Risikomanagement in der Präeklampsie – Rolle von Acetylsalicylsäure

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Conflict of Interest – Disclosure (last 3 years)
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Affiliations/Financial Relationships	Company
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Honoraria for advisory board activities	Bayer Daiichi Sankyo
Participation in clinical trials	none
Research funding	none
Financial shares and options	none

Präeklampsie

Hypertensive Erkrankung der Schwangerschaft (Schwangerschaftshypertonie), charakterisiert durch prognostisch richtungsweisende Leitsymptome Hypertonie und Proteinurinurie.

Auftreten weltweit bei ca. 3% (2-8%) aller Schwangerschaften. Häufigste Ursache der maternalen und perinatalen Morbidität und Mortalität.

Genotypische und phänotypische Risikofaktoren bekannt (Erstgebärende, höheres Alter, vorbestehende Erkrankungen wie Hypertonie, Diabetes u.a.)

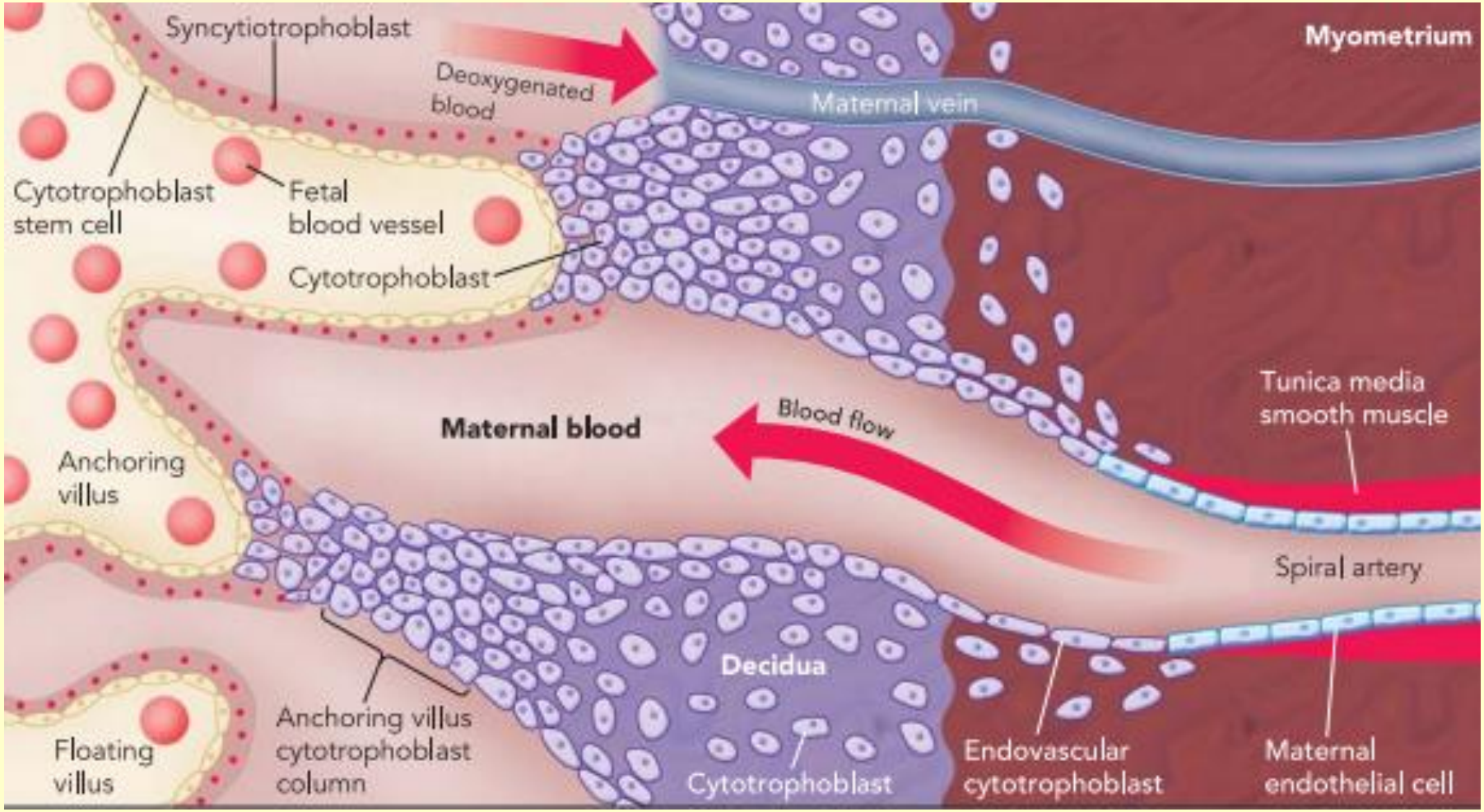
Keine kausale Therapie derzeit möglich. Daher therapeutische Fokussierung auf Prävention, inklusive frühzeitigem Erkennen und ggf. Behandlung von Risikopatienten

