Vasopressin in hemorrhagic shock: a systematic review and meta-analysis of randomized animal trials.

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Supplemental Material

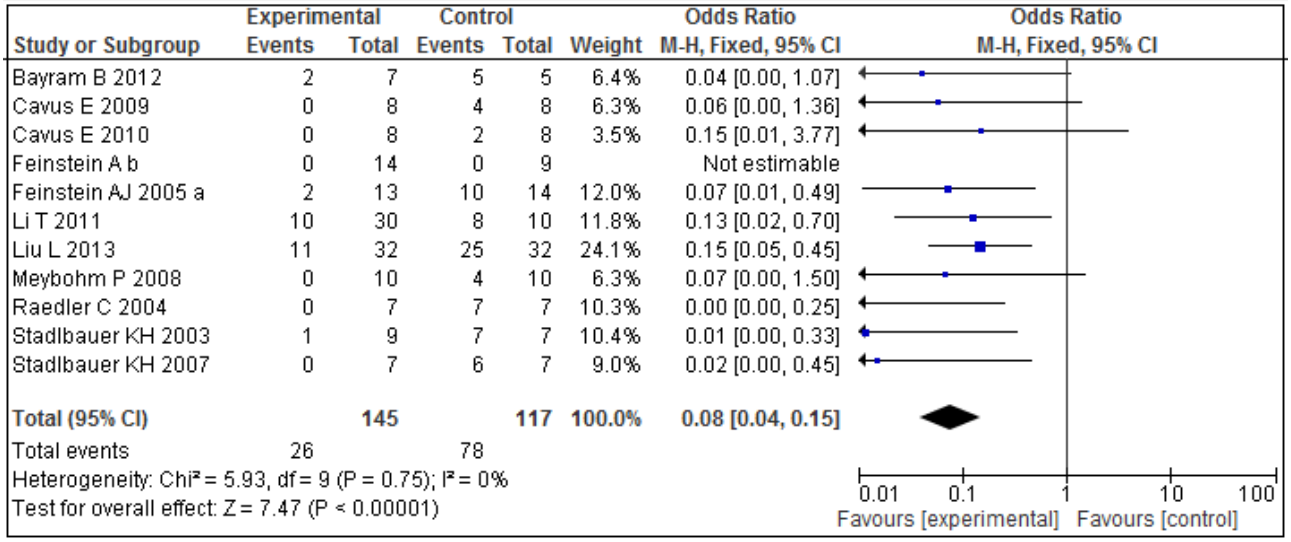


