Arterial Hypertension, VEGF and Microcirculation

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Tours, Déc 2010

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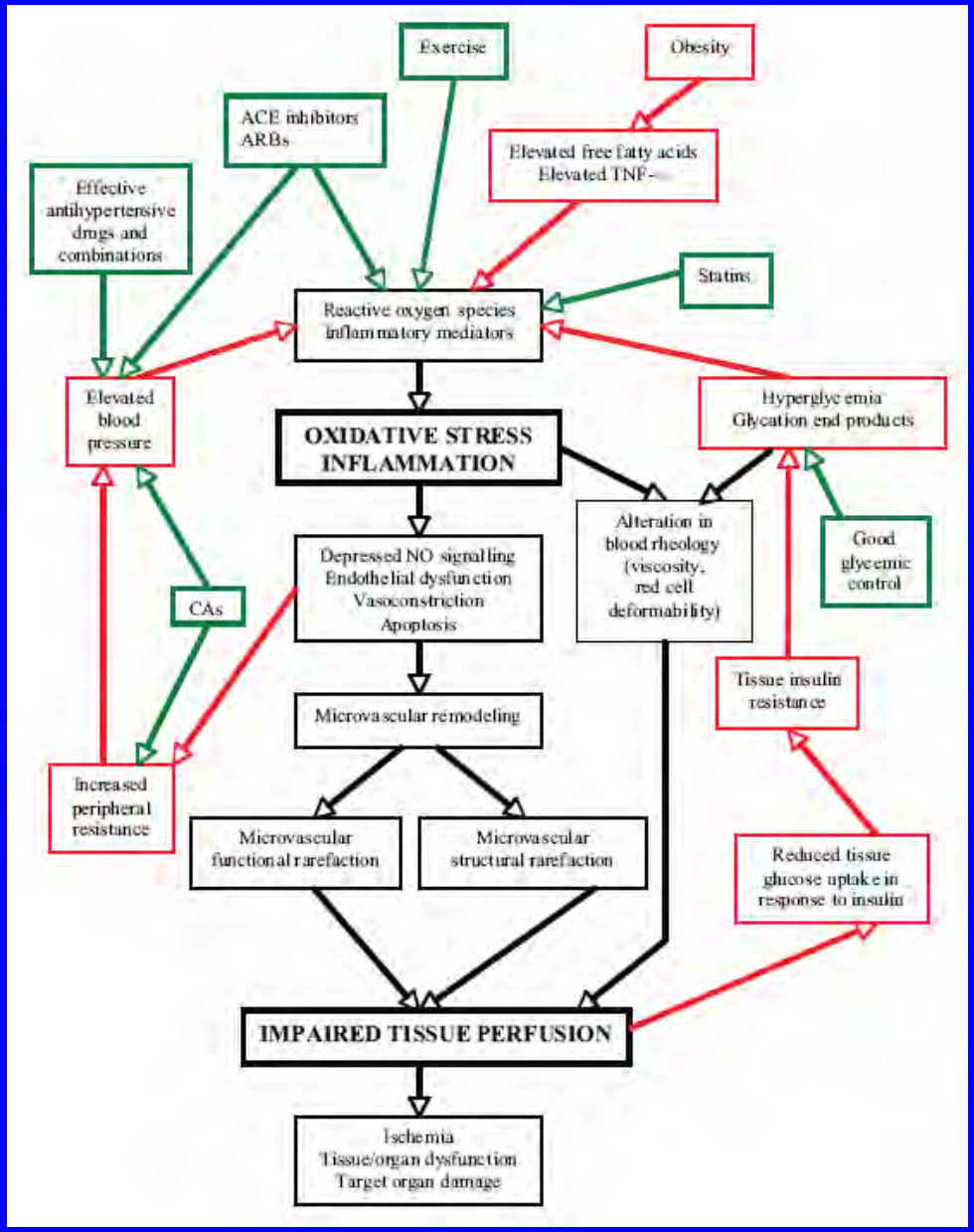
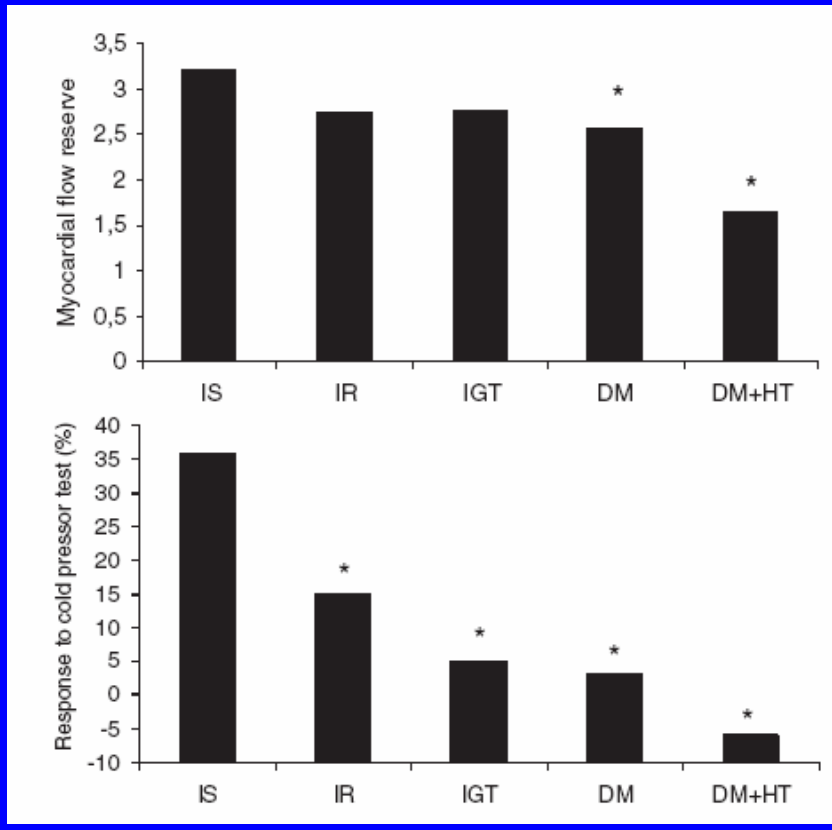
Microcirculation abnormalities are proven at early stages of arterial hypertension, as well as various diseases linked to cardiovascular morbidity.

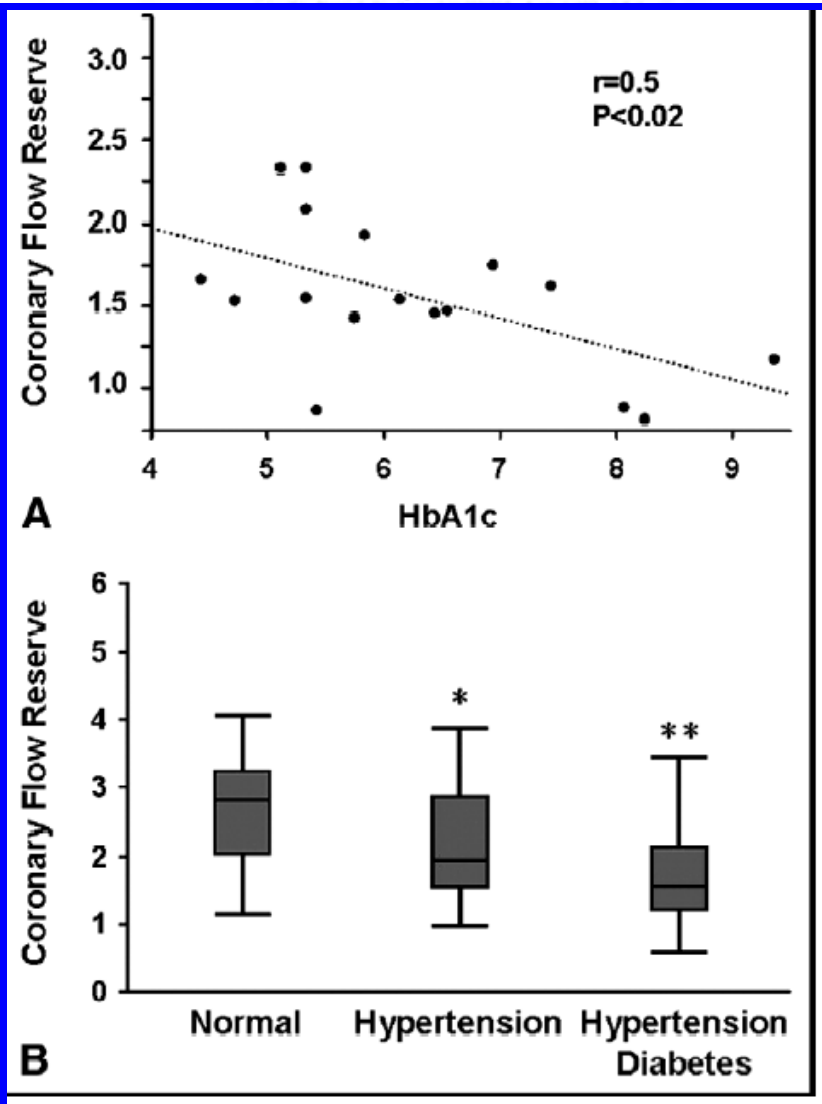


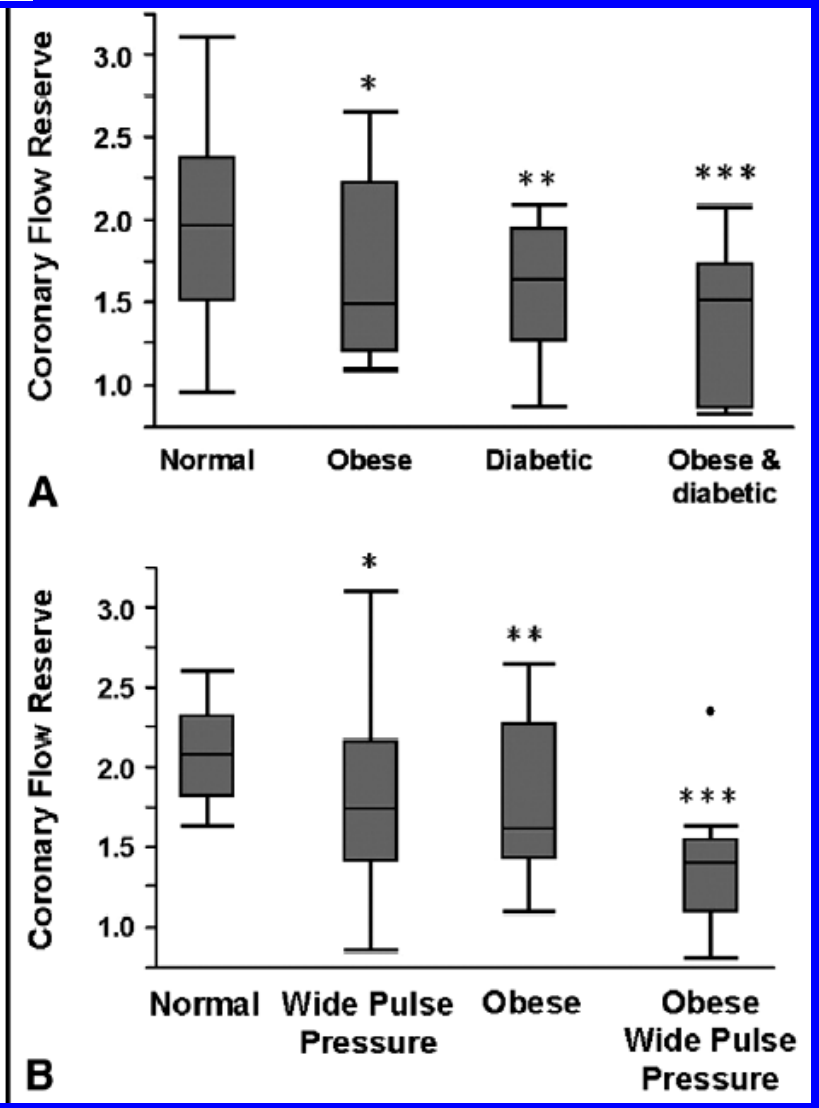


Levy BI, Circ 2008;118:968

Impact of Individual and Cumulative Coronary Risk Factors on Coronary Flow Reserve Assessed by Dobutamine Stress Echocardiography

Saeed A.L. Ahmari, MD, T. Jared Bunch, MD, Karen Modesto, MD, Vicky Stussy, RDCS, Amy Dichak, RDCS, James B. Seward, MD, Patricia A. Pellikka, MD, and Krishnaswamy Chandrasekaran, MD*



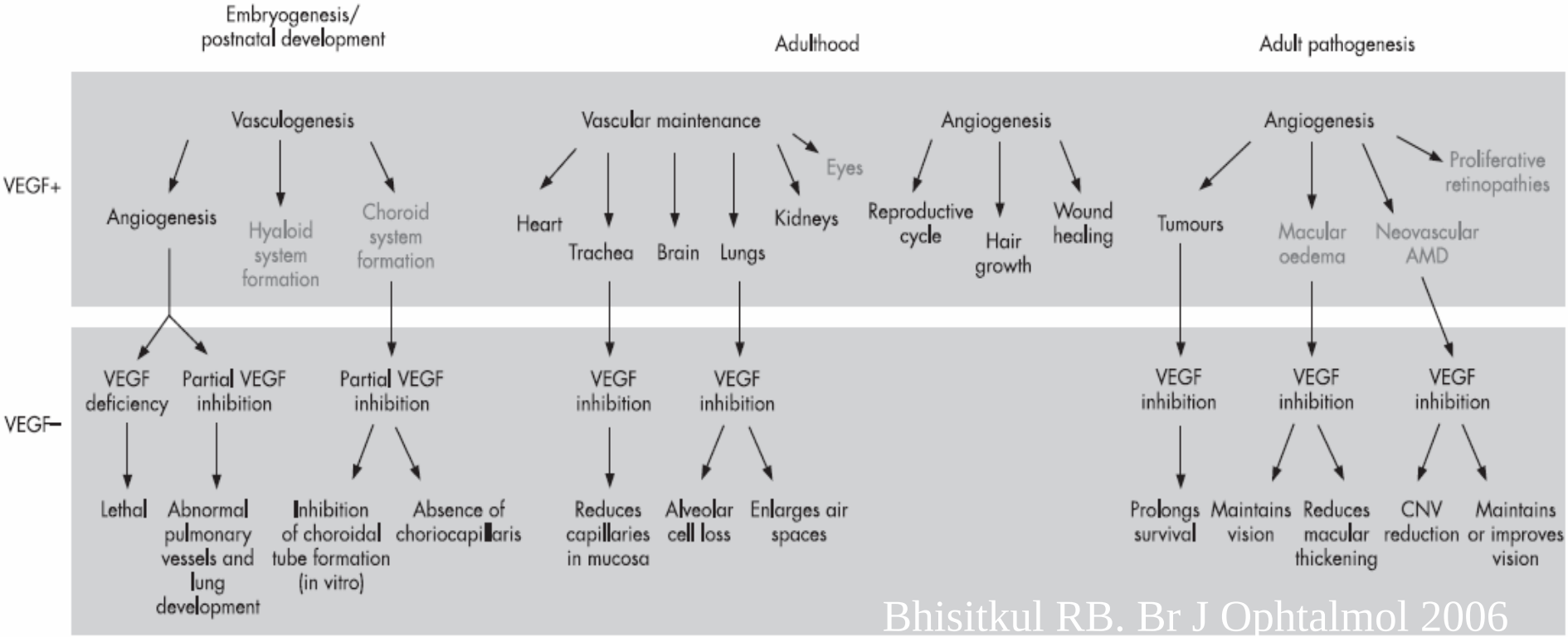


Am J Cardiol 2008

VEGF

Proangiogenic growth factor essential for embryonic development

Traditionally thought to have limited role in normal adult physiology

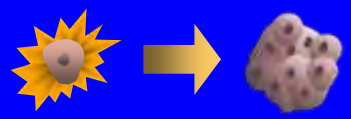


Bhisitkul RB. Br J Ophtalmol 2006

Targeting the microvasculature in human pathology

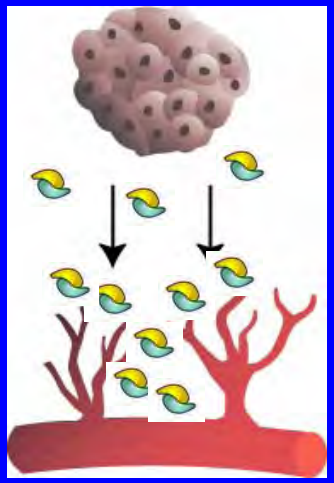
Capillary expansion / Capillary rarefaction

