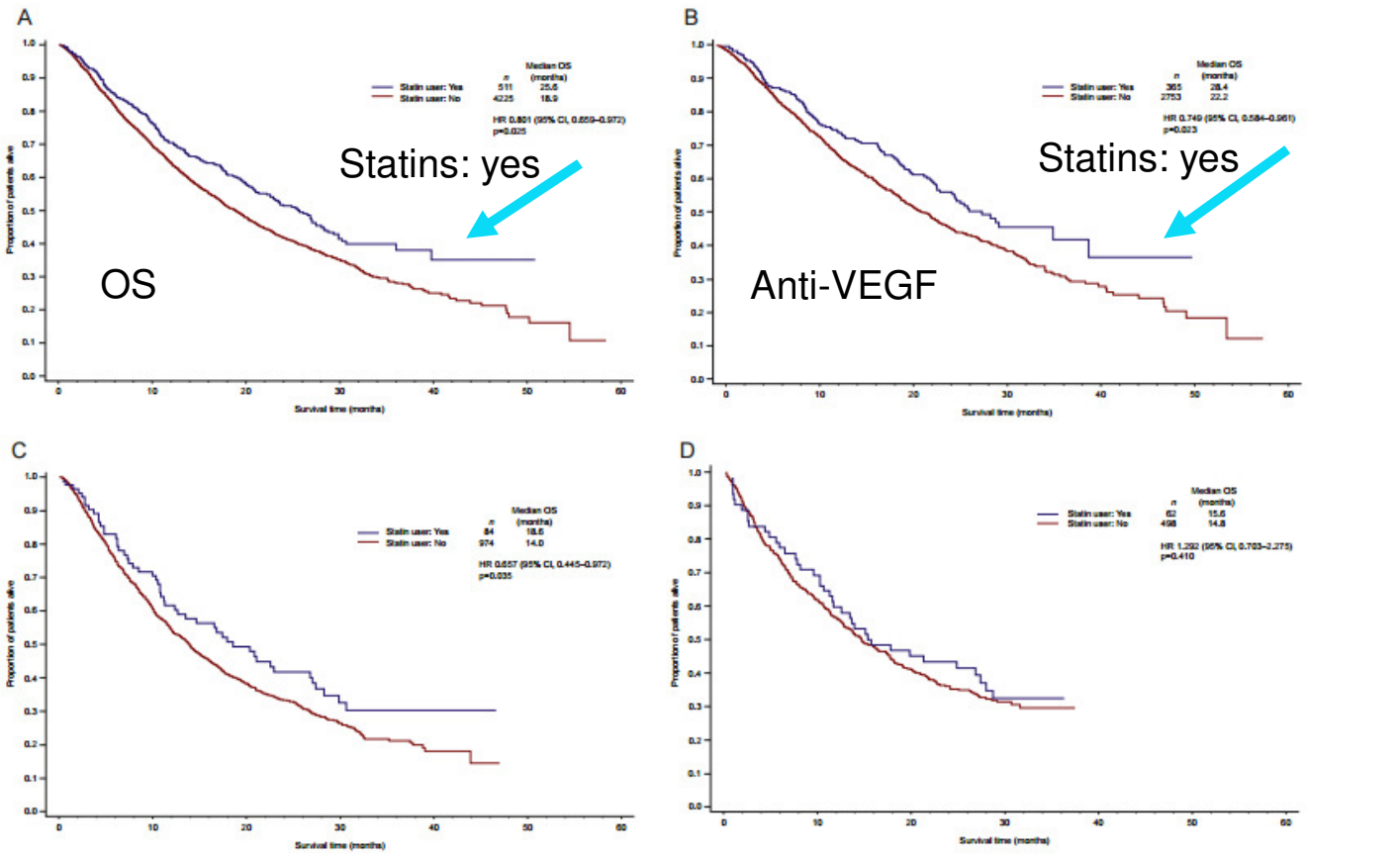


Fig. 1. Kaplan–Meier estimates of OS for (A) the overall cohort, (B) patients receiving VEGF-targeted therapy, (C) patients receiving mTOR-targeted therapy and (D) patients receiving IFN-a therapy stratified by statin users versus non-users.