Fig 6a: AVP or terlipressin vs fluid resuscitation

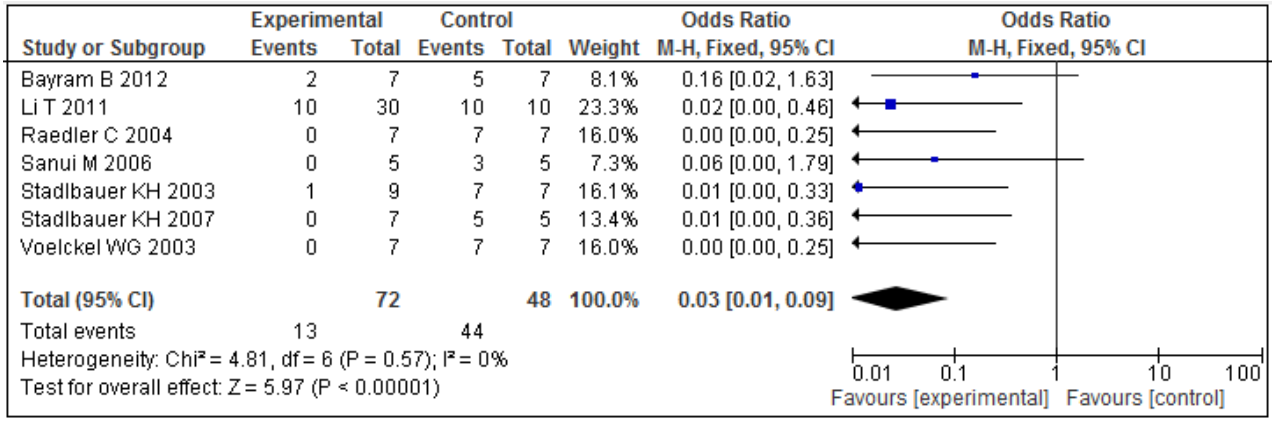


Fig 6b: AVP or terlipressin vs placebo

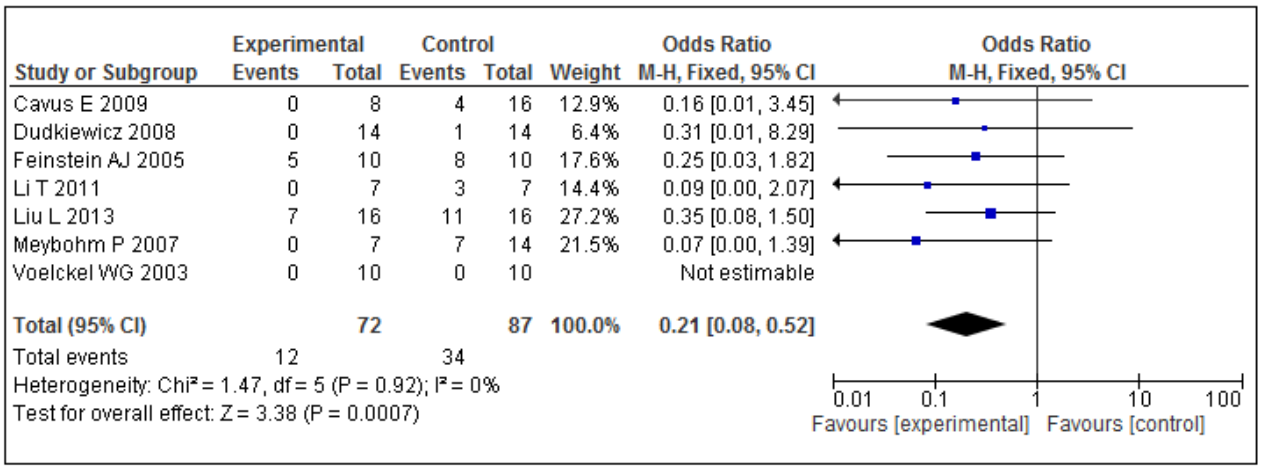


Fig 6c: AVP vs other vasoconstrictive drugs

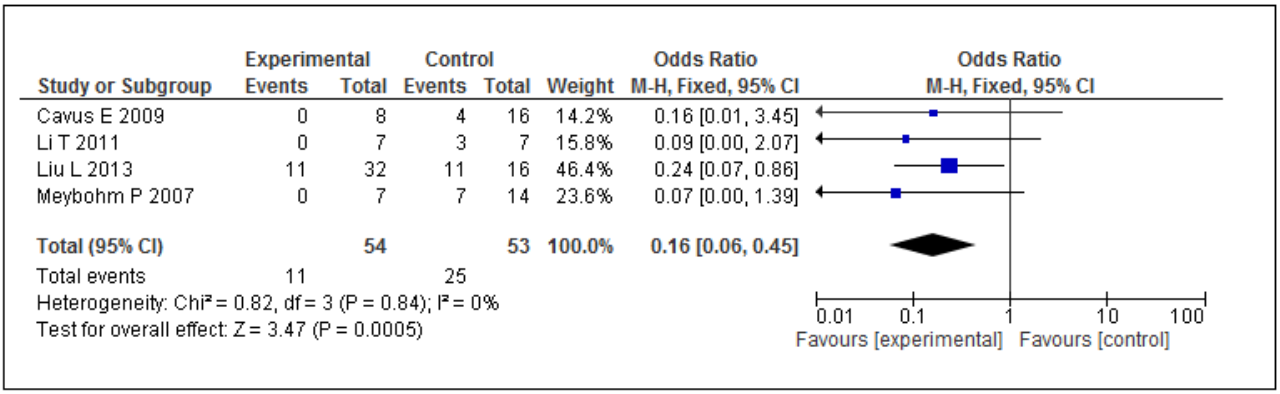