Einziger derzeit erprobter medikamentöser Ansatz: Acetylsalicylsäure (z.B.Aspirin)

Effektivität nachgewiesen aber sehr variabel – Gründe?

Normale Plazentation

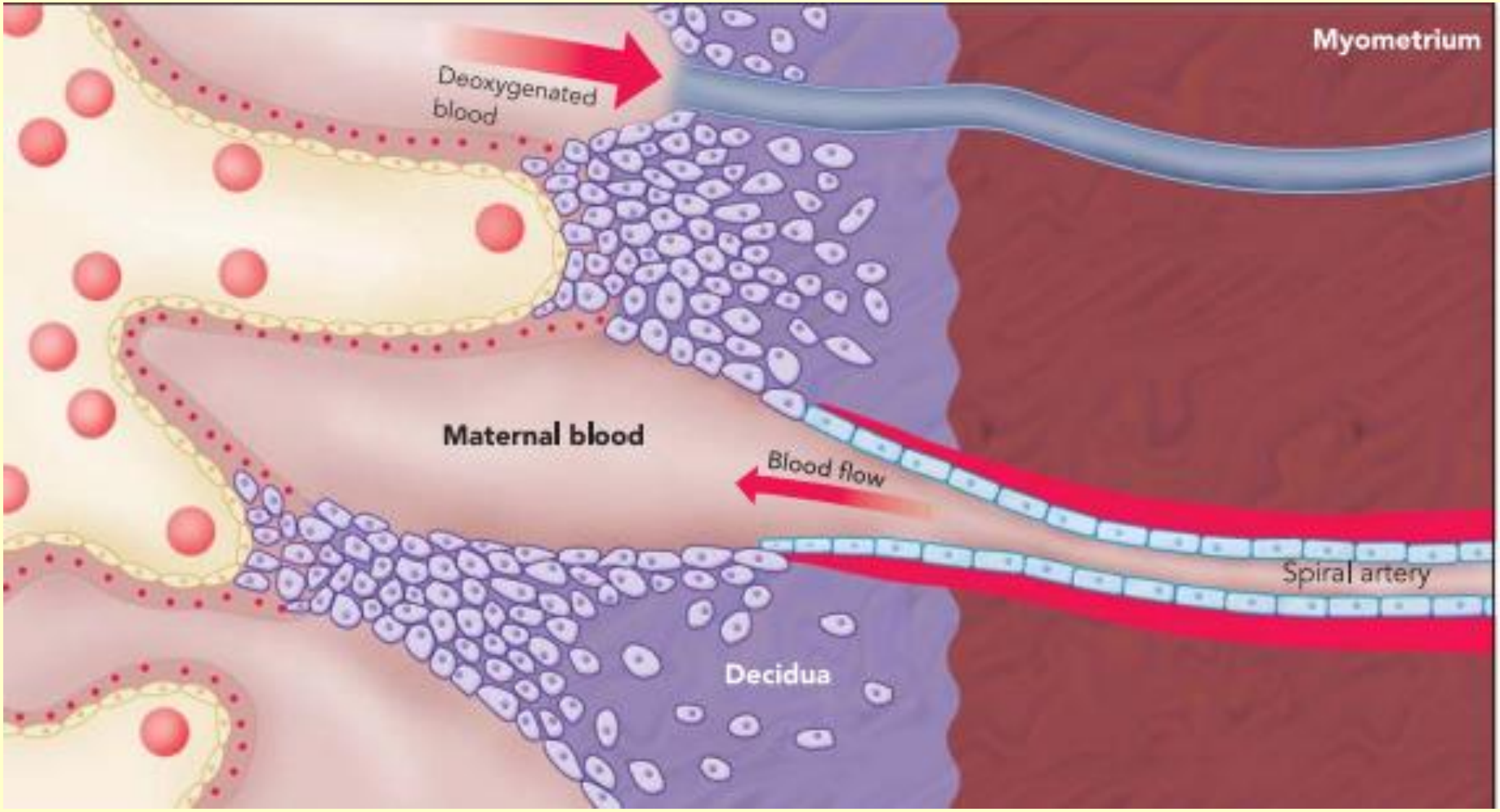
Invasion fetaler Cytotrophophoblasten in die maternalen Spiralarterien mit Differenzierung von einem epithelialen In einen endothelialen Phänotyp unter dem Einfluß angiogener Faktoren (PIGF, VEGF). Folge ist Transformation der Spiralarterien von kleinkalibrigen Widerstands- in großkalibrige Kapazitätsgefäße. Zunahme der Plazenta-perfusion mit ständiger Anpassung an die metabolischen Bedürfnisse des Feten



