

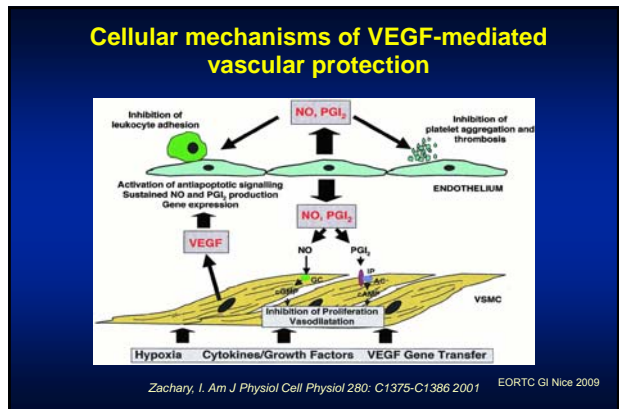
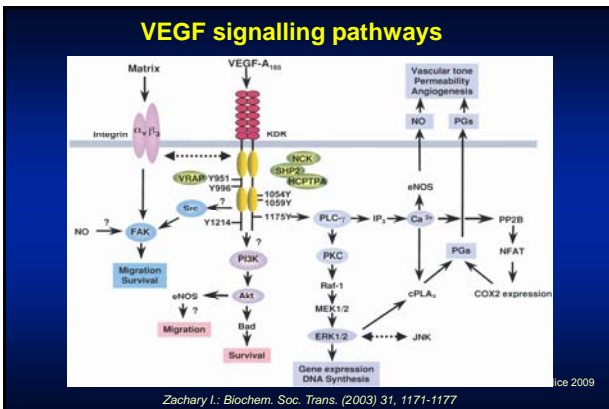
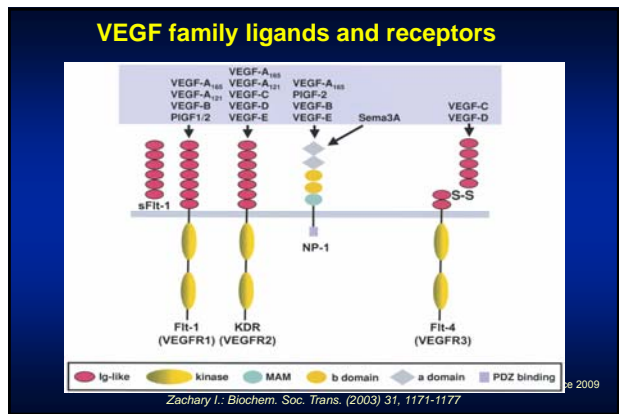
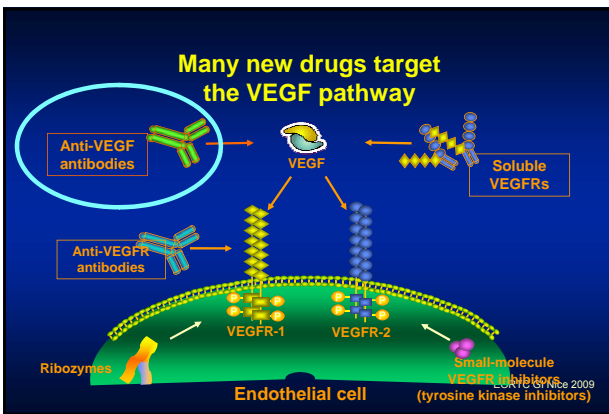
Coagulation and blood pressure disorders related to anti-angiogenic therapy

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Antiangiogenic agent	Targets (inhibition of...)
Bevacizumab	VEGF activity
IFN-alpha	VEGF transcription
VEGF-Trap	VEGF
AE 941 (Neovastat)	binding to VEGFR
Sunitinib	VEGFR-1 & 2, PDGF TK
Sorafenib	VEGFR-2, PDGFR, RAF TK
PTK787/ZK2284	VEGFR-1 & 2, PDGFR, c-kit TK
Axitinib	VEGFR-1,2 & 3, PDGFR, c-kit TK
SU6668	VEGFR-2, FGFR, PDGFR TK
SU5416 (semaxanib)	VEGFR-2 TK
ZD6474 (vandetinib)	VEGFR-2 and EGFR TK

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Pande A: *Anticancer Res* 27:3465-70 2007



Risks of proteinuria and hypertension with Bevacizumab

- Meta-analysis of 7 randomized trials (1850 pts)

Bevacizumab	Proteinuria			Hypertension		
	%	Relative risk	P	%	Relative risk	P
Low dose	21-42	1.4	0.003	3-32	3.0	<0.001
High dose	22-63	2.2	<0.001	18-36	7.5	<0.001

Zhu X.: Am J Kidney Dis 49:186-93 2007

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Bevacizumab: effect on blood pressure and capillary density

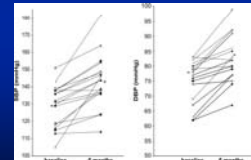
18 patients, bevacizumab 5-7.5mg/Kg, intravital video microscopy and doppler flowmetry with iontophoresis (pilocarpine test)

Systolic BP diastolic

Table 2. Mean values of SBP, DBP, and capillary density at baseline and after 6 months

n = 18	Baseline	6 months	P (paired Student's t-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)	96 ± 13	81 ± 11	0.0001

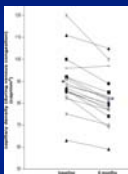
SBP, systolic blood pressure; DBP, diastolic blood pressure.