Fig 6d: AVP vs NE

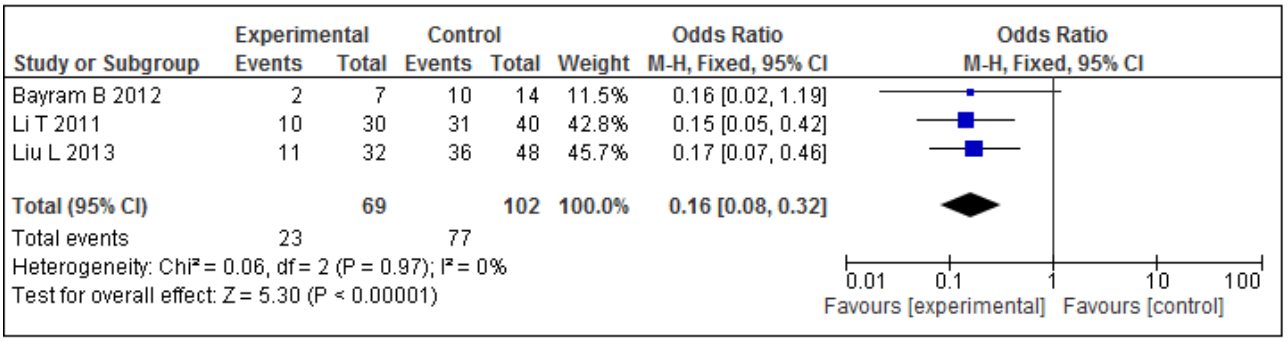


Fig. 7a: AVP or terlipressin vs all other strategies in rats

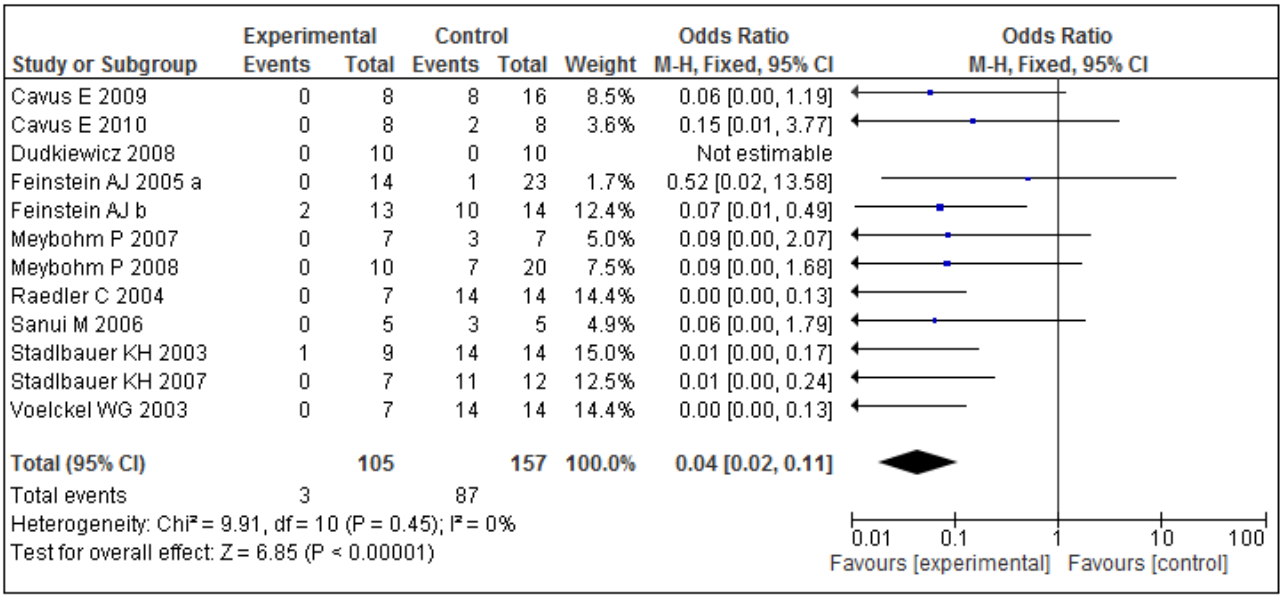


Fig. 7b: AVP vs all other strategies in pigs.