(Wang et al, Physiol. 24: 147–158, 2009)

Plazentation in der Präeklampsie

Die Transformation der Cytotrophoblasten in den endothelialen, invasiven Phänotyp unter dem Einfluß angiogener Faktoren wird durch Bildung antiangiogener Faktoren (sFlt-1, Endoglin u.a.) gehemmt . Die kleinkalibrigen Spiralarterien persistieren und behalten ihren pulsatilen Blutfluß bei. Folgen sind unzureichende Vaskularisierung im Plazentarkreislauf mit starken Schwankungen von Perfusionsdruck und pO_2. Folge ist oxidativer Stress, Perfusionsdruckstörunen und endotheliale Dysfuktion (Entzündungsreaktionen) auch im maternalen Kreislauf.



(Wang et al, Physiol 24: 147–158, 2009)

Warum Aspirin?

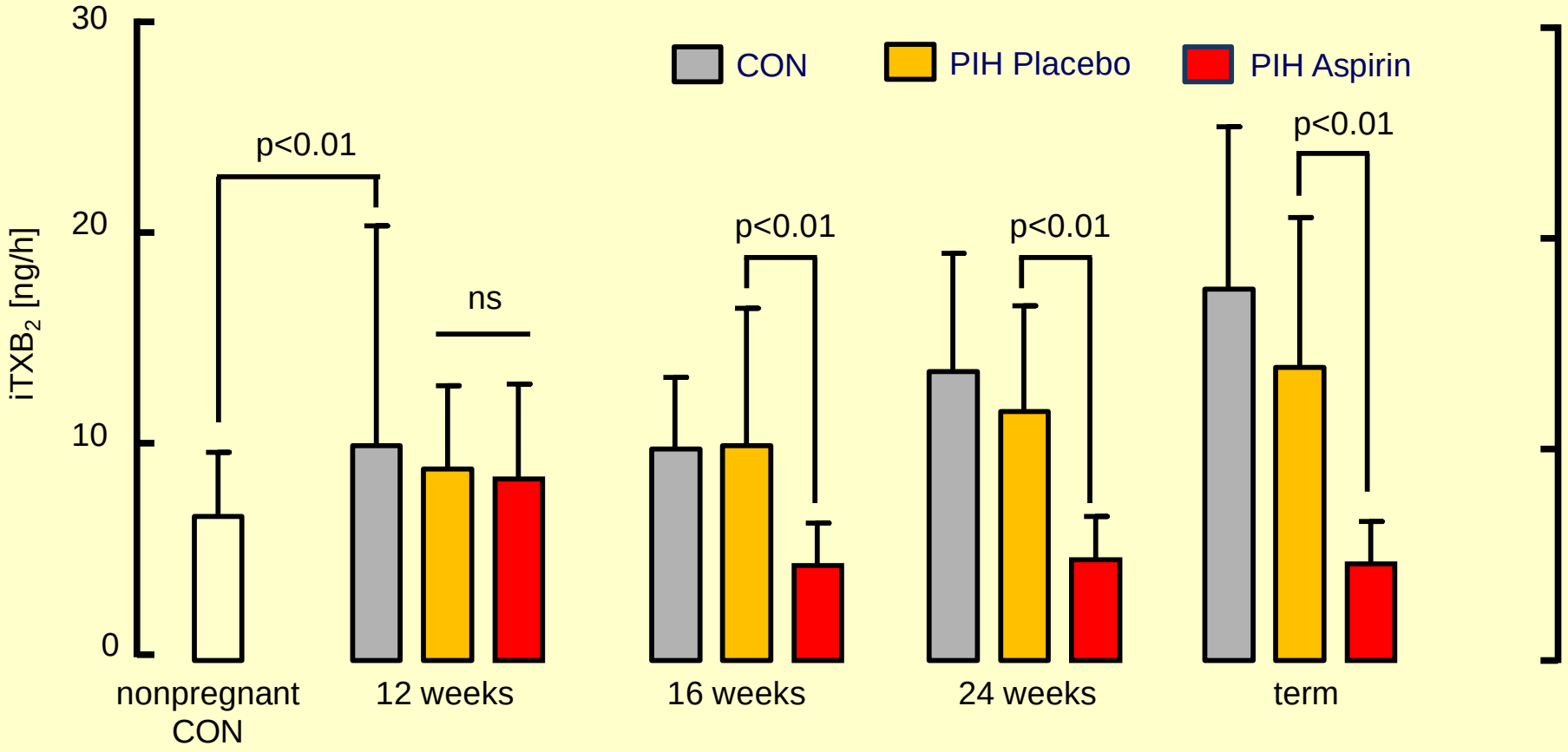
Einziges Medikament mit nachgewiesener aber sehr variabler Wirksamkeit zur Prophylaxe einer Präeklampsie bei Risikoschwangerschaften