The Angiogenic Switch and Antiangiogenic Therapy

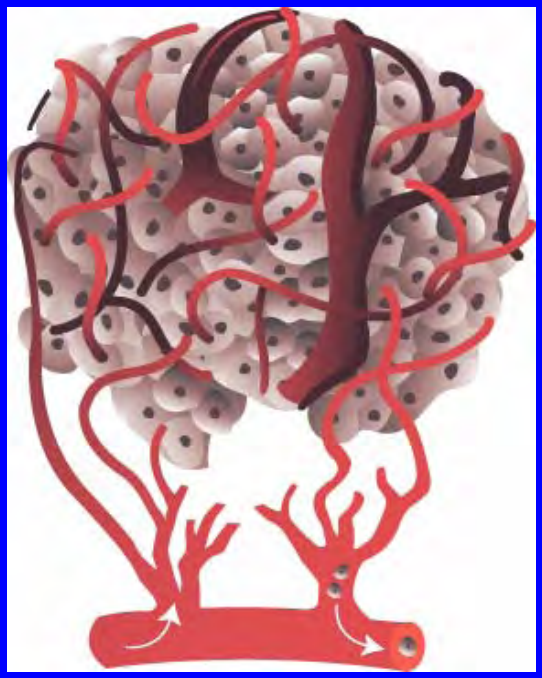


Somatic mutation

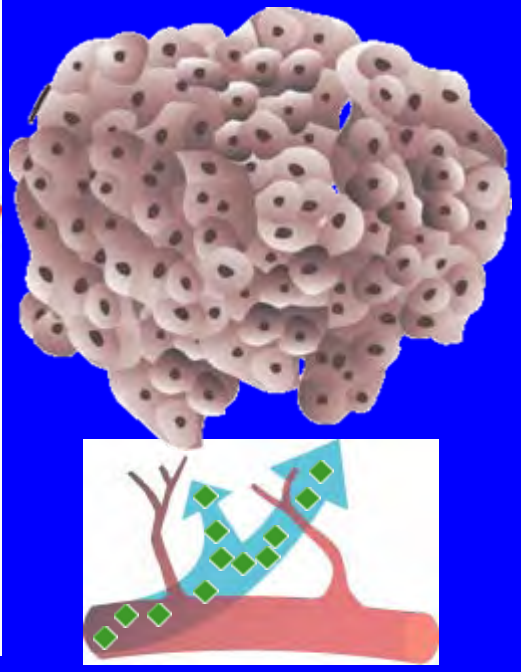
Small avascular tumor



Tumor secretion of angiogenic factors stimulates angiogenesis



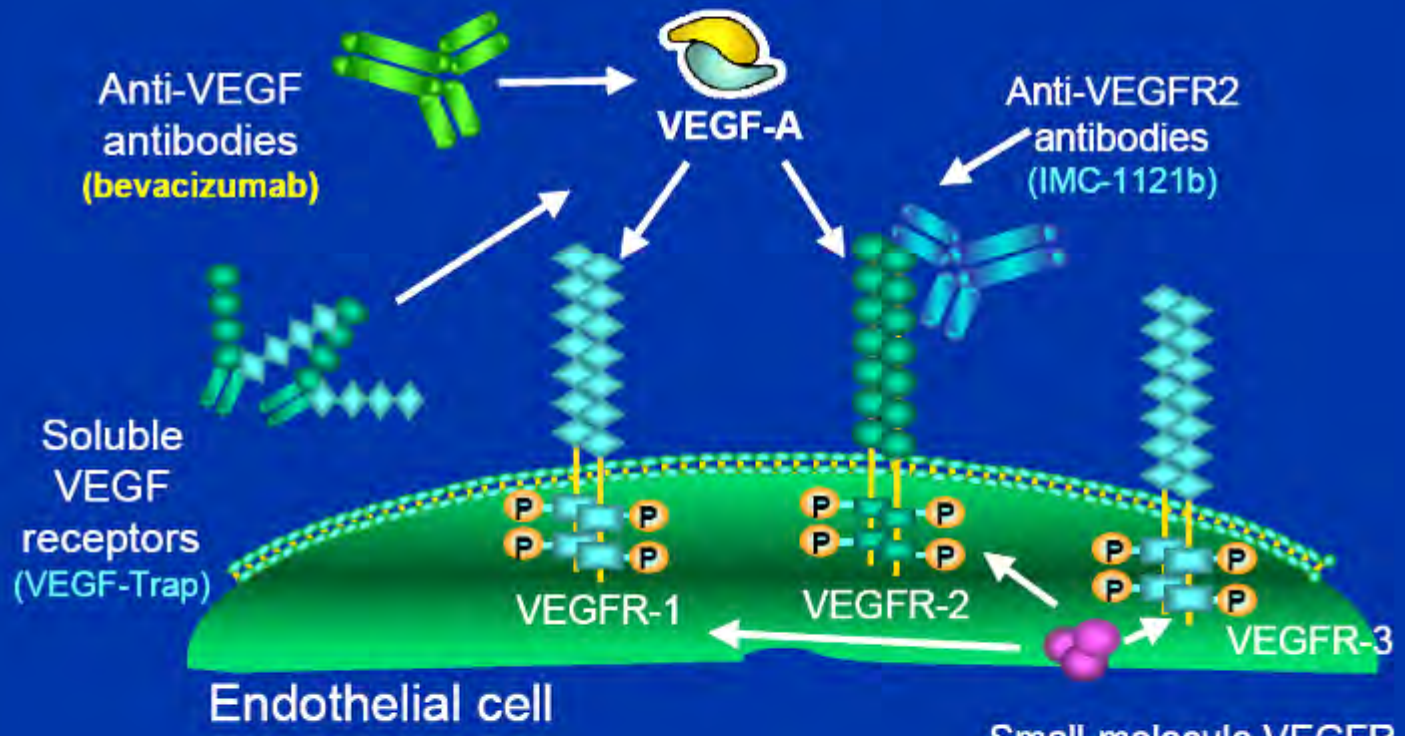
Rapid tumor growth and metastasis



Angiogenic inhibitors may reverse this vascularization

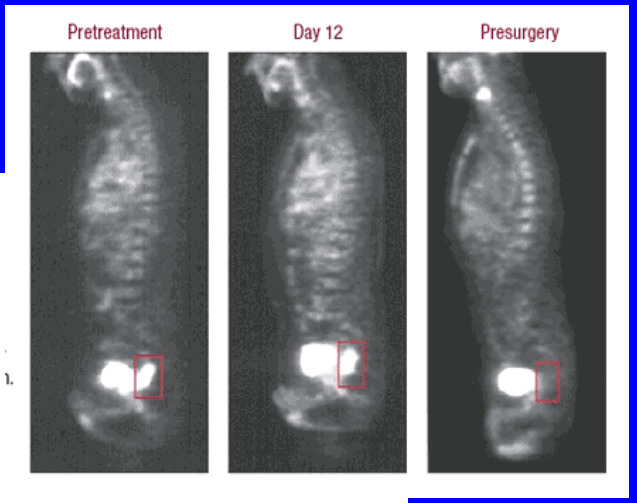
Carmeliet and Jain. *Nature*. 2000;407:249.

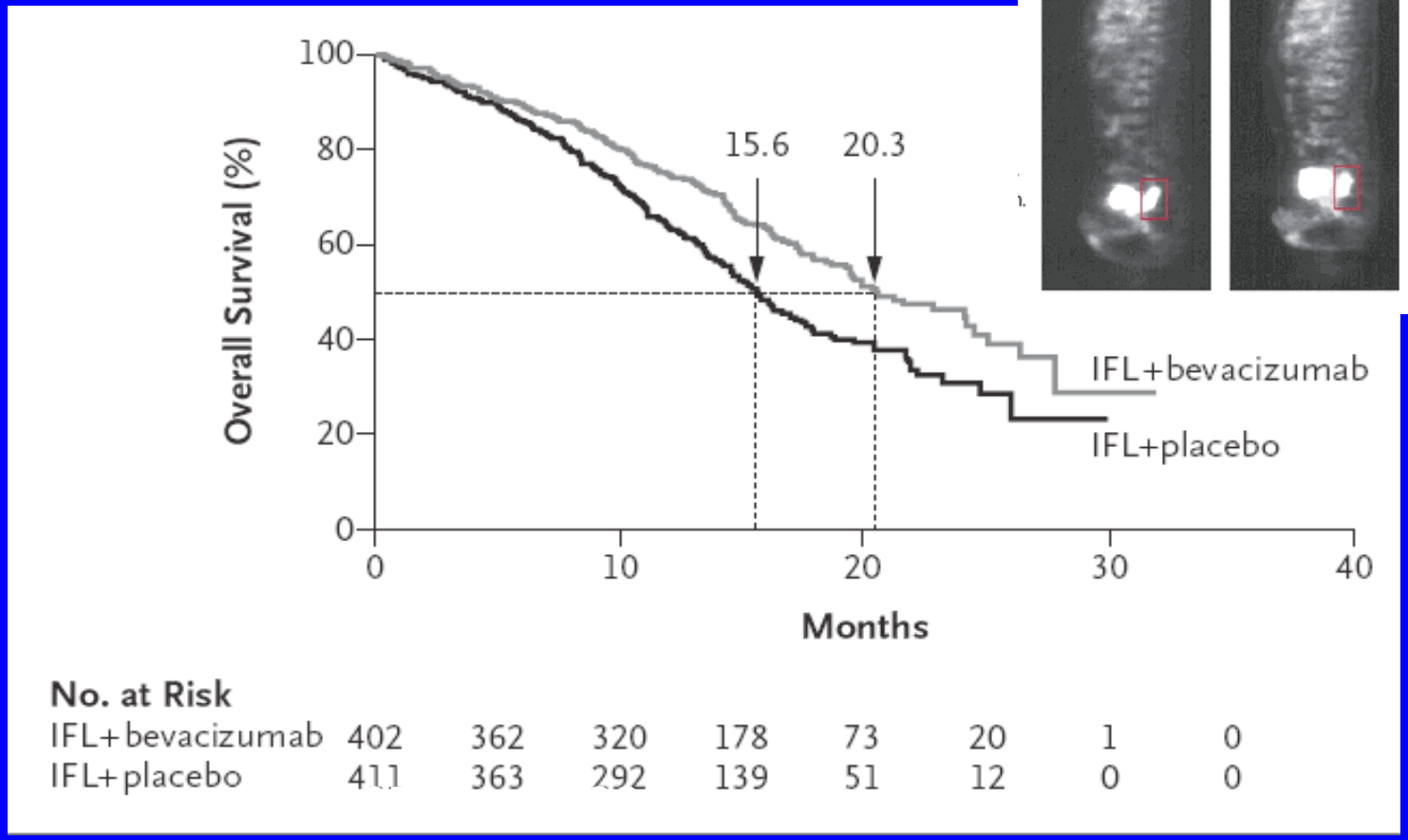
Agents Targeting the VEGF Pathway (>20)