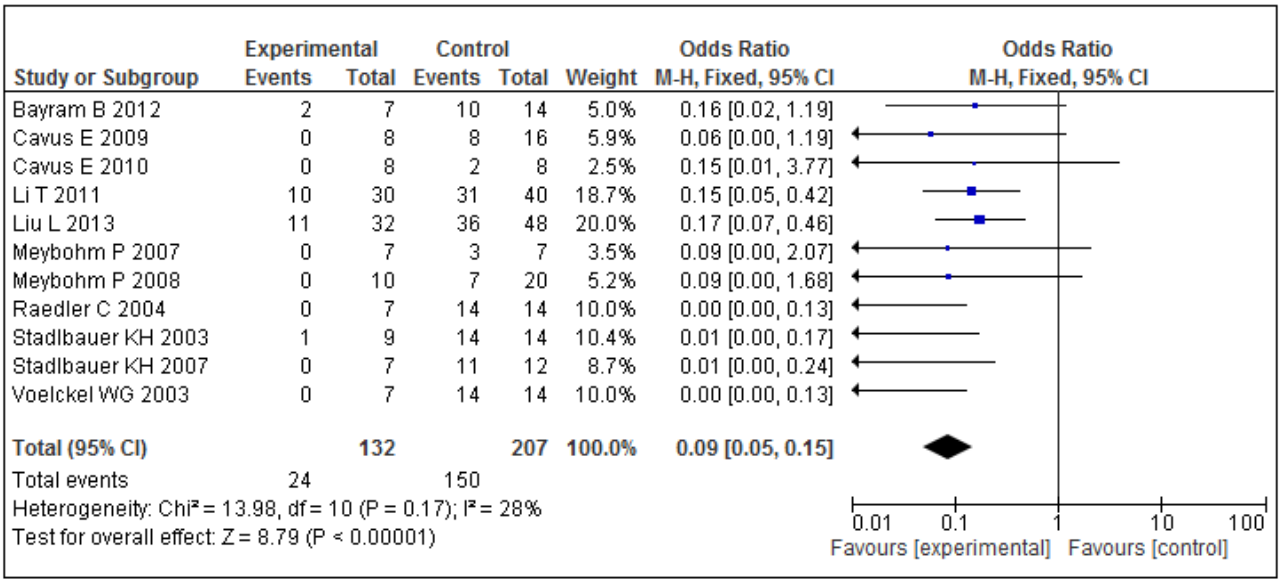


Fig. 8: Meta-analysis performed considering only studies were hemorrhagic shock was due to bleeding occurring in the splanchnic area.

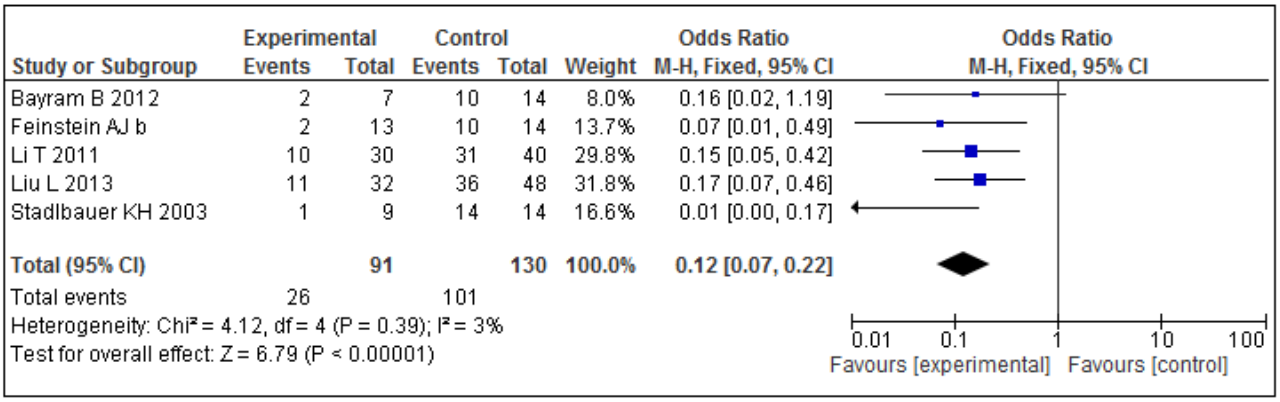
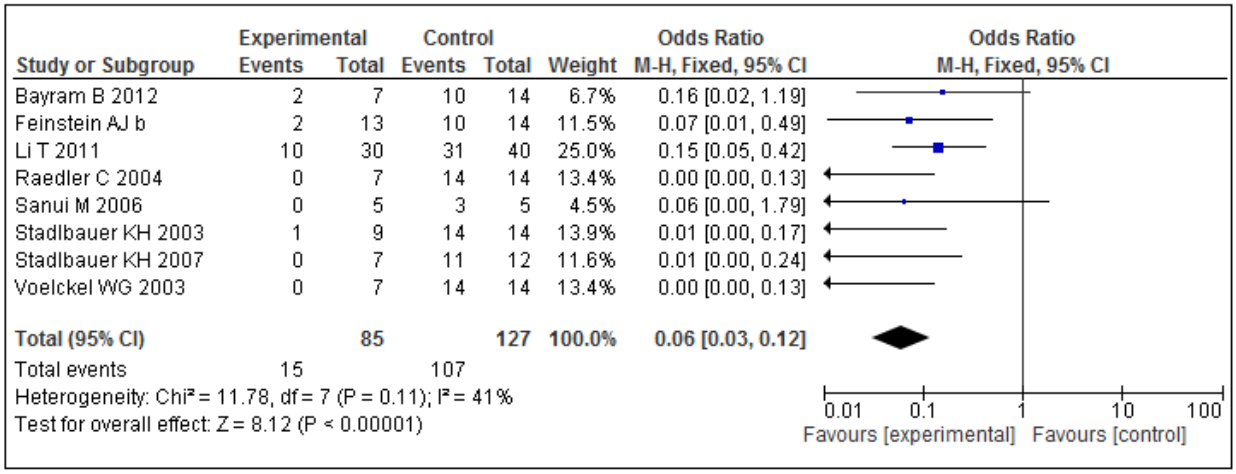