Pharmakologischer Ansatz: Irreversible Hemmung von Thromboxan– (Thrombozyten) induzierten thrombotischen und (systemischen) Entzündungsreaktionen

keine wesentlichen toxischen Effekte auf Feten oder Mutter bekannt. Keine (klinisch relevante) Konstriktion des Ductus Botalli

Keine klinisch relevanten Blutungen bei rechtzeitigem Absetzen ante partum

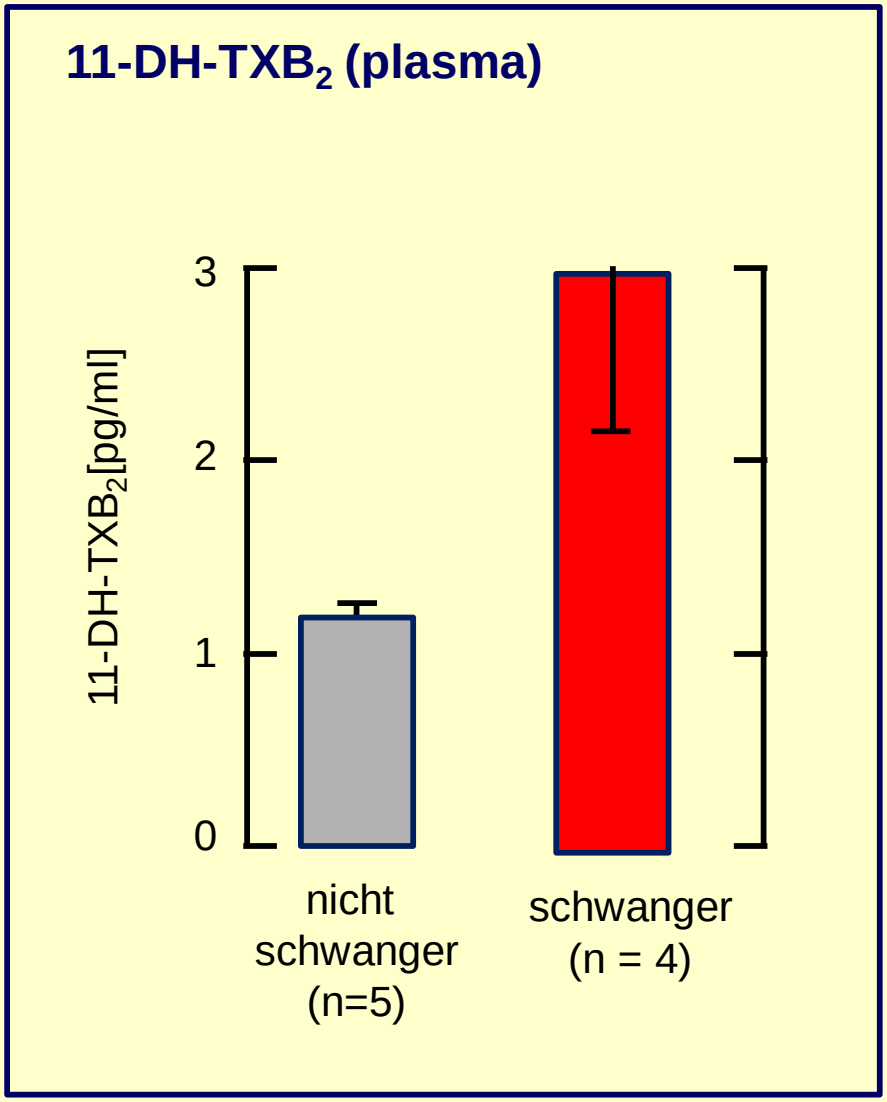
Renal excretion of immunoractive TXB_2 ($iTXB_2$) during and after gestation in normotensive gravidae (CON) and gravidae at high risk of PIH treted with aspirin (60 mg/day) or placebo