Agents in yellow=FDA approved

Efficacy of Bevacizumab in CRC cancer

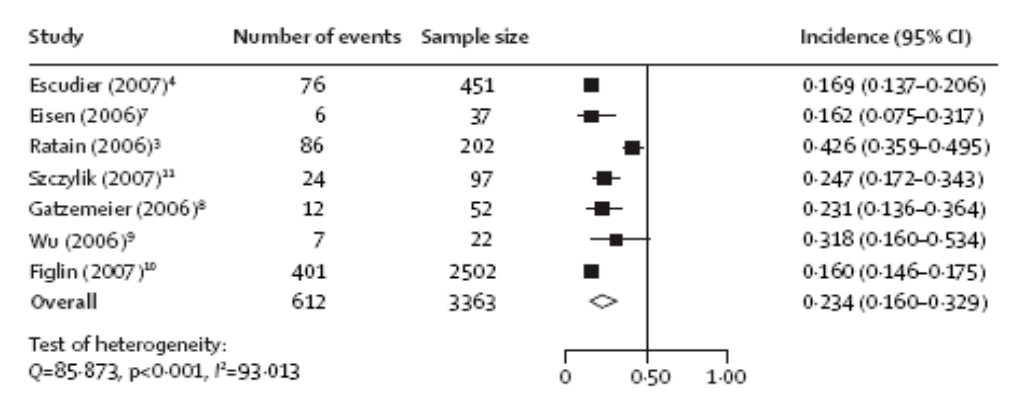




Hurwitz et al. *NEJM 2004*

Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis

Shenhong Wu, John J Chen, Andrzej Kudelka, Janice Lu, Xiaolei Zhu



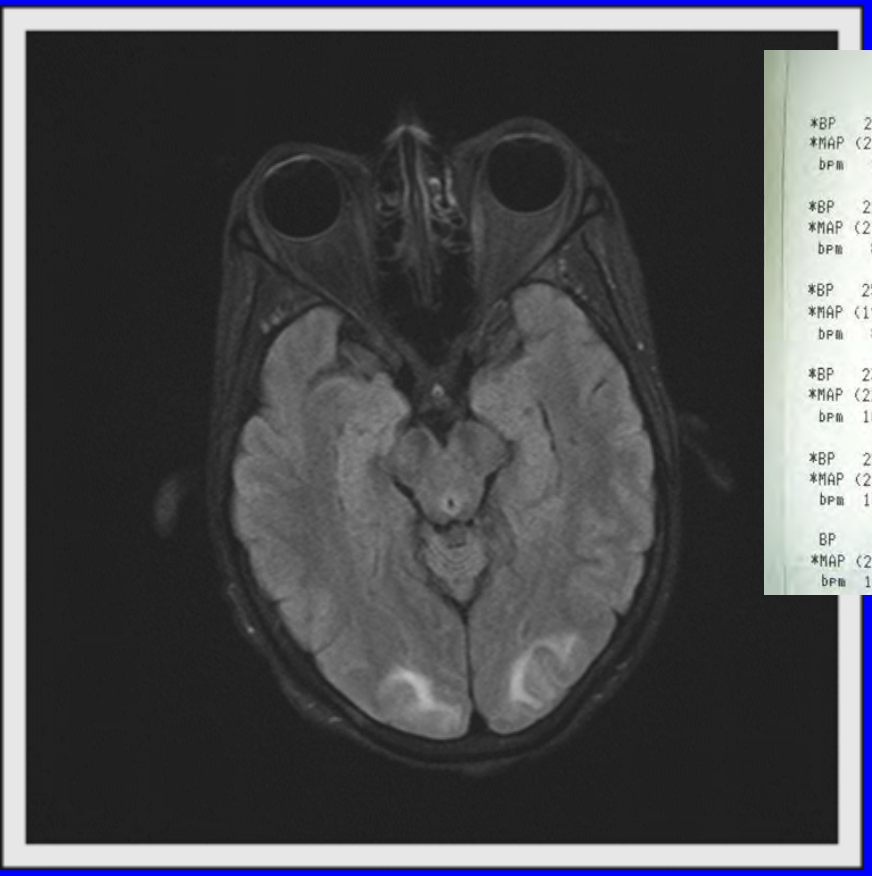
	Molecular target	Incidence of hypertension (95% CI)	Relative risk of hypertension (95% CI)	Ref
Sorafenib	VEGFR-2 and VEGFR-3*; Raf; PDGFR; C-KIT; FLT-3; RET	23·4% (16·0–32·9)	6·1 (2·4–15·3)	This study
Sunitinib	VEGFR-1 and VEGFR-2*; PDGFR; C-KIT; FLT-3; RET	22·5% (19·5–25·9)	3·9 (2·6–5·9)	Zhu X, unpublished data
Bevacizumab	VEGF*	25·4% (21·3–30·1)†	7·5 (4·2–13·4)‡	19
AG013736	VEGFR-1, VEGFR-2, and VEGFR-3*; PDGFR; C-KIT	57·7%	NA	24
VEGF Trap	VEGF*	31·6%	NA	25

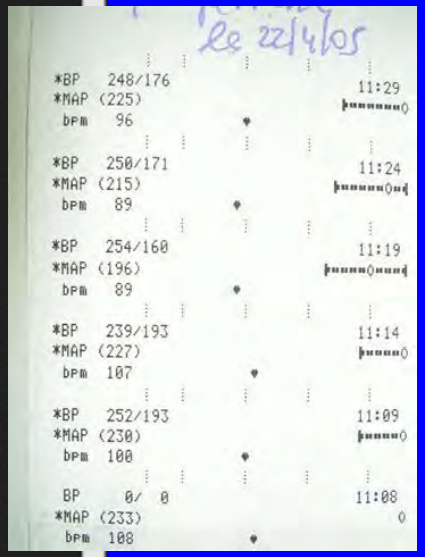
VEGFR=vascular endothelial growth factor receptor. PDGFR=platelet-derived growth-factor receptor. *Targets directly involved in angiogenesis. †Incidence is calculated from patients receiving high-dose bevacizumab (10 or 15 mg/kg per dose) by a meta-analysis using the fixed-effects model. ‡Relative risk is derived from patients receiving high-dose bevacizumab (10 or 15 mg/kg per dose) by use of fixed-effects model. NA=not available.

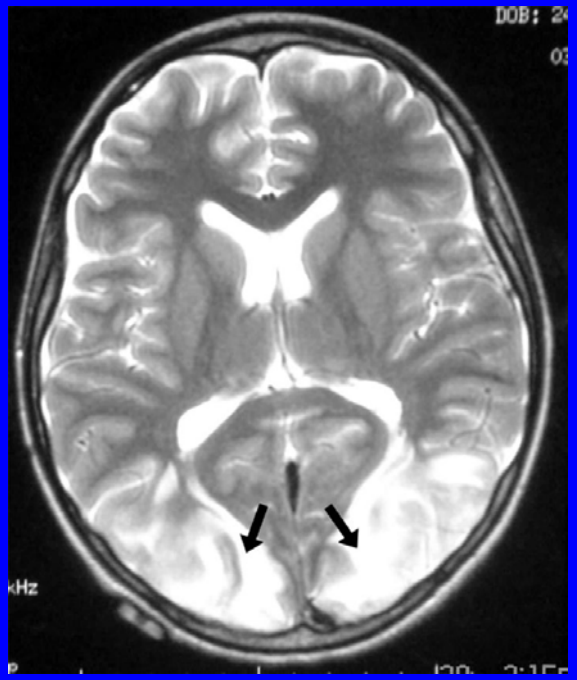
Table 2: Risk of hypertension with angiogenesis inhibitors

Lancet Oncology 2008

Rare cases of reversible posterior leucoencephalopathy syndrome





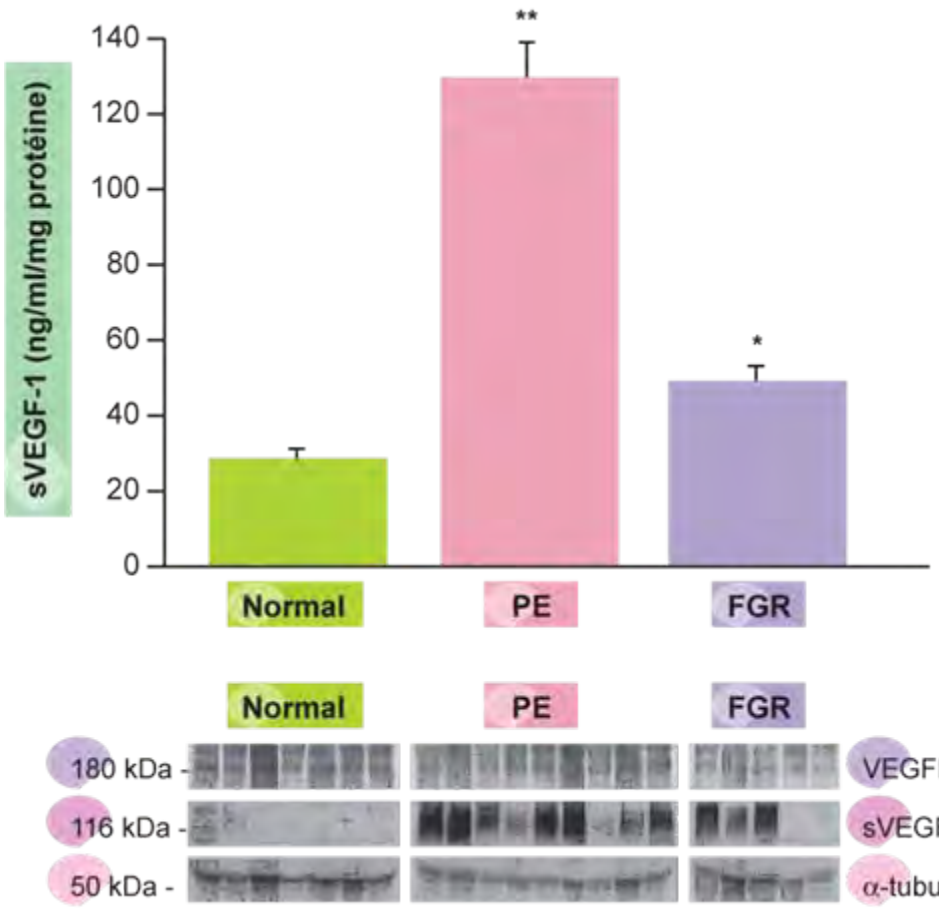


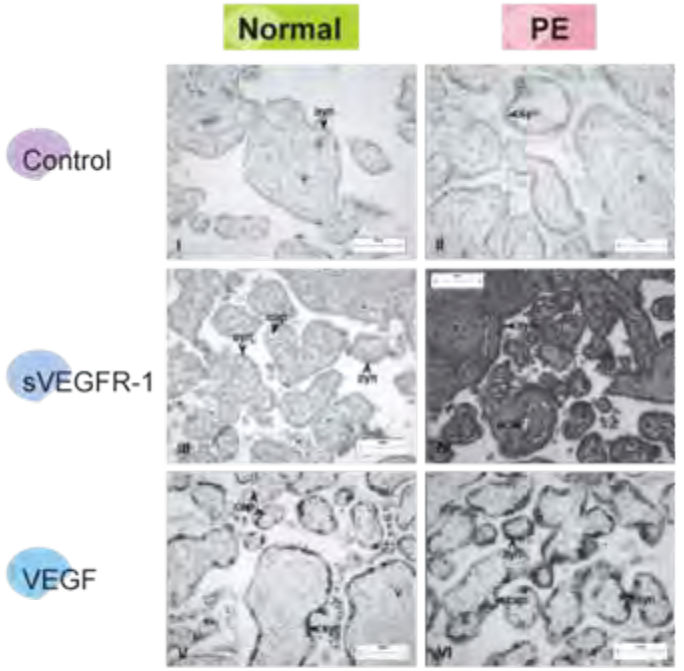
Stott VL, Int Med J. 2005
Glusker P: N Engl J Med 2006
Oczan C: N Engl J Med 2006
Govindarajan R, J Clin Onc 2006
Allen, J. A., Arch Neurol 2006

Preeclampsia

- Elevated Placental Soluble Vascular Endothelial Growth Factor Receptor-1 Inhibits Angiogenesis in Preeclampsia
  - Ahmad S, Ahmed A. Circulation Research. 2004;95:884.

Preeclampsia





Ahmad, S. et al. Circ Res 2004;95:884-891

Et pendant ce temps , en cardiologie...

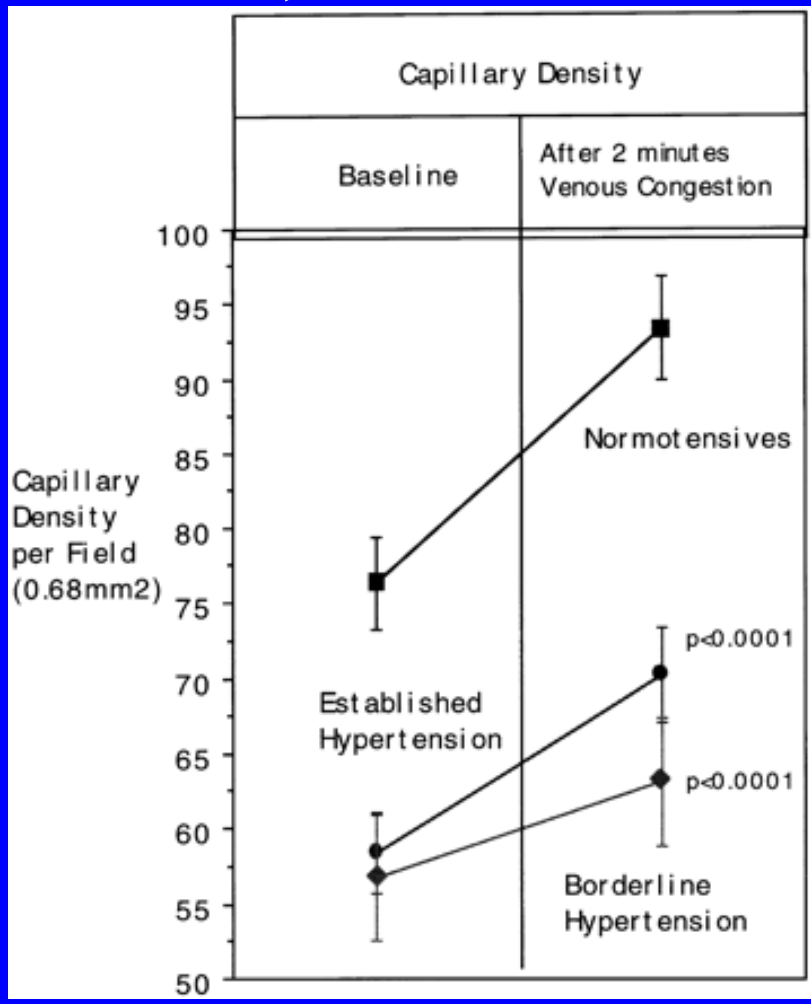
- VEGF: hemodynamic role
  - Dose-related decrease in MAP via nitric oxide and prostacyclin synthesis
  - VIVA trial showed hypotension as dose-limiting effect of infusional VEGF

Circ 2003

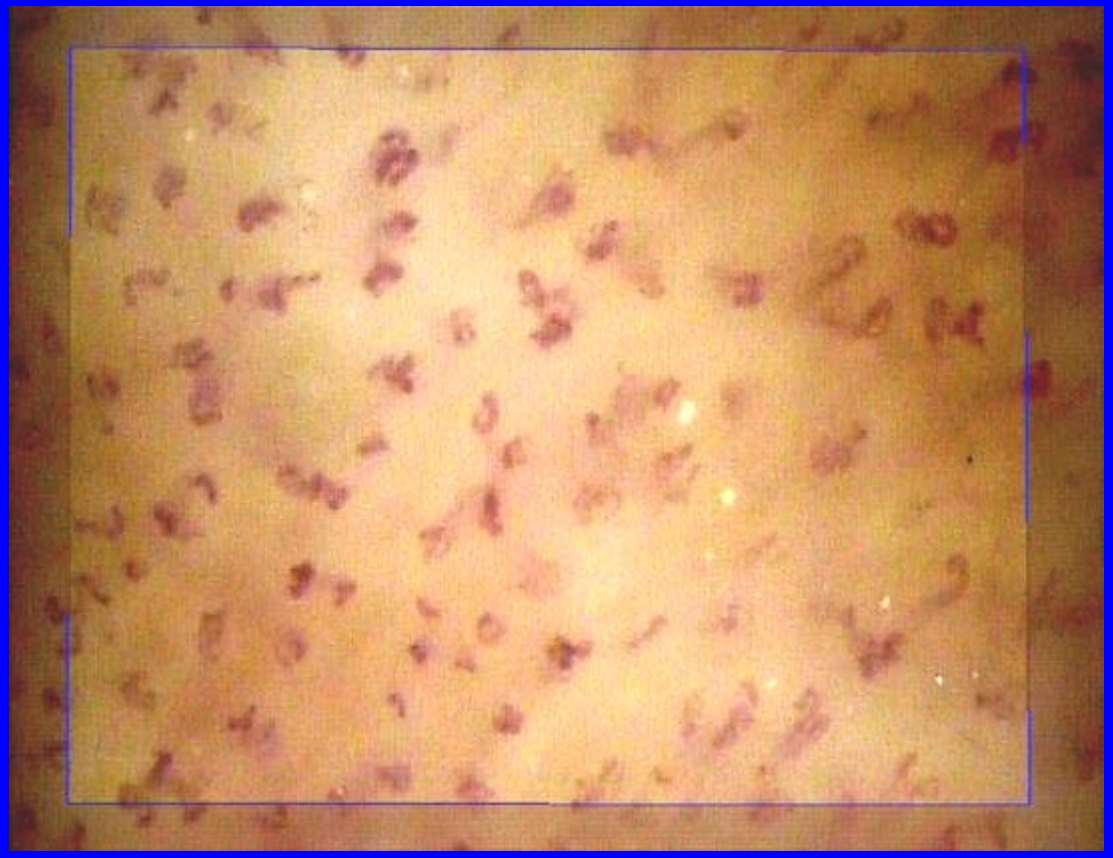
Rarefaction of Skin Capillaries in Borderline Essential Hypertension Suggests an Early Structural Abnormality