Fig. 9: meta-analysis performed excluding studies with zero mortality rate.



Fig, 10:meta-analysis performed considering only studies that used mortality as the primary endpoint

Trial	AVP or terlipressin dosages	Fluid administration in AVP group	Vasopressors dosages In control groups	Fluid administration in vasopressor groups	Fluid administration in fluid resuscitation groups	AVP + VASOPRESSORS
Bayram B [3]	Terlipressin: 50 µg/kg	LR 2 mL/kg per min (PAM target 40 mmHg)	-	-	Bolus of LR (4 mL/kg) + 2 mL/kg/min (PAM target 40 mmHg)	NO
Cavus E [31]	AVP: bolus of 0.2U/kg + infusion 2U/kg/h	HSS 4mL/kg over 2min	-	-	LR (40mL/kg) +HES 130/0.4 (20mL/kg) over 30min	NO
Cavus E [55]	AVP: bolus 0.2U/kg + infusion 0.04U/kg/min	HSS (4mL/kg) over 2min	NE (bolus 20 ɣg/kg + 1 ɣg/kg/min infusion)	HSS (4mL/kg) over 2min	6% HES 130/0.4 (20 mL/kg) + LR (40 mL/kg) over 30 min;	NO
Dudkiewicz M [56]	AVP titrated to maintain a CPP > 70 mm Hg and CVP > 12 mm Hg	NS 1 L + unlimited NS to SAP>100 plus 250 mg/kg mannitol	NE titrated to maintain a CPP > 70 mm Hg and CVP > 12 mm Hg	NS 1 L + unlimited NS to SAP>100 plus 250 mg/kg mannitol	-	NO
Feinstein AJ	AVP: 0.1 U/kg	NS titrated to MAP > 60	PE: 0.05 mg/kg + bolus to MAP	NS titrated to MAP > 60	NS titrated to	NO

[8]	+ bolus to MAP > 60 mmHg	mmHg (only 1 group)	> 60 mmHg	mmHg (only 1 group)	MAP > 60 mmHg	
Feinstein AJ [32]	AVP 0.1 U/kg + continuous AVP (0.4U/kg/hr)	NS bolus 10 mL/kg + NS was infused to MAP>70mmHg	-	-	NS bolus 10 mL/kg + NS was infused to MAP > 70 mmHg	NO
Li T [11]	AVP 0.1 U/kg	Two volume of LR	NE 1 mg/kg	Two volumes of LR	Two volumes of LR solution; One volume of blood + one volume of LR	AVP 0.1 U/kg + NE 1 mg/kg + LR 2 volumes or blood 1 volume + LR 1 volume
Liu L [39]	AVP 0.04 or 0.4 U/kg	LR (17.5 mL/kg or 8.75mL/kg or 1 mL/kg)	NE 3 μg/kg	LR (17.5 mL/kg or 8.75mL/kg or 1 mL/kg)	LR (17.5 mL/kg or 8.75mL/kg or 1 mL/kg)	AVP 0.04 or 0.4 U/kg + NE 3 μg/kg + LR (17.5 mL/kg or 8.75mL/kg or 1 mL/kg)