R McKay et al European Journal of Cancer 52 (2016) 155-162

Case study: Anti-VEGF therapy

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- No JVD, lungs clear, loud S4, trace ankle edema
- Labs: Cr 1.1, TC 227, LDL 129, HDL 31, BNP 18, LVEF 55 with mild LVH

Case Study: What should be done?

- Control BP with what meds?

stopped triamterene, used furosemide for edema, started carvedilol, added amlodipine eventually, used hydralazine intermittently

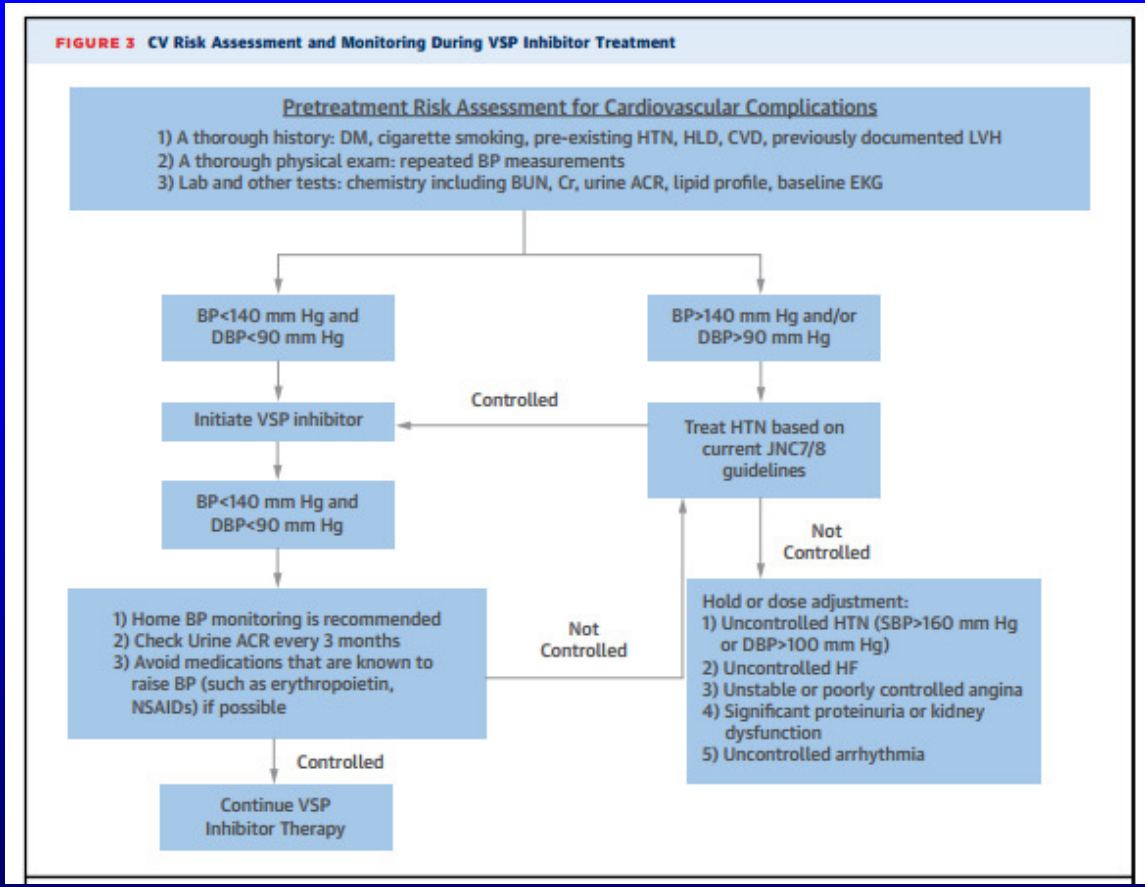
- How do we follow this patient going forward?

periodic BNP, rarely EF measured only for progressive dyspnea

- Any other general recs?

sodium restriction, exercise, lipid therapy, aspirin

How do we best approach cardiac issues during antiangiogenic therapy?