Antonios TFT et al. Hypertension. 1999;34:655

Variable	Borderline Hypertensive Patients (n=18)	Established Hypertensive Patients (n=45)	Normotensive Controls (n=32)	*P* value by ANOVA
Age, y	45.4±3.4	47±0±1.8	51.5±2.1	0.179
Gender, men/women	11/7	29/16	18/14	
Weight, kg	76.9±3.7	84.5±3.1	74.2±2.2	0.314
Height, cm	170.0±2.6	171.9±1.5	171.4±1.5	0.787
Body mass index, kg/m^2	26.1±1.0	28.6±0.9†	25.2±0.6	0.009
Hip/waist ratio	119.5±3.0	113.6±1.8*	120.2±2.7	0.065
Blood pressure, mm Hg				
Supine	136/83±3/1†	156/98±2/1‡	126/77±2/1	<0.0001



Videocapillaroscopy



1 mm

1 mm

X 200

Capillary density is the mean of 4 fields measurements in a selected 3 by 3 mm area of the middle third of the phalanx

Objective

As far as microvascular rarefaction has been reported in all forms of human and experimental HT, we tested the hypothesis that anti VEGF therapy could induce microvascular rarefaction in non-tumoral tissues and, thus, result in an increase in BP.

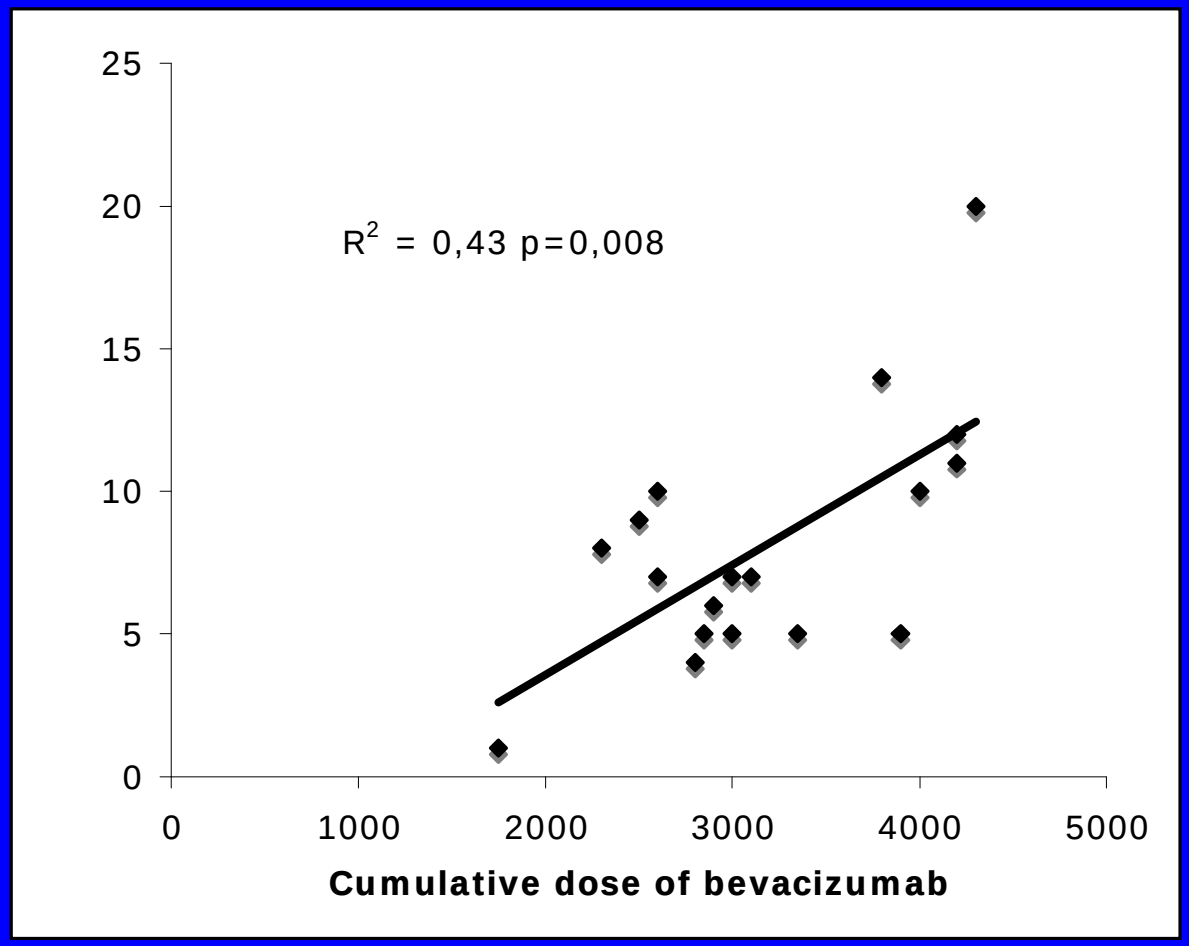
Results

N=18	Baseline	6 months	P (student paired test)
SBP (mmHg)	129 ± 13	145 ± 17	0.0001
DBP (mmHg)	75 ± 7	82 ± 7	0.0001
Basal capillary density (cap/field)	84 ± 13	75 ± 12	0.0001
Maximal capillary density (cap/field)	90 ± 13	81 ± 11	0.0001

No significant change in weight, serum creatinine, or other biological parameters occured during the follow-up.

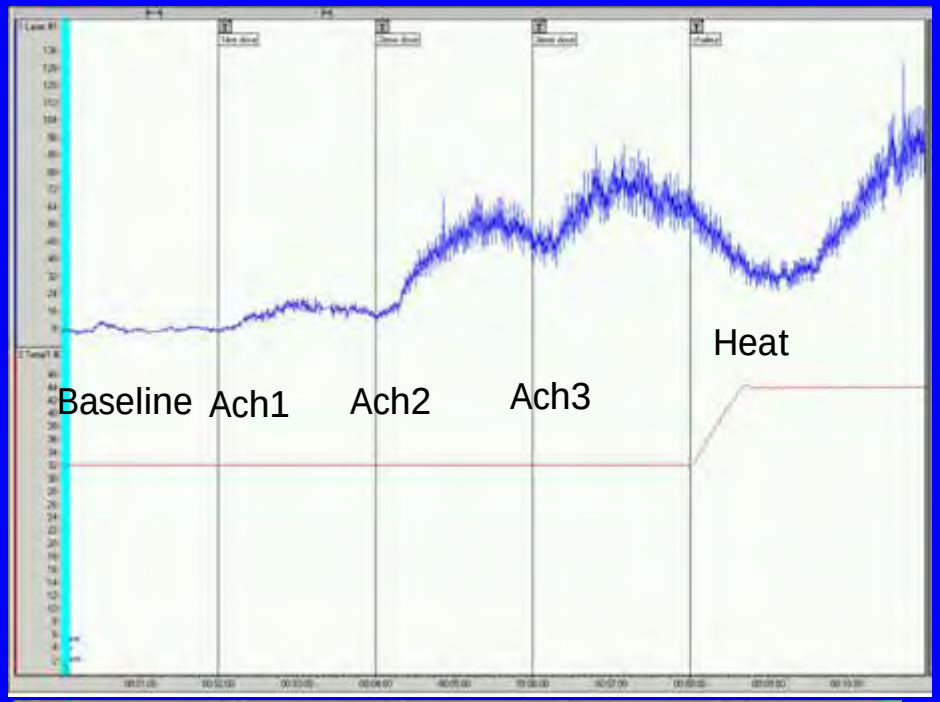
Mourad JJ. Ann Oncol. 2008 ;19:927

Bevacizumab dose-dependent effect on capillary density

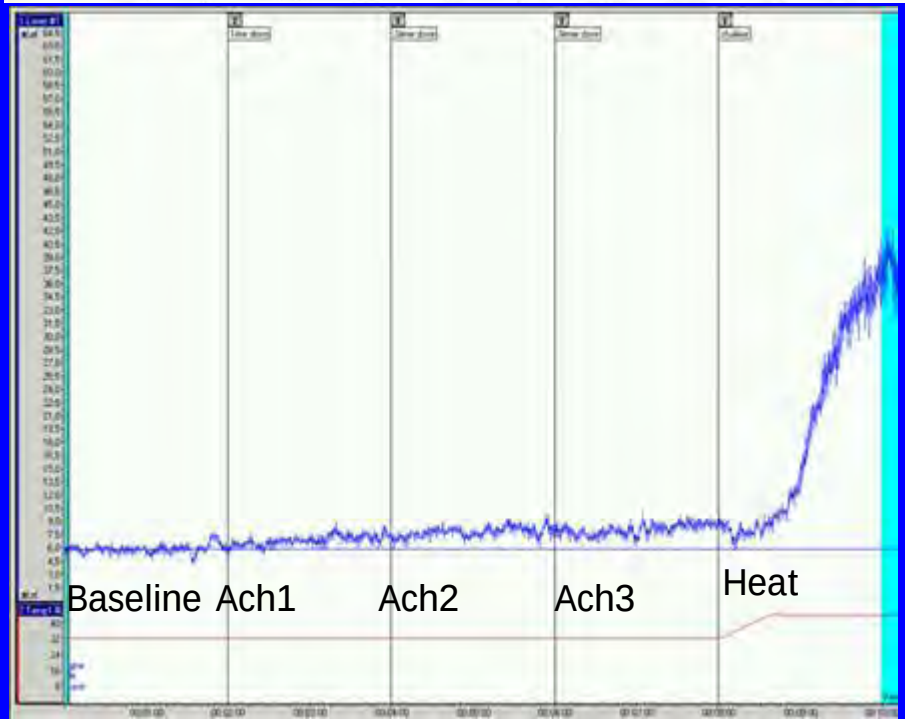


Mourad JJ . Ann Oncol. 2008 ;19:927

Before treatment

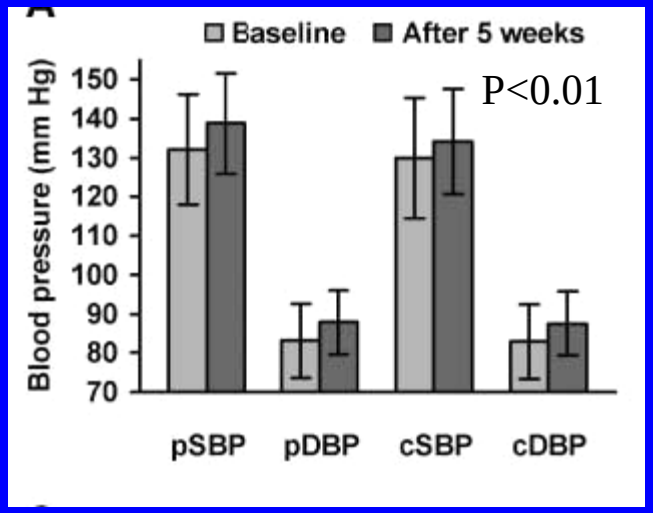


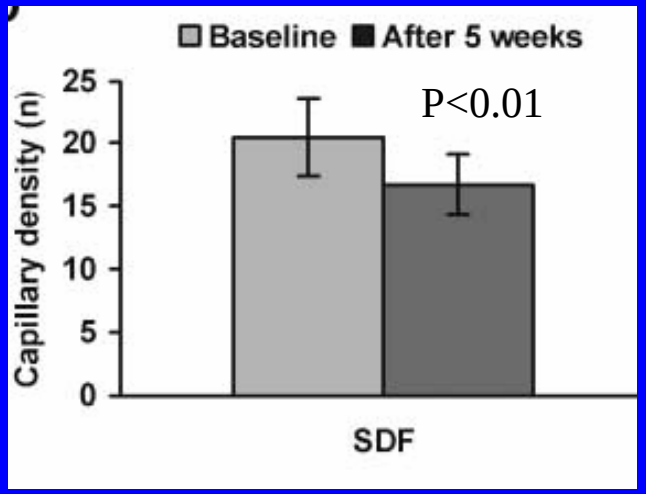
At 6 months



Hypertension and Rarefaction during Treatment with Telatinib, a Small Molecule Angiogenesis Inhibitor

Neeltje Steeghs,[1,3] Hans Gelderblom,[1] Jos op 't Roodt,[2] Olaf Christensen,[5] Prabhu Rajagopalan,[5] Marcel Hovens,[3] Hein Putter,[4] Ton J. Rabelink,[2] and Eelco de Koning[2]





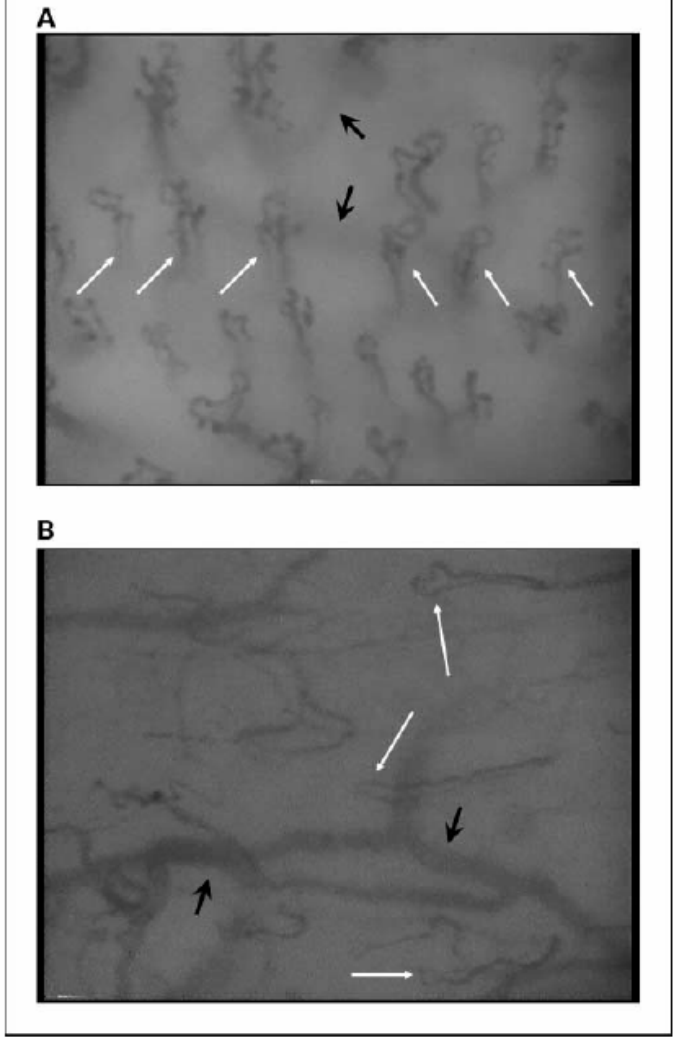


Fig. 2. SDF images demonstrating visible capillary loops of a representative patient. *A*, at baseline. *B*, after 5 wk of telatinib treatment. Black arrows, larger venules; white arrows, individual superficial capillary loops.