Meybohm P [13]	AVP bolus 10 U + 2 U/kg/hr	HHS 4 mL/kg during 2 minutes	NE 1000 ɣg + infusion of 60 ɣg/kg/hr	HHS 4 mL/kg during 2 minutes	-	NO
Meybohm P [57]	AVP bolus 0.2Ukg + 2 UI/kg/h	HHS (4 mL/kg over 2min) + LR 10 ml/kg/h and HES 10 ml/kg H	-	-	LR (40 mL/kg) and HES 130/0.4 (20mLkg) + LR 10 ml/kg/h and HES 10 ml/kg H	NO
Raedler C [10]	AVP 0.4 U/kg bolus + 0.04 ml/kg/min	HES 1000 mL and LR 1000 mL (after 30 min)	-	-	LR 1000 Ml + HES 1000 mL (up to 8 ml/kg/min) + HES 1000 mL and LR 1000 mL after 30 min	NO
Sanui M [21]	AVP 0.2 U/kg bolus + 0.1 U/kg/min	NS 10 mL/kg + crystalloids MAP target > 60 mm Hg	-	-	NS 10 mL/kg + crystalloids MAP target > 60 mm Hg	NO
Stadlbauer KH [30]	AVP 0.4 U/kg + 0.08 U/kg/min	Whole blood (~40 ml/kg) LR 25 ml/kg and 25 ml/kg 3% gelatin solution	-	-	LR 25 ml/kg and 25 ml/kg 3% gelatin solution	NO

Stadlbauer KH [40]	AVP 0.4 U/kg	LR 25 mL/kg + 25 mL/kg 3% gelatin (after 30 min)	-	.	LR 25 mL/kg	NO
Voelckel WG [1]	AVP 0.8 U/kg	3 mL/kg/h	PE 200 ɣg/kg	3 mL/kg/h	-	NO

Tab. 3: dosages of AVP/terlipressin, vasopressors and fluid resuscitation in studies included in meta-analysis. LR: Lactate Ringer; HES: hydroxyethylstarch; HSS: hypertonic-saline-starch solution; CPP: cerebral perfusion pressure; CVP: central venous pressure; PE: phenylephrine; NS, normal saline; HHS: HyperHAES

STUDY (First Author and Year of pubblication)	PRIMARY ENDPOINT OF THE STUDY	SETTING
Bayram B. 2012	Increase in MAP Survival rates	Liver Trauma
Cavus E 2010	Changes of bis-pectral index (BIS) Changes of cerebral perfusion	Liver Trauma
Cavus E 2009	Haemodynamic and cerebral variables	Liver Trauma
Dudkiewicz M 2008	Maintain tissue oxygenation during cerebral perfusion pressure management	Blunt trauma to the head and bilateral chests
Feinstein AJ 2005	ICP Physiologic resuscitation parameters	Percussion traumatic brain Injury followed by hemorrhage
Feinstein AJ 2005	Mortality Fluid requirement Pulmonary function	Severe chest trauma
Li T 2011	12-h animal survival rate Tissue blood flow Mitochondrial function of liver and kidney	Splenic parenchyma and one of splenic artery transection
Liu L 2013	Maintain and stabilize hemodynamic parameters	Transection of the splenic parenchyma, the splenic artery and vein
Meybohm P 2007	Cerebral perfusion pressure (CPP) and brain metabolism	Liver bleeding
Meybohm P 2008	Cerebral perfusion pressure (CPP) and protein S100B	Liver trauma
Raedler C 2004	Hemodynamic variables Short-term survival	Liver trauma
Sanui M 2006	Intracranial pressure (ICP) Survival	Traumatic brain injury

Stadlbauer KH 2003	Hemodynamic variables Survival	Liver trauma
Stadlbauer KH 2007	Hemodynamic variables Survival	Abdominal vascular injury
Voelckel WG 2003	Hemodynamic variables Regional blood flow Short-term survival	Liver trauma

Tab. 4: Primary endpoint of animal studies