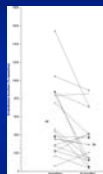
Mourad, J.-J. et al. Ann Oncol 2008 19:927-934

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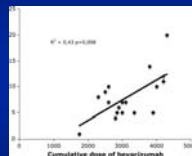
Bevacizumab: effect on capillary density and function



Maximal capillary density at 0 and 6 months of TTT



Vasodilatory response to pilocarpine at 0 and 6 months of TTT



Capillary density in relation to bevacizumab cumulative dose

Mourad, J.-J. et al. Ann Oncol 2008 19:927-934

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Management of bevacizumab hypertension: retrospective review

Drugs	No of patients	Controlled BP	Uncontrolled BP
ACE-I	16	16	0
Beta-blocker	3	3	0
Ca ⁺⁺ channel blocker	6	6	0
Diuretics	1	1	0
ACE-I + any	15	13	2
ACE-II in combination	5	2	3
Other combinations	9	6	3
Total	55	47 (85%)	8 (15%)

Pande A: Anticancer Res 27:3465-70 2007

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Hypertension and bevacizumab: Summary and recommendations

Hypertension rarely results in discontinuation of bevacizumab treatment or hospitalisation and is managed effectively using oral antihypertensives

Pre-existing hypertension should be adequately controlled in patients receiving bevacizumab therapy

Monitor blood pressure while patients are on therapy

In patients with severe hypertension requiring medical therapy, bevacizumab should be temporarily interrupted until adequate control is achieved

If hypertension cannot be controlled with medical therapy, bevacizumab should be permanently discontinued

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Bevacizumab Summary of Product Characteristics 2008

BE CAREFUL!

- Bevacizumab + pamidronate => 33.9% proteinuria (versus 18.5% with beva alone, $p = 0.026$)
Miller JCO 23: 792-9 2005

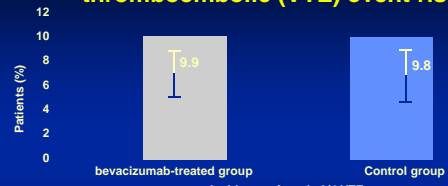
=> Avoid nephrotoxic medications such as NSAID, biphosphonates, nephrotoxic AB while treating with bevacizumab

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Bevacizumab and coagulation

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Bevacizumab and venous thromboembolic (VTE) event risk



- Pooled analysis of 5 randomized studies with 1745 patients with CRC
 - VTE increased risk (chemo± bev):
HR 0.89 [95%CI: 0.66 - 1.20] $P=0.44$
- BE CAREFUL: Data valid for CRC patients only!**

Scappaticci, et al. JNCI 99:1232-9 2007

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Bevacizumab and arterial thromboembolic (ATE) event risk

Table 1. Studies in the pooled population and number of patients with an arterial thromboembolic event*

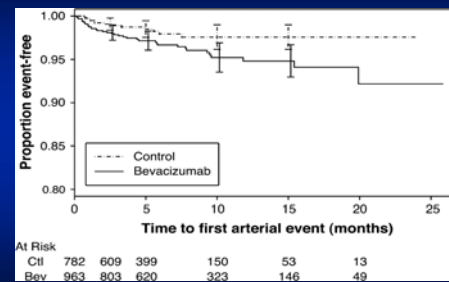
Study reference	Tumor type	Chemo regimen	Control group		Bevacizumab-treated group		
			No. of patients with an event	No. of patients	No. of patients with an event	No. of patients	
AVF0101g (7)	Colorectal	5FL	3	396	5FL or FULV	20	361
AVF0101g (7)	Breast	Cap	1	217	Cap	1	229
AVF0101g (8)	Colorectal	FULV	3	384	FULV	10	388
AVF0101g (8)	Colorectal	FULV	1	18	FULV	3	47
AVF0101g (8)	NSCLC	Carb/Tax	1	10	Carb/Tax	3	46
Total			13	782		37	843

- ATE increased risk (chemo± bev):
HR 2.0 [95%CI: 1.05 - 3.75] $P=0.031$
- Absolute rates: HR 1.8 [95%CI: 0.94 - 3.33] $P=0.076$
 - chemo alone: 3.1/100 patients/year
 - Chemo + bev: 5.5/100 patients/year
- Independent risks factors: Previous ATE ($P<0.001$), $\geq 65y$ ($P=0.01$)

Scappaticci, et al. JNCI 99:1232-9 2007

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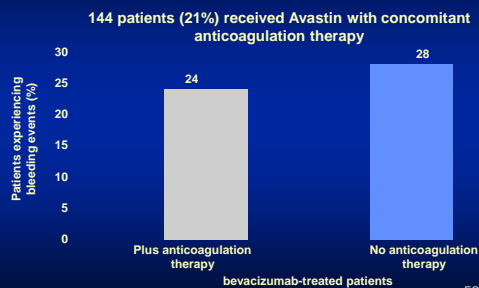
Kaplan-Meier analysis of time-to-arterial thromboembolic event



Scappaticci, et al. JNCI 99:1232-9 2007

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N016966: Anticoagulation and bleeding risk in bevacizumab-treated patients



Saltz, et al. JCO 26:2013-19 2008

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Aspirin use and bleeding events in bevacizumab treated patients

- 1,745 patients from five randomised bevacizumab trials (breast, colorectal, NSCLC)
- Aspirin => 1.3x increased risk in grade 3/4 bleeding events in both beva and control arms
- No significant increase of bleeding risk with the use of bevacizumab

Scappaticci, et al. JNCI 99:1232-9 2007

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Conclusions

- The consequences of VEGF activity inhibition on the vascular endothelium homeostasis may explain the occurrence of hypertension and thrombo-embolic events
- Hypertension is easily controlled by classical anti-hypertensive schemes (except for ACE-II)
- Classical anticoagulation or anti-aggregant (aspirin) treatments can be safely given concomitantly with bevacizumab

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