Clin Cancer Res 2008

VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature

Tomomi Kamba,[1] Betty Y. Y. Tam,[2] Hiroya Hashizume,[1] Amy Haskell,[1]
Barbara Sennino,[1] Michael R. Mancuso,[1] Scott M. Norberg,[1] Shaun M. O'Brien,[1]
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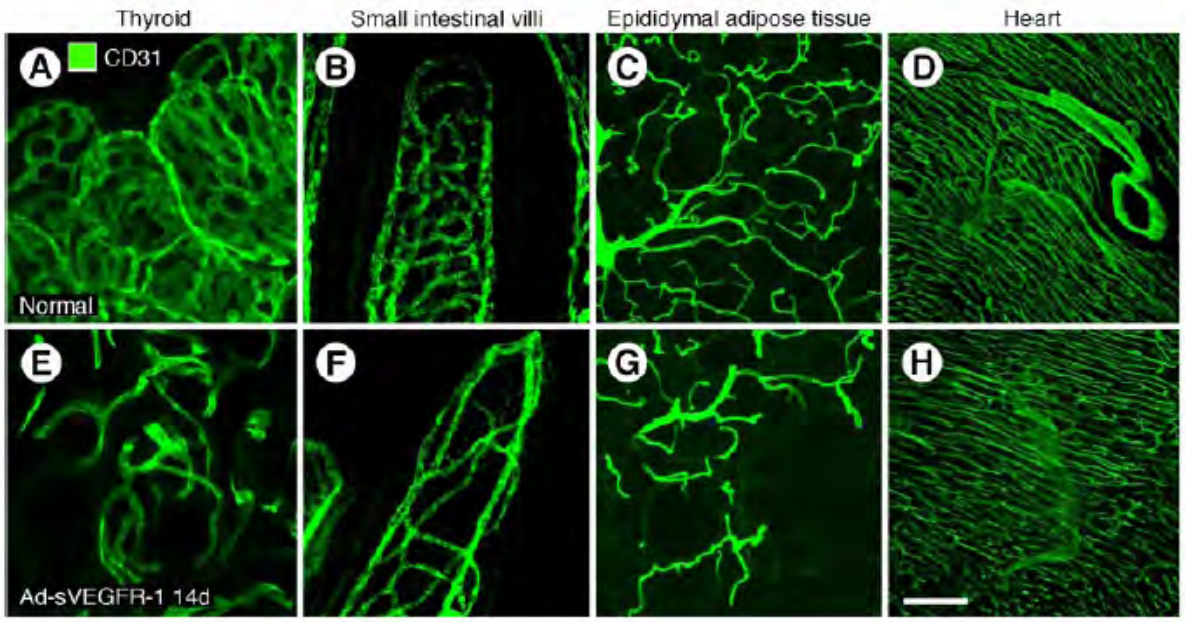
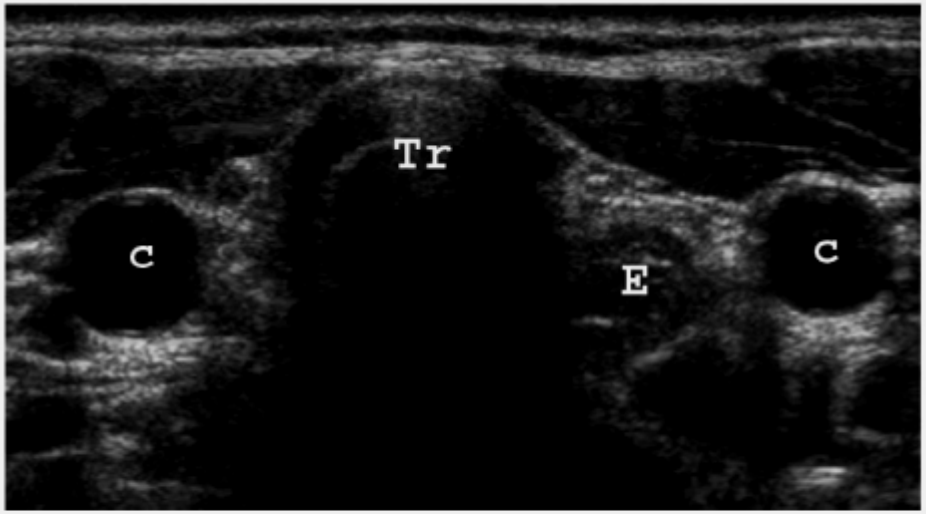
Shuji Joho,[3] Matthew L. Springer,[3] Calvin J. Kuo,[2] and Donald M. McDonald[1]



Kamba T. Am J Physiol 2006

Hypothyroidism after Sunitinib Treatment for Patients with Gastrointestinal Stromal Tumors

Jayesh Desai, MD; Leila Yassa, MD; Ellen Marqusee, MD; Suzanne George, MD; Mary C. Frates, MD; Ming Hui Chen, Jeffrey A. Morgan, MD; Samuel S. Dychter, MD; P. Reed Larsen, MD; George D. Demetri, MD; and Erik K. Alexander, M



No thyroid tissue is visualized. C = carotid artery; E = esophagus; TR = trachea.

Table. Serum Thyroid-Stimulating Hormone Concentrations in 15 Patients Who Developed Hypothyroidism during Sunitinib Therapy for the Treatment of Gastrointestinal Stromal Tumors

Patient	Age, *y*	Duration of Sunitinib Therapy, *wk*	Time to Persistent Elevation of TSH Levels, *wk*	TSH Concentrations during Sunitinib Therapy, *mU/L*		Evidence of Thyroiditis†
				Baseline	Maximum	
1	37	98	55	1.6	288	No
2	36	151	53	3.9	247	Yes
3	26	79	71	4.6	99	No
4	57	102	84	0.9	94	Yes
5	68	105	38	0.7	56	No
6	77	94	29	2.4	32	No
7	69	167	94	1.5	31	No
8	37	162	28	2.4	30	Yes
9	44	99	64	0.4	24	Yes
10	68	17	12	2.8	12	No
11	45	129	12	3.7	11	No
12	73	86	86	2.2	11	No
13	47	95	53	1.8	9.0	No
14	58	132	41	1.3	7.6	Yes
15	44	37	31	1.4	7.2	Yes

During the phase I/II trial of sunitinib, 15 of 42(36%) patients developed hypothyroidism after an average of 50 weeks of therapy (range, 12 to 94 weeks)

Ann Intern Med 2006

See also Mannavola D; JCEM 2007

Role of VEGF in maintaining renal structure and function under normotensive and hypertensive conditions

Andrew Advani*†‡, Darren J. Kelly†, Suzanne L. Advani*†‡, Alison J. Cox†, Kerri Thai*, Yuan Zhang†, Kathryn E. White‡, Renae M. Gow†, Sally M. Marshall‡, Brent M. Steer*, Philip A. Marsden*, P. Elizabeth Rakoczy§, and Richard E. Gilbert*†¶

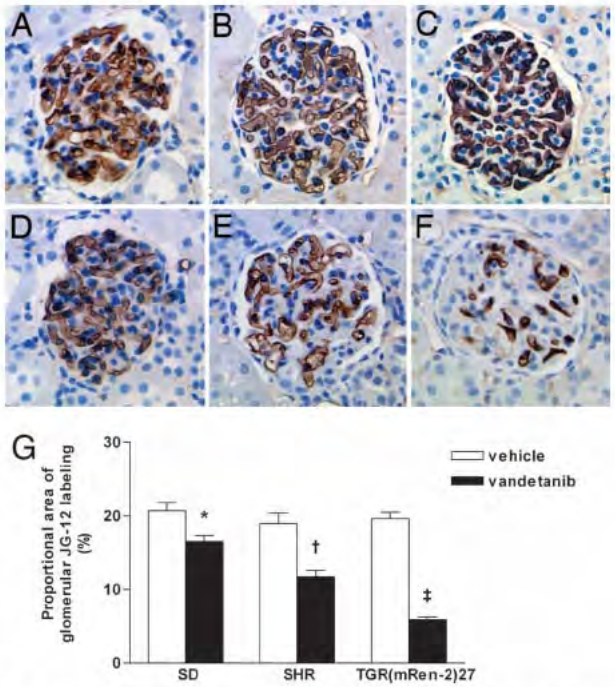
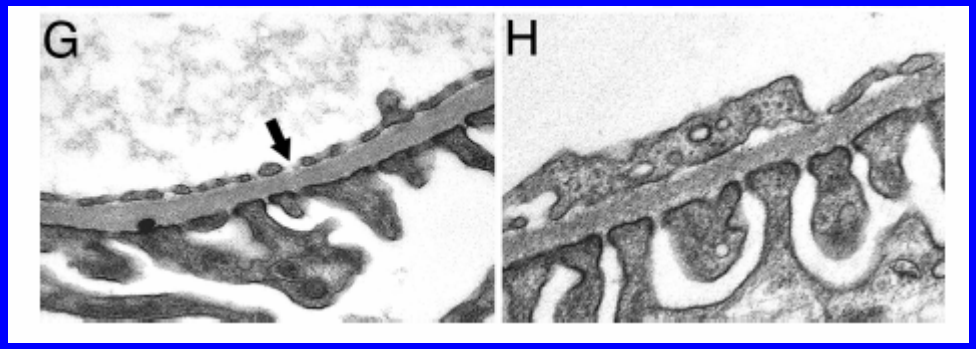


Fig. 3. Endothelial cell immunohistochemistry (JG-12 labeling) in kidney sections from vehicle-treated animals. (*A–C*) SD rat (*A*), SHR (*B*), TGR(mRen-2)27 rat (*C*). (*D–F*) After vandetanib, SD rat (*D*), SHR (*E*), and TGR(mRen-2)27 rat (*F*). (Magnification: ×400.) (*G*) Quantitative assessment of glomerular capillary endothelial density, $n = 10$ per group. *, $P < 0.05$ vs. SD + vehicle; †, $P < 0.001$ vs. SHR + vehicle; ‡, $P < 0.001$ vs. TGR(mRen-2)27 + vehicle.



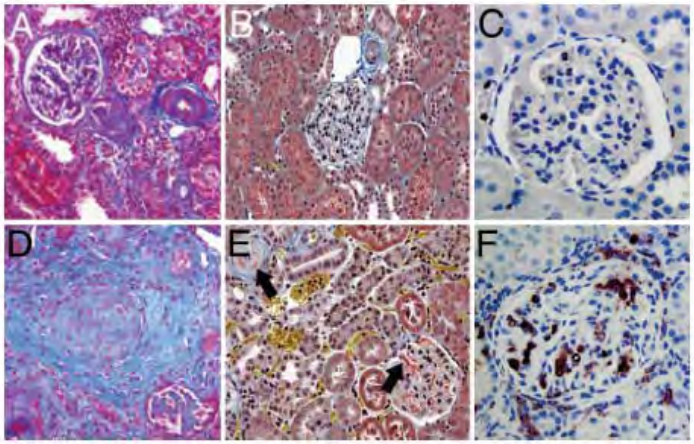


Fig. 5. Kidney sections from TGR(mRen-2)27 rats treated with vehicle (*A–C*) and after vandetanib (*D–F*), stained with Masson's trichrome (*A* and *D*; magnification ×200), Martius scarlet blue (*B* and *E*; magnification ×200) and after ED-1 labeling (*C* and *F*; magnification ×400). Vandetanib treatment led to myointimal proliferation and collagen deposition (blue, *D*), with intraarteriolar and intraglomerular fibrin deposition (red, arrow, *E*). ED1 immunostaining showed glomerular and cortical interstitial macrophage infiltration with vandetanib (*F*).