Li, W et al, JACC 2015, p1160-78

- First line therapy: RAS inhibitors, amlodipine
- carvedilol can be very useful second line
- should we use NO producing agents: long-term nitrates?

Are there **inhibitors** on the cancer therapy horizon that could be concerning for the development of Hypertension and Cardiovascular Events??

There is a balance between protein synthesis and degradation in the myocardium

The NEW ENGLAND JOURNAL of MEDICINE

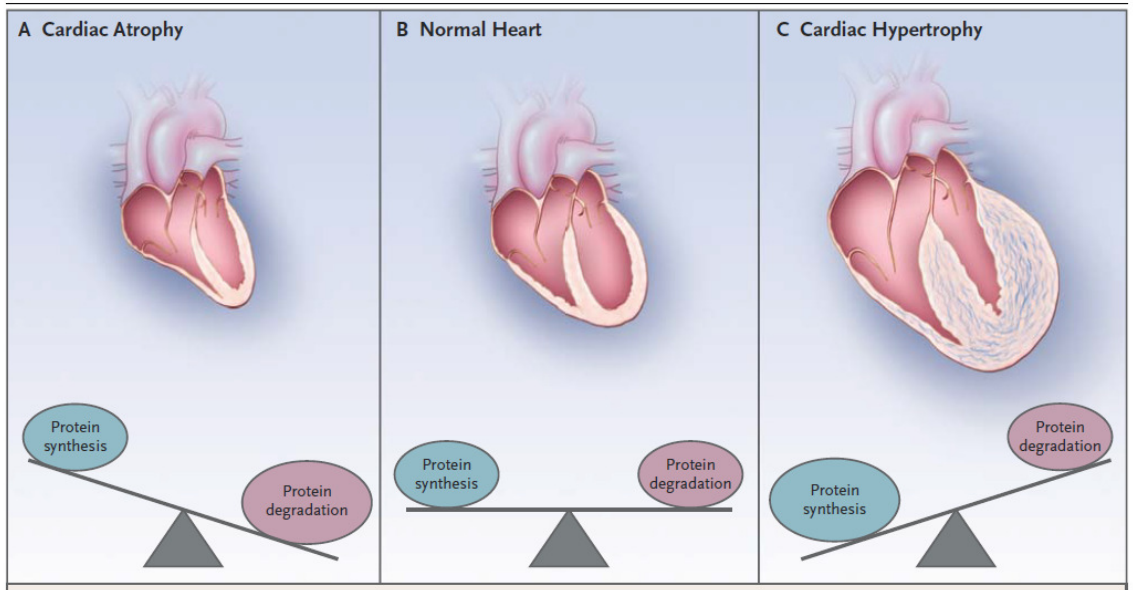


Figure 1. Association of the Development of Cardiac Atrophy and Hypertrophy with Changes in the Balance between Protein Synthesis and Protein Degradation.

The development of cardiac atrophy involves both the inhibition of protein synthesis and a simultaneous increase in the rates of protein degradation (Panel A), resulting in shorter half-lives of individual cardiac proteins, as compared with the half-lives of proteins in a steady state, when protein synthesis and degradation are balanced (Panel B). The development of cardiac hypertrophy involves both an increased fractional synthesis rate of proteins and the suppression of protein degradation (Panel C), resulting in longer half-lives of cardiac proteins.[7-10]

Monte S. Willis, M.D., Ph.D., and Cam Patterson, M.D., M.B.A.
NEJM 2013;368:455-64.