PNAS 2007;104:14448

VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature

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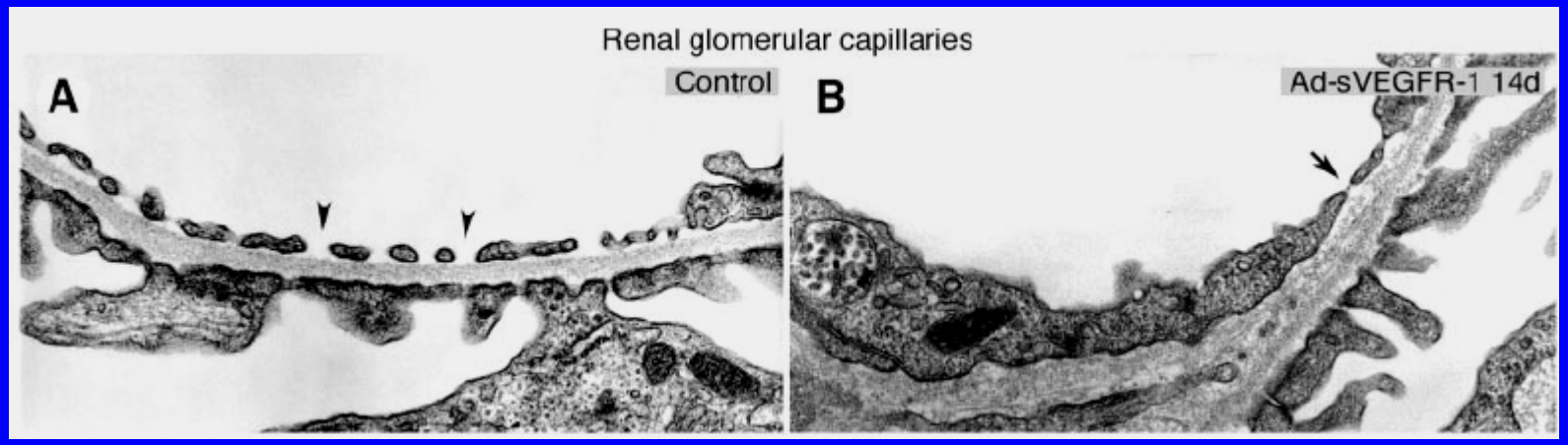
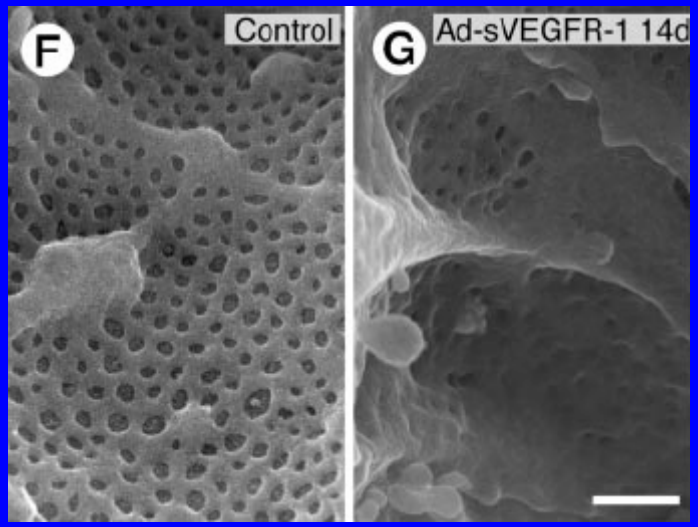
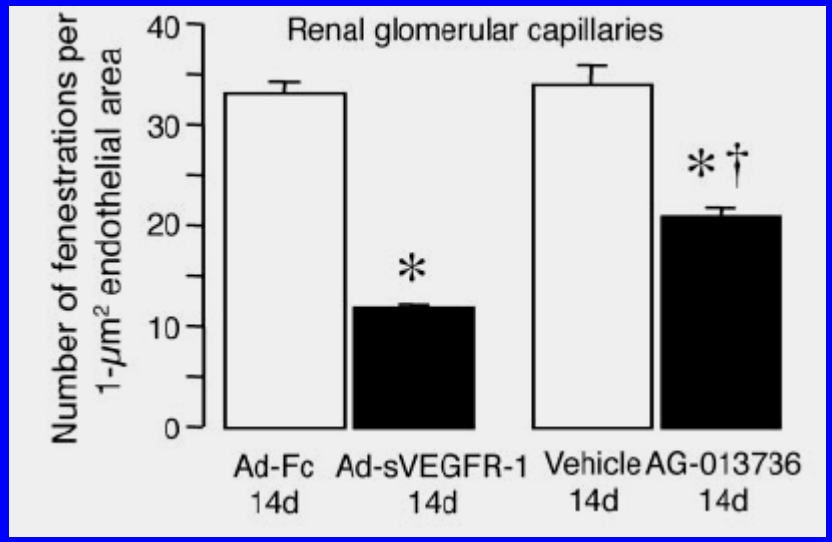






Kamba T. Am J Physiol 2006

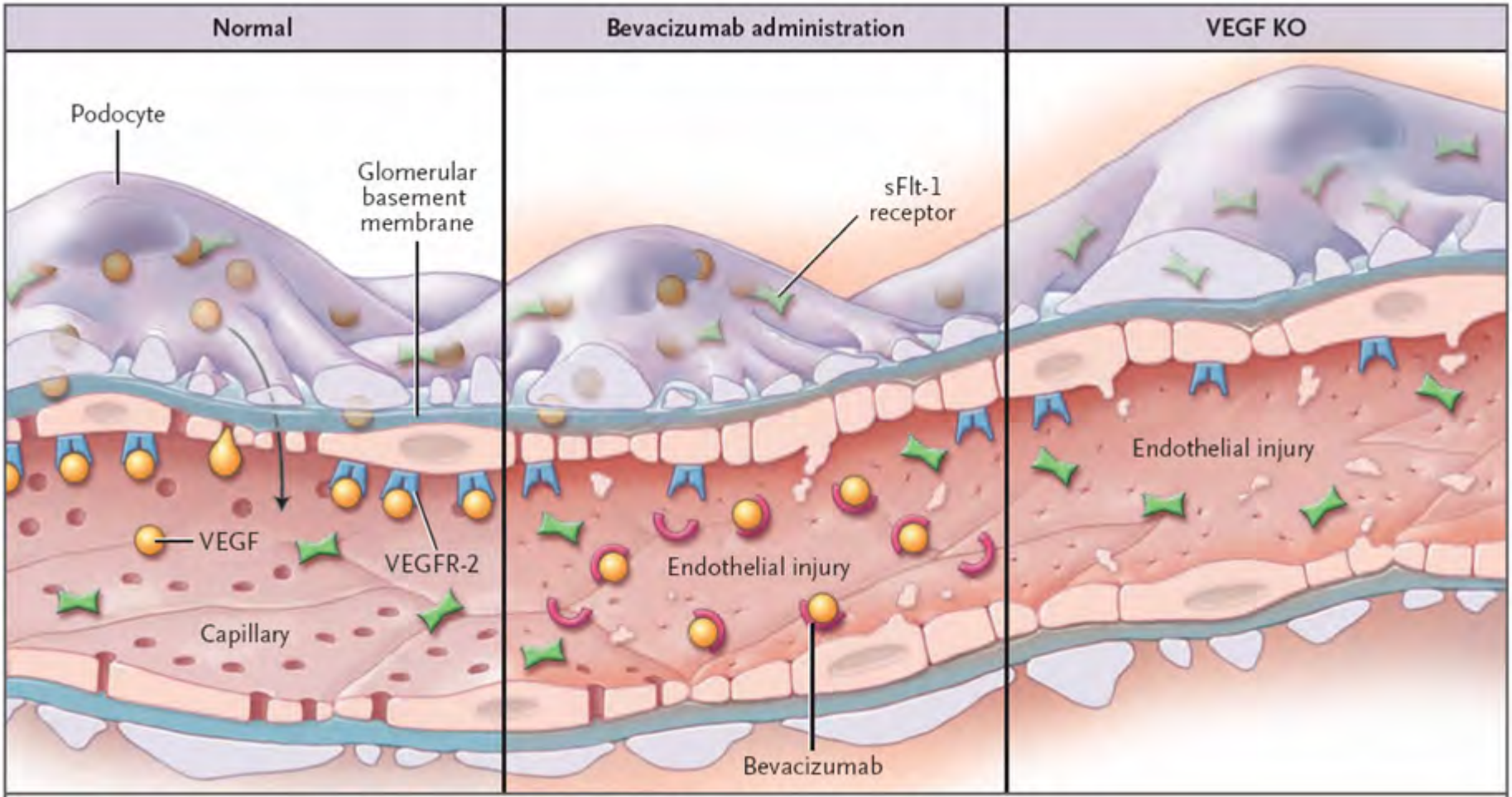


Figure 3. Hypothetical Model of Disruption of VEGF Signaling in Renal Thrombotic Microangiopathy.

Eremina V NEJM 2008

VEGF plays a key role in vascular homeostasis

- Normal blood vessels are generally thought not to require VEGF for survival
- Inhibition of VEGF signaling for 1 to 3 weeks revealed significant capillary regression in pancreatic islets, thyroid, adrenal cortex, pituitary, choroid plexus, small intestinal villi, and epididymal adipose tissue.
- The amount of regression was dose-dependent and varied from organ to organ, with a maximum of 68% in thyroid, but was less in normal organs than in tumors in the mouse models studied.
- All VEGF inhibitors studied had this effect.

Kamba T. Am J Physiol 2006

HTN: NCI Common Toxicity Criteria

- Grade 1 asx, transient increase (< 24hr)greater than 20mmHg (diastolic) or to greater than 150/100 mmHg

- Grade 2 recurrent or persistent (>24 hrs) or sx increase greater than 20 mmHg (diastolic) or to greater than 150/100 mmHg

- Grade 3 HTN requiring therapy or more intensive therapy than previously

- Grade 4 hypertensive crisis

Hypertension as a predictive factor of Sunitinib activity (metastatic renal carcinoma)

32 patients followed for 6 months

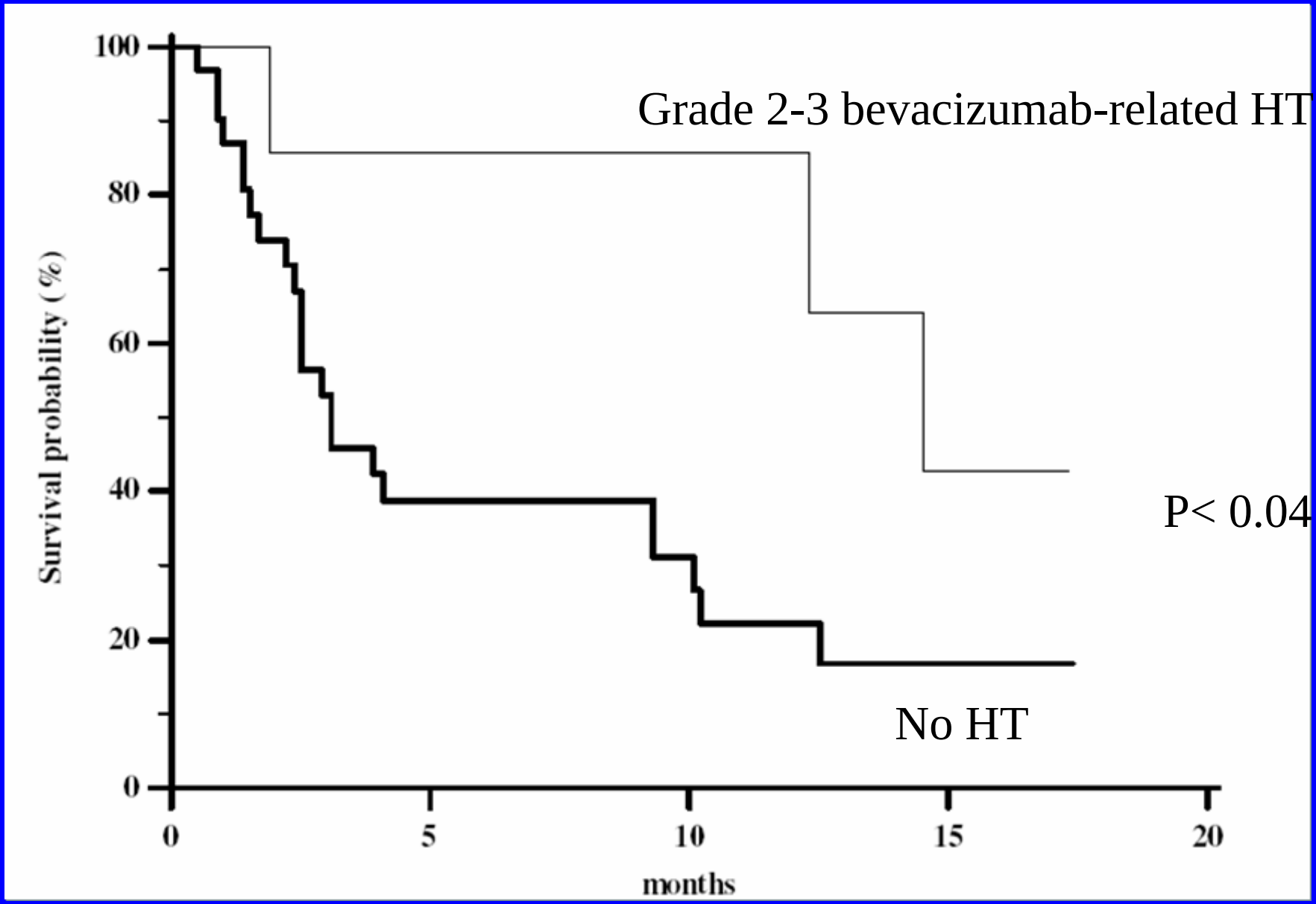
22% hypertensive

The appearance of HT (grade 3) was associated with better response to sunitinib ($p<0.02$)

Rixe O et al. Ann Oncol 2007;18:1125

	Patients with bevacizumab-related hypertension	Patients without bevacizumab-related hypertension	p
M/F	3/5 (37.5%)	22/9 (71%)	ns
Age at diagnosis (range)	53 yrs (48-70)	58 yrs (30-69)	ns
Primary tumor (colon/rectum)	6/2	24/7	ns
Sites of metastasis (%)			
Liver	6 (43%)	26 (60%)	ns
Lung	2 (14%)	6 (14%)	
Peritoneum	1 (7%)	4 (9%)	
Distant lymph-nodes	4 (29%)	6 (14%)	
Bone	1 (7%)	1 (2%)	
Response rate (%)	6/8 (75%)	10/31 (32%)	0.04
Median PFS (months)	14.5	3.1	0.04

Scartozzi M et al; Ann Oncology oct 2008; Epub



Scartozzi M et al; Ann Oncology oct 2008; Epub

Clinical Course of Advanced Non–Small-Cell Lung Cancer Patients Experiencing Hypertension During Treatment With Bevacizumab in Combination With Carboplatin and Paclitaxel on ECOG 4599

Suzanne E. Dahlberg, Alan B. Sandler, Julie R. Brahmer, Joan H. Schiller, and David H. Johnson

High blood pressure (HBP) by the end of cycle 1 was defined as blood pressure 150/100 at any previous time or at least a 20-mmHg increase in diastolic blood pressure from baseline.

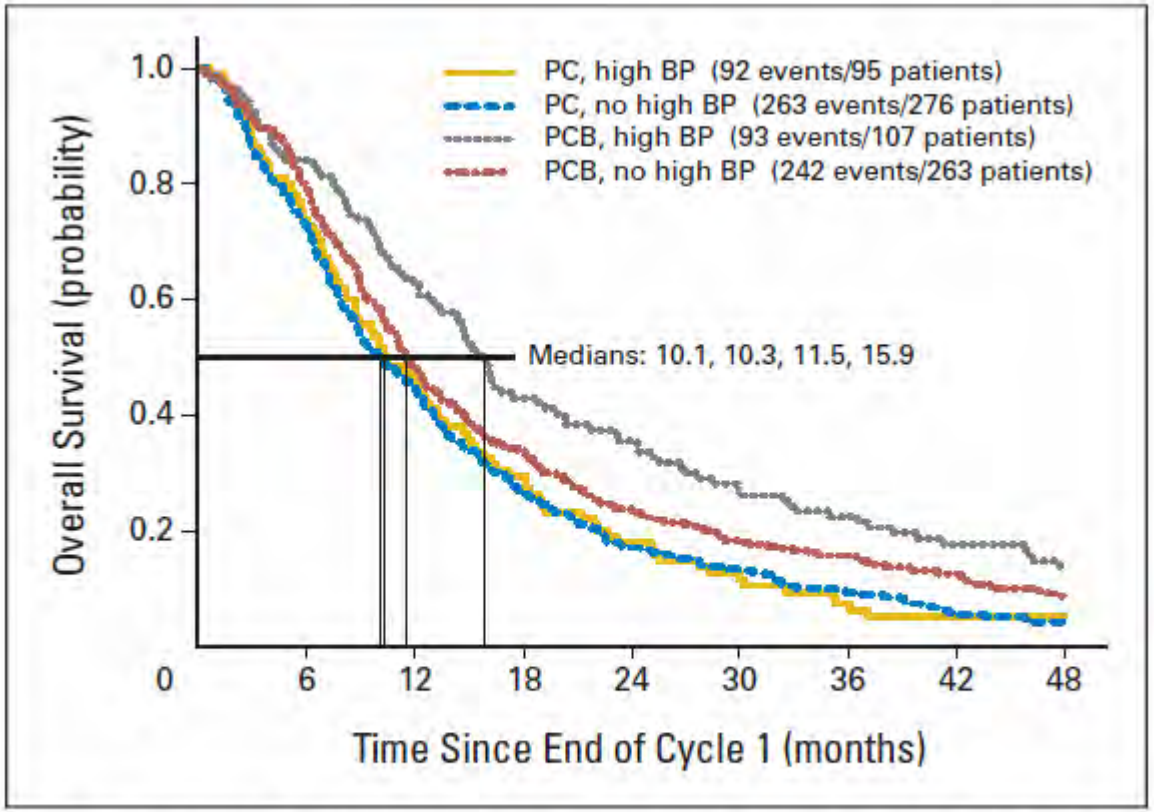


Fig 1. Landmark analysis of overall survival after one cycle of therapy. PC, carboplatin and paclitaxel; BP, blood pressure; PCB, PC + bevacizumab.

J Clin Oncol 2010 28:949-954

Combination Targeted Therapy With Sorafenib and Bevacizumab Results in Enhanced Toxicity and Antitumor Activity

Nilofer S. Azad, Edwin M. Posadas, Virginia E. Kwitkowski, Seth M. Steinberg, Lokesh Jain, Christina M. Annunziata, Lori Minasian, Gisele Sarosy, Herbert L. Kotz, Ahalya Premkumar, Liang Cao, Deborah McNally, Catherine Chow, Helen X. Chen, John J. Wright, William D. Figg, and Elise C. Kohn

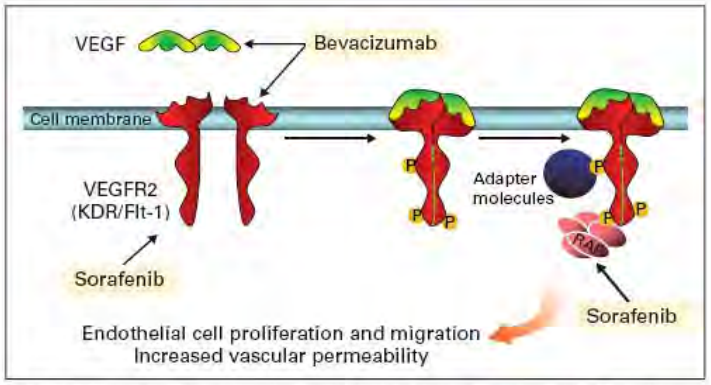


Fig 1. Targeting the vascular endothelial growth factor (VEGF) pathway. Sorafenib and bevacizumab cooperate to dampen the signaling of the VEGF pathway in series. Bevacizumab binds free VEGF, whereas sorafenib targets the VEGF-2 receptor as well as Raf kinase, which is a downstream effector of the VEGF receptor.

Table 1. Dose Levels

Dose Level	No. of Patients	Sorafenib (mg bid)	Bevacizumab (mg/kg q 2 weeks)	Range of Cycles
1	Cohort 1: 6 Cohort 2: 27	200	5	1-22+
2	6	200	10	3-6
3	0	400	10	(did not accrue)

Table 3. Grade 2 to 5 Toxicity by Maximum Grade per Patient (N = 39)*

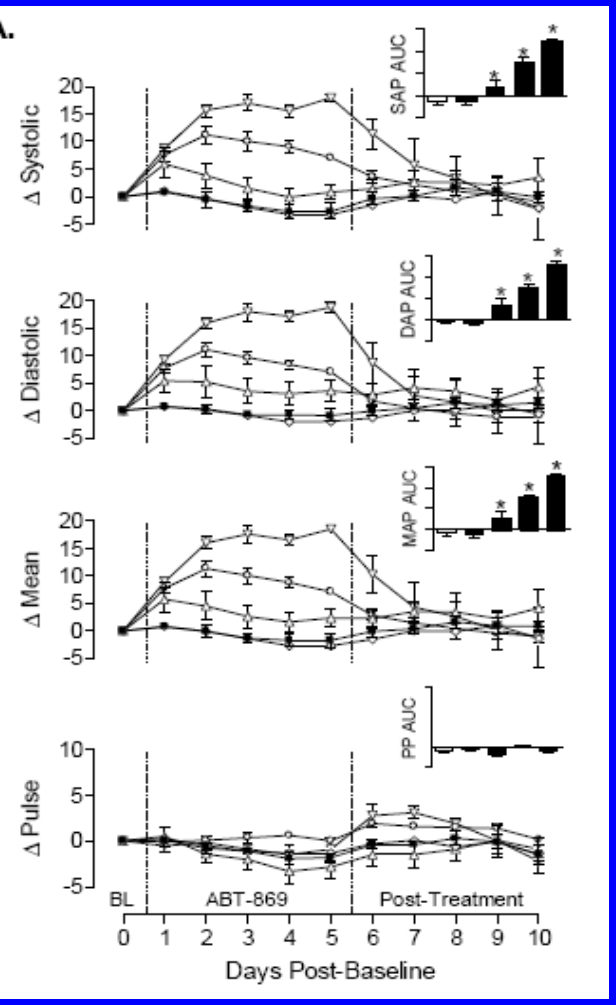
	Toxicity Grade (No. of patients)					
	Grade 2		Grade 3		Grade 4	
Toxicity	DL1	DL2	DL1	DL2	DL1	DL2
Diarrhea	1	1	4	1	0	0
Fatigue	10	2	3	0	0	0
Fistula	1	1	0	0	0	0
Hand-foot syndrome	18†	4	0	1	0	0
Hypertension	12	1	8	4	1	0
Perforation	0	0	1	0	0	0
Proteinuria	3	1	0	2‡	0	0
Thrombocytopenia	1	0	0	1‡	0	0
Thrombosis	0	0	2	0	1	0
Transaminitis	9	0	3	0	1	0

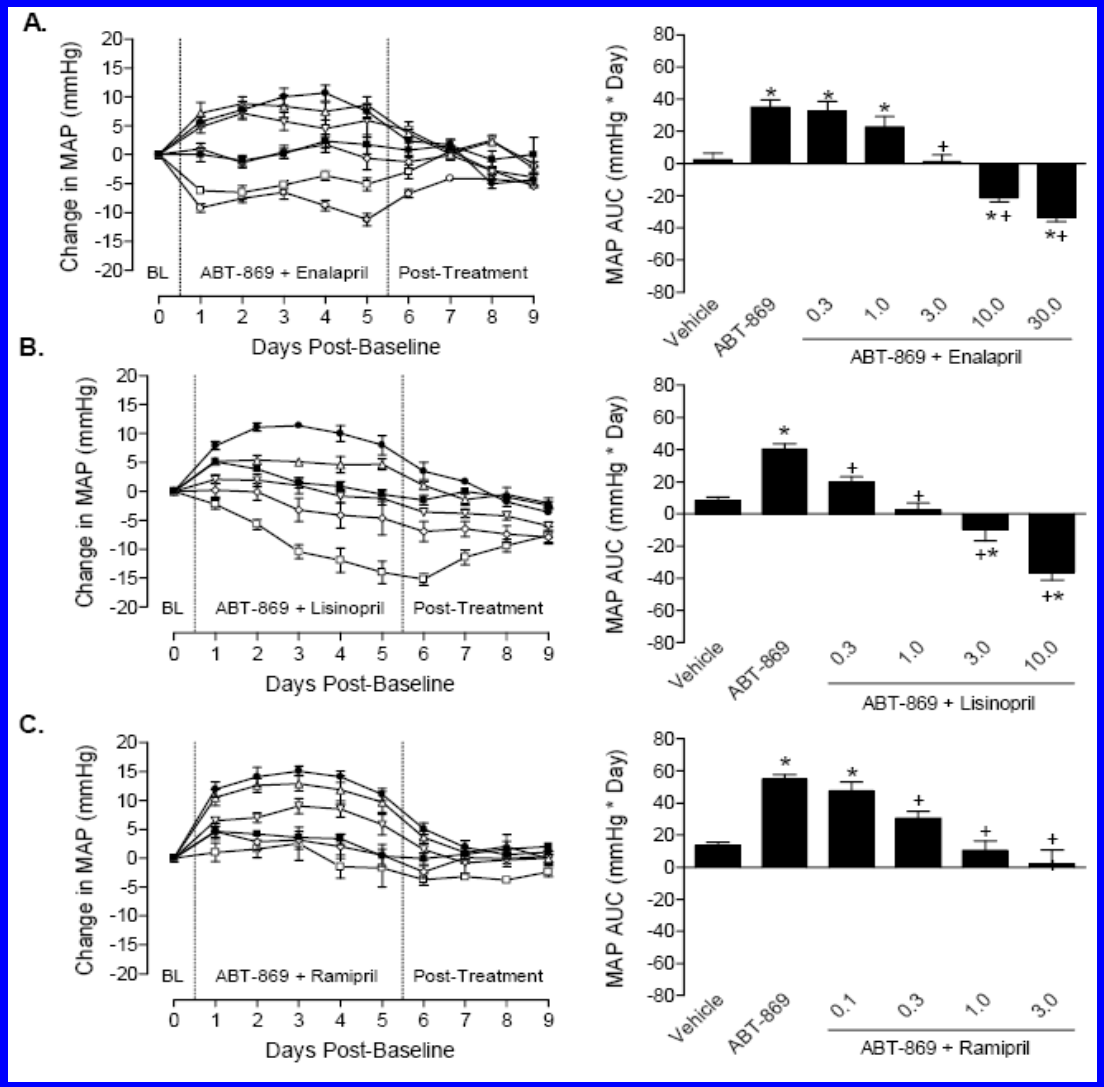
Abbreviations: DL1, dose level 1; DL2, dose level 2.
*Cohort 2 (translational) patients enrolled on DL1 dosage (n = 24).
†Recurrent grade 2 hand-foot syndrome was the dose-limiting toxicity in DL1.
‡Dose-limiting toxicity in DL2.

HT : 26 patients/39 (67%)

J Clin Oncol 2008

Effect of the Multi-targeted Receptor Tyrosine Kinase Inhibitor, ABT-869, on Blood Pressure in Conscious Rats and Mice: Reversal with Anti-Hypertensive Agents and Effect on Tumor Growth Inhibition.





Franklin P; J Pharmacol Exp Ther. 2009 Mar 2. [Epub]