Properties of bortezomib and the second-generation proteasome inhibitors

Proteasome inhibitor	IC_{50} $\beta5/\beta2/\beta1$ (nM)	IC_{50} NF-κB (nM)	Dissociation $t_{1/2}$ (min)
Bortezomib	2.4–7.9/590–4200/24–74 [16,18,25]	36–40 [18,25,39]	110 [18]
MLN9708 [18]	3.4/3500/31	62	18
CEP-18770 [19,20]	3.8/>100/<100	NR	NR—slowly reversible
Carfilzomib [16]	6/3600/2400	NR	Irreversible
PR-047 [21]	36/NR/NR	NR	Irreversible
NPI-0052	3.5/28/430 [25]	13–20 [25,39]	Irreversible

Abbreviations: IV, intravenous; MCL, mantle cell lymphoma; MM, multiple myeloma; NR, not reported; SC, subcutan

Dick, LR and Fleming, PE
Drug Discovery Today ;15 (5/6) March 2010

A report of 6 cases describing carfilzomib related cardiac dysfunction and the patterns of cardiotoxicity

Table 2. Summary of Clinical, Echocardiography, and Biomarker Response During and After Carfilzomib Therapy

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Carfilzomib exposure						
Dosing (mg/m^2)	20×1 then 27	27	20	20	27	20×1 then 27
Duration of therapy (mo)	3	5	6	1	3	3
Total cumulative dose (mg/m^2)	405	903	972	141	540	444
Baseline						
NYHA	I	I	I	I	I	I
LVEF	50–55	60–65	55	55–60	58	68
BNP (pg/mL)	N/A	79†	594*,†	N/A	N/A	N/A
Troponin (ng/mL)	N/A	N/A	<0.05	N/A	N/A	N/A
With carfilzomib						
Worst NYHA	III	II	III	III	III	III
Nadir of LVEF (%)	25–30	47	50	<20	25–30	44
Highest BNP or NT-proBNP† (pg/mL)	1,837†	170†	2,988†	2,026	640	744
Highest troponin	<0.05	<0.05	<0.05	2.5	0.01	<0.05
Recovery						
Carfilzomib discontinuation	Permanent	Temporary	Permanent	Permanent	Permanent	Temporary
Heart Failure Therapy Initiated	Beta-blocker; ACE-I; loop diuretic	None	Beta-blocker; ARB	Beta-blocker; ACE-I	Beta-blocker; aldosterone antagonist	Beta-blocker; aldosterone antagonist; loop diuretic
Best NYHA	I	II	III	I	II	II
Summary of Cardiac Events	**HF, LV dysfunction**	**Mild LV and RV dysfunction**	**HF**	**ACS, HF, QTc, LV dysfunction**	**HF, LV dysfunction**	**HF, LV dysfunction**

LV, left ventricular; RV, right ventricular; ACS, acute coronary syndrome; QTc. QTc prolongation.
*NT-proBNP 3 months before starting carfilzomib therapy.
†NT-proBNP.

Grandin, E J Cardiac Failure 2015; p138-144

Cardiovascular SAEs in RCTs
Phase 3 Carfilzomib Trials

- ASPIRE Trial

Table 3. Adverse Events in the Safety Population.*

Event	Carfilzomib Group (N=392)		Control Group (N=389)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
	number of patients (percent)			
Dyspnea	76 (19.4)	11 (2.8)	58 (14.9)	7 (1.8)
Hypertension	56 (14.3)	17 (4.3)	27 (6.9)	7 (1.8)
Acute renal failure†	33 (8.4)	13 (3.3)	28 (7.2)	12 (3.1)
Cardiac failure‡	25 (6.4)	15 (3.8)	16 (4.1)	7 (1.8)
Ischemic heart disease§	23 (5.9)	13 (3.3)	18 (4.6)	8 (2.1)

Total Cardiac AEs	26.6%	11.4%	15.6%	5.7%
Total Cardiac AEs + Dyspnoea	46%	14.2%	30.5%	7.5%
DVT/PE	10.2%		6.2%	

Stewart, AK et al, NEJM 2015, p.142-152.

Renal Cell Cancer and TKIs
Conclusion

- Vascular changes during chemotherapy are important and responsible for HTN, HF and thrombosis
- Prevention and early treatment of cardiac damage is possible
- Newer therapies that result in HTN have important cardiac safety considerations