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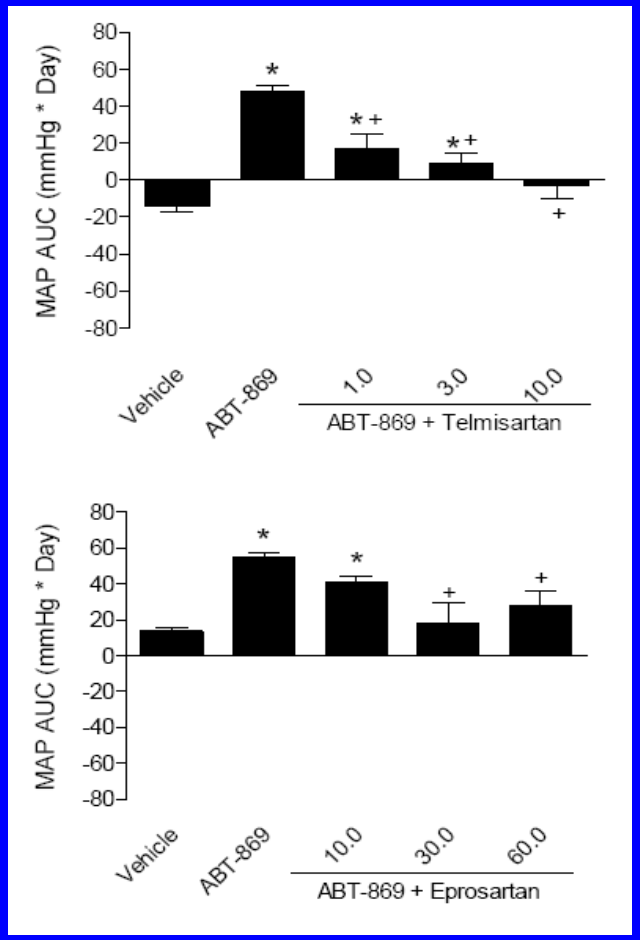
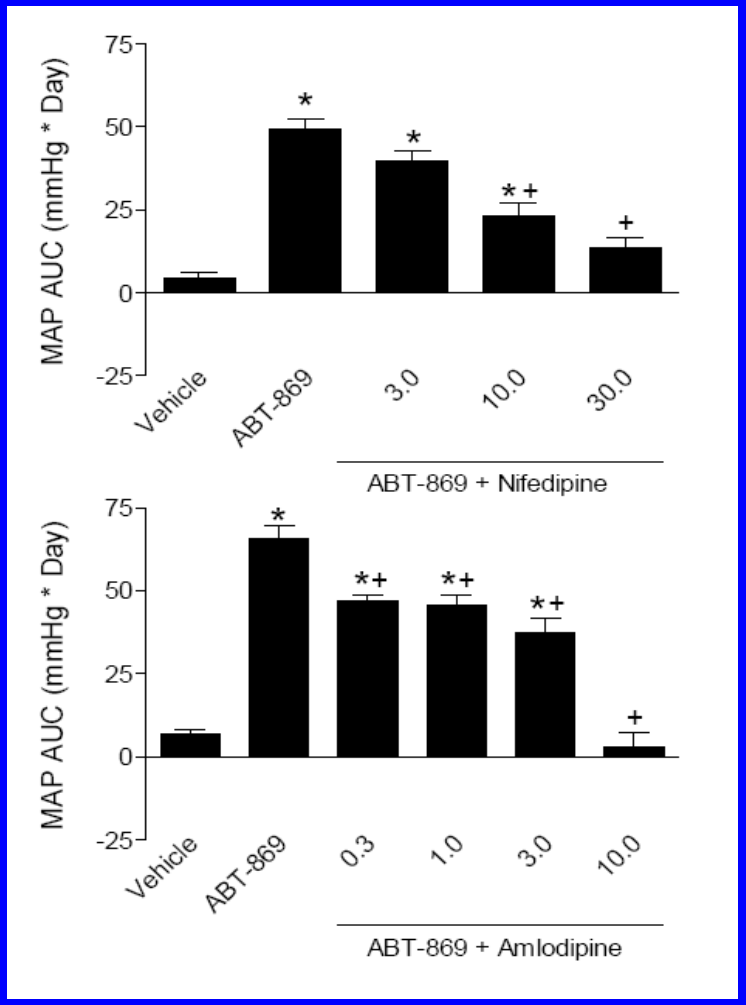
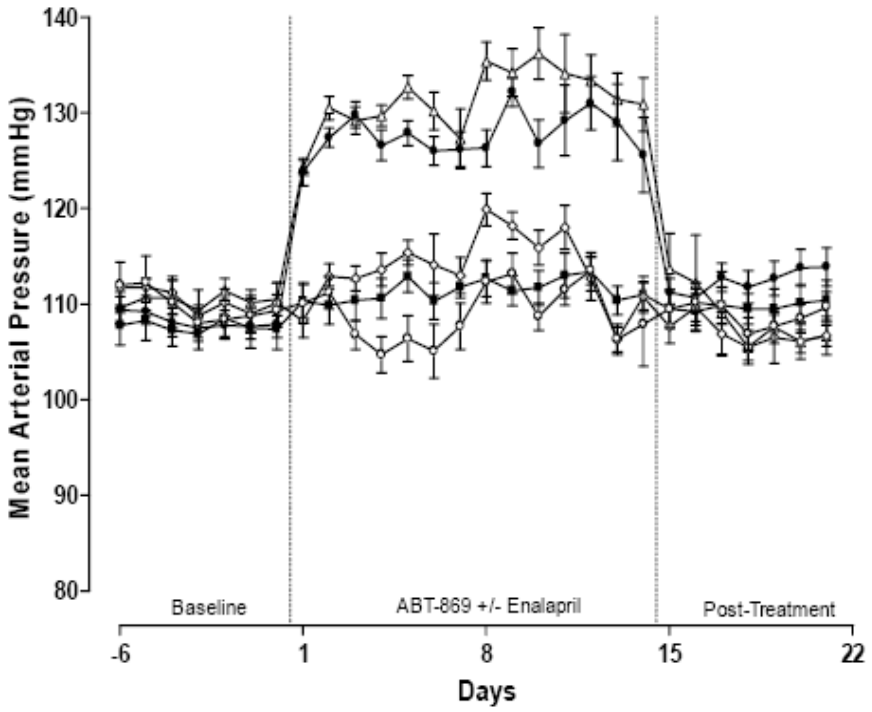
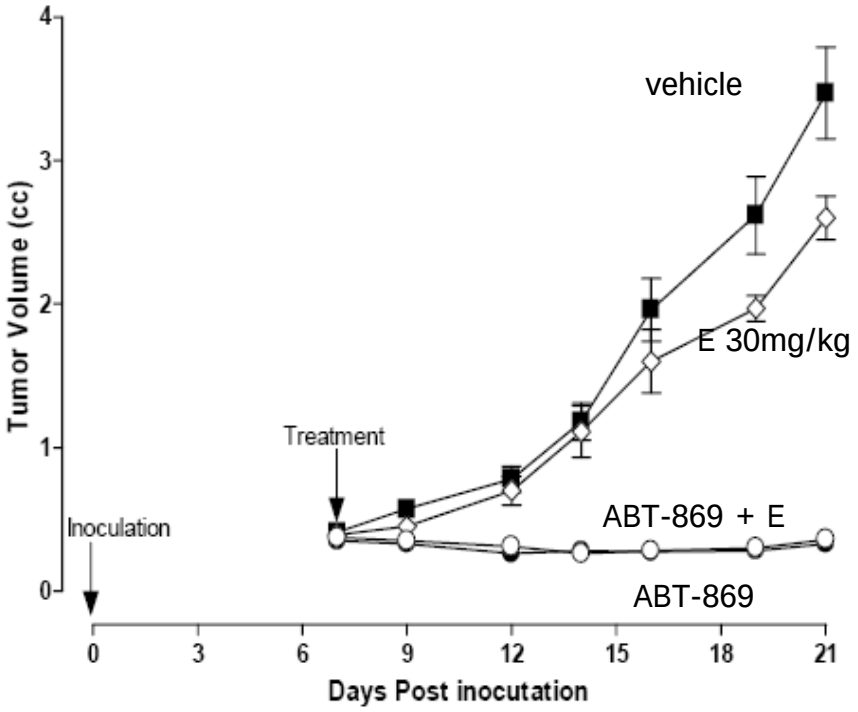




Franklin P; J Pharmacol Exp Ther. 2009 Mar 2. [Epub]

Reversal of drug-induced HT with enalapril does not block anti-tumor efficacy of ABT-869.





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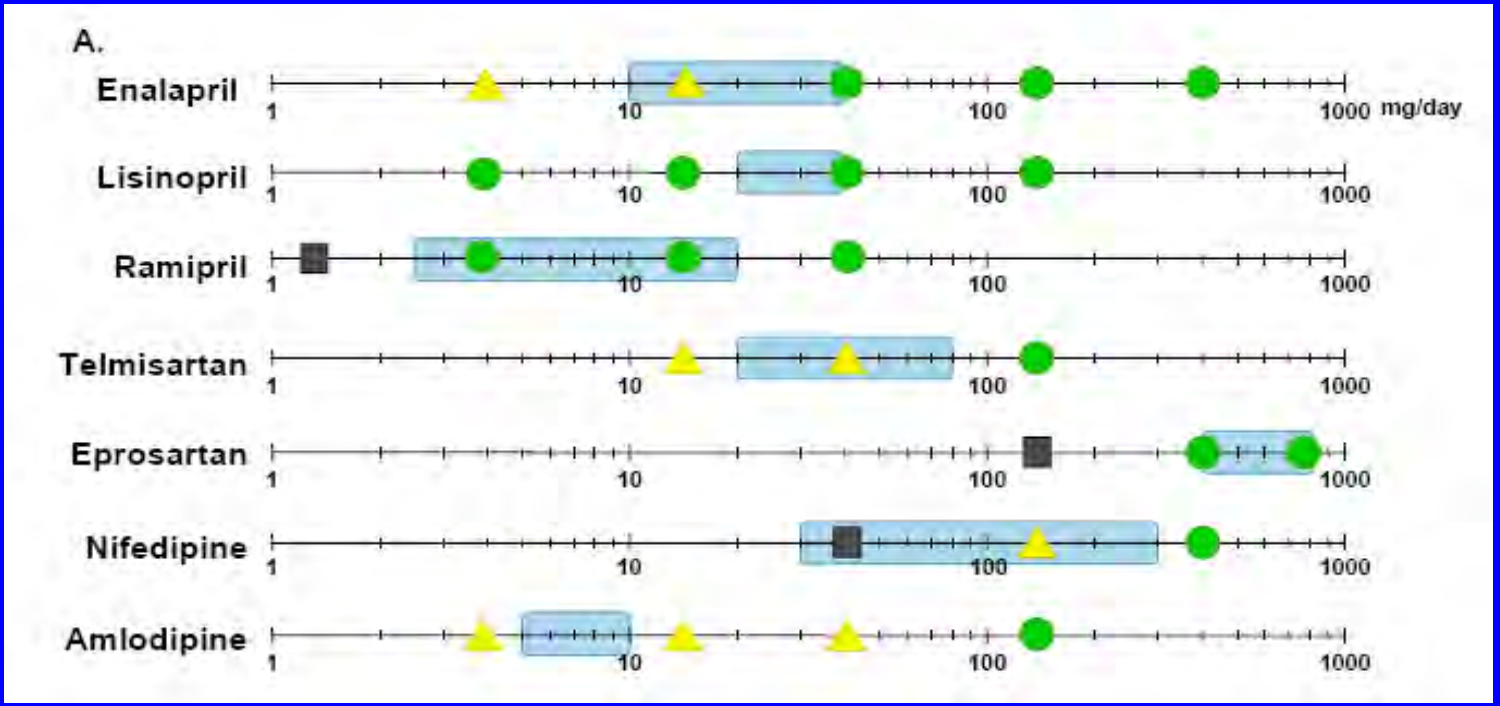
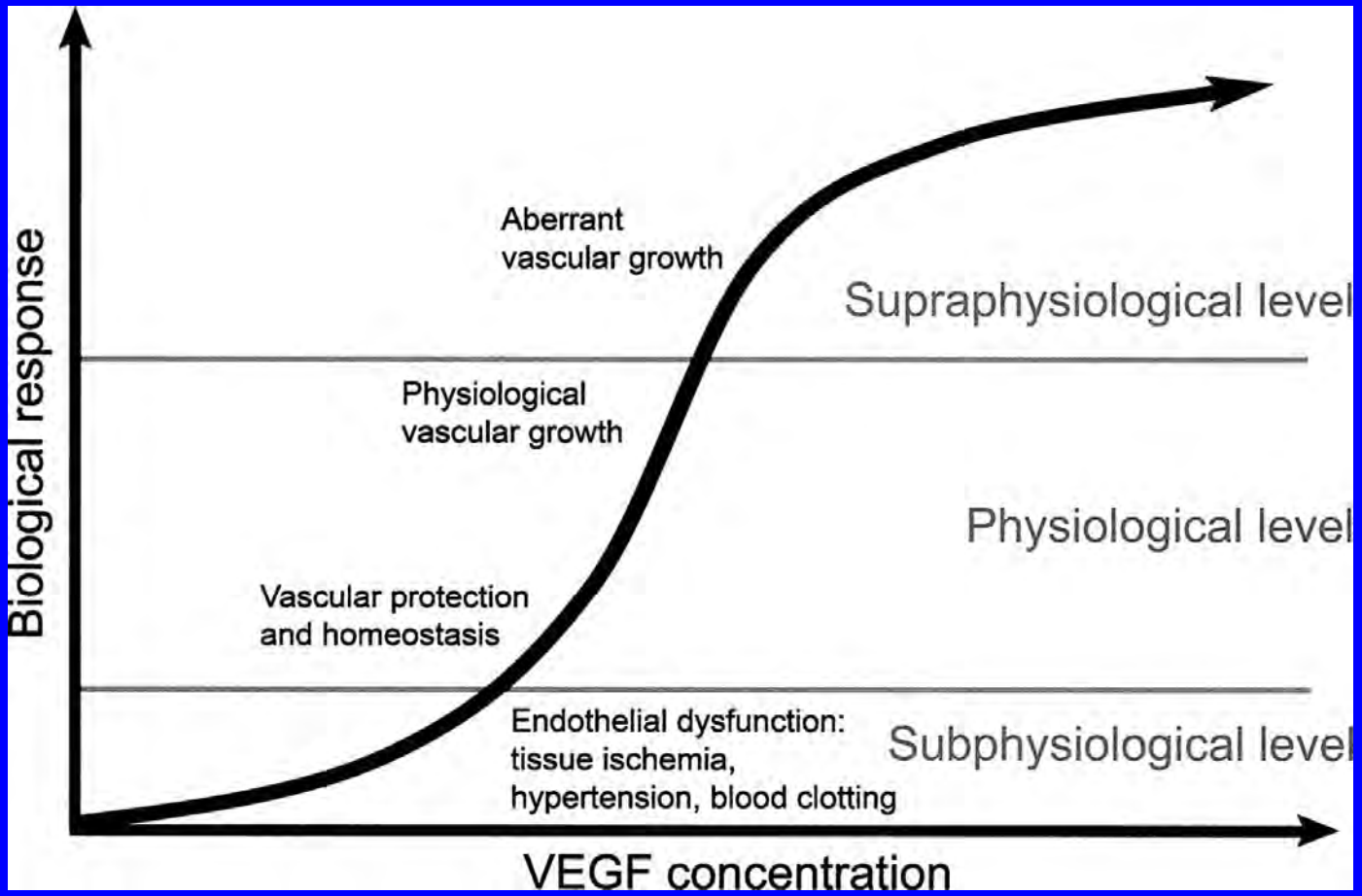


● Doses that completely prevented increases in BP elicited by ABT-869

▲ Doses that partially prevented increases in BP elicited by ABT-869

Franklin P; J Pharmacol Exp Ther. 2009 Mar 2. [Epub]

The Biological Response of VEGF-A in Adults Is Dependent on its Local Tissue Concentration



Yla-Herttuala, S. . J Am Coll Cardiol 2007;49:1015

Effets vasculaires et rénaux des médicaments anti-angiogéniques

Recommandations Françaises pour la Pratique (Société de Néphrologie, Société Française d'Hypertension Artérielle, Association Pédagogique Nationale des Enseignants de Thérapeutique et la Fédération Françophone de Cancérologie Digestive)

Jean-Michel Halimi, Michel Azizi, Guillaume Bobrie, Olivier Bouché, Gilbert Deray, Gaetan des Guetz, Thierry Lecomte, Bernard Levy, Jean-Jacques Mourad, Dominique Nochy, Stéphane Oudard, Philippe Rieu, Dil Sahali

Principes retenus

- Il n y a pas lieu de retarder l'administration d'une 1re dose d'un traitement AA en raison de l'existence d'une HTA observée en ambulatoire ou de chiffres de PA élevés observés en hôpital de jour (hors urgence hypertensive, exceptionnelle) ou d'une protéinurie (hors protéinurie massive, exceptionnelle)

-Un patient devant recevoir une 1re administration d'un traitement AA doit en bénéficier dans l'immense majorité des cas quelle que soit sa PA le jour où il est admis pour recevoir ce traitement.

-Il n'y a pas lieu d'administrer un traitement anti-hypertenseur oral ou par voie veineuse avant administration d'un traitement AA, même si les chiffres de PA mesurés à cette occasion sont élevés.

d) Le patient devant recevoir une 1re administration d'un traitement AA n'a pas de raison particulière de présenter une urgence hypertensive, exceptionnelle. Celle-ci, si elle existe, doit être prise en charge par une équipe spécialisée

Conclusion

- Pharmacological blockage of VEGF pathway results in endothelial dysfunction and capillary rarefaction in humans.
- Both changes are closely associated and could be responsible for the rise in blood pressure observed in patients receiving this treatment.
- Taken together, these results suggest that VEGF plays a crucial role in microvascular structure and function, glomerular endothelial integrity and blood pressure homeostasis in adults.