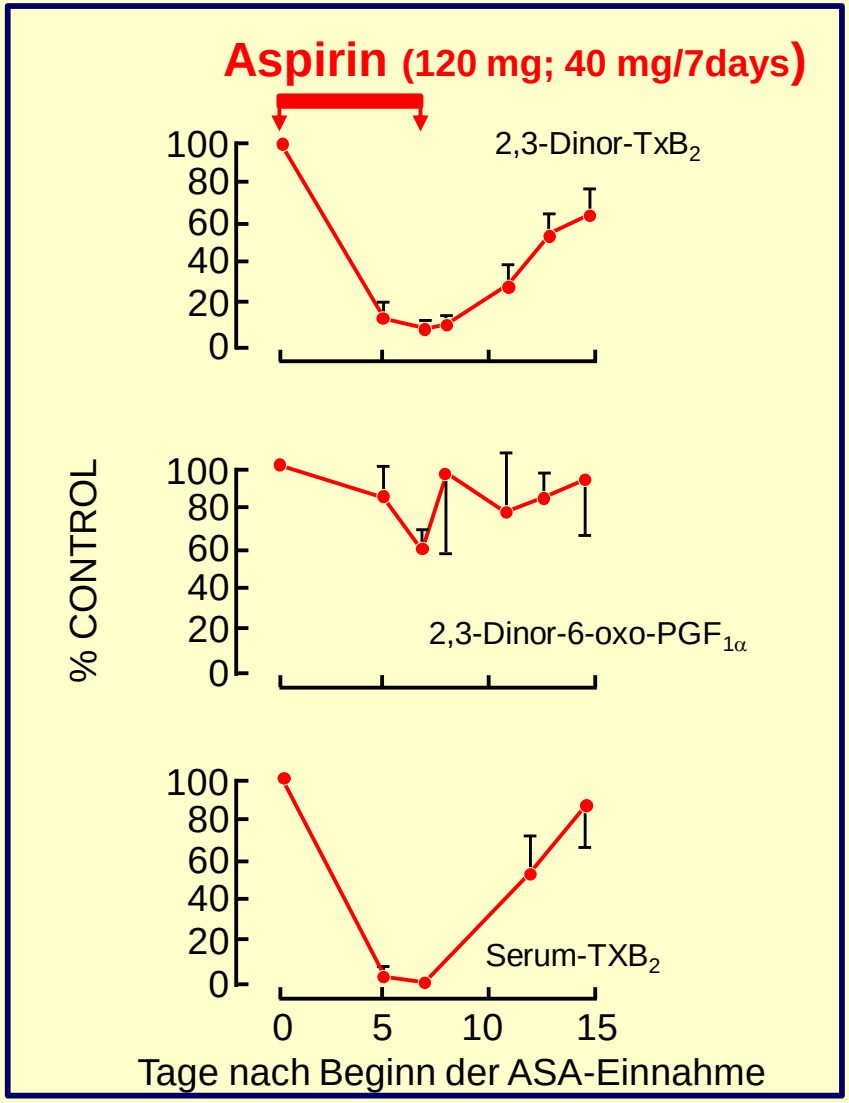


start of treatment: 12. week of gestation (mean ± SD)

(mod. after Benigni et al, NEJM 321:357-362; 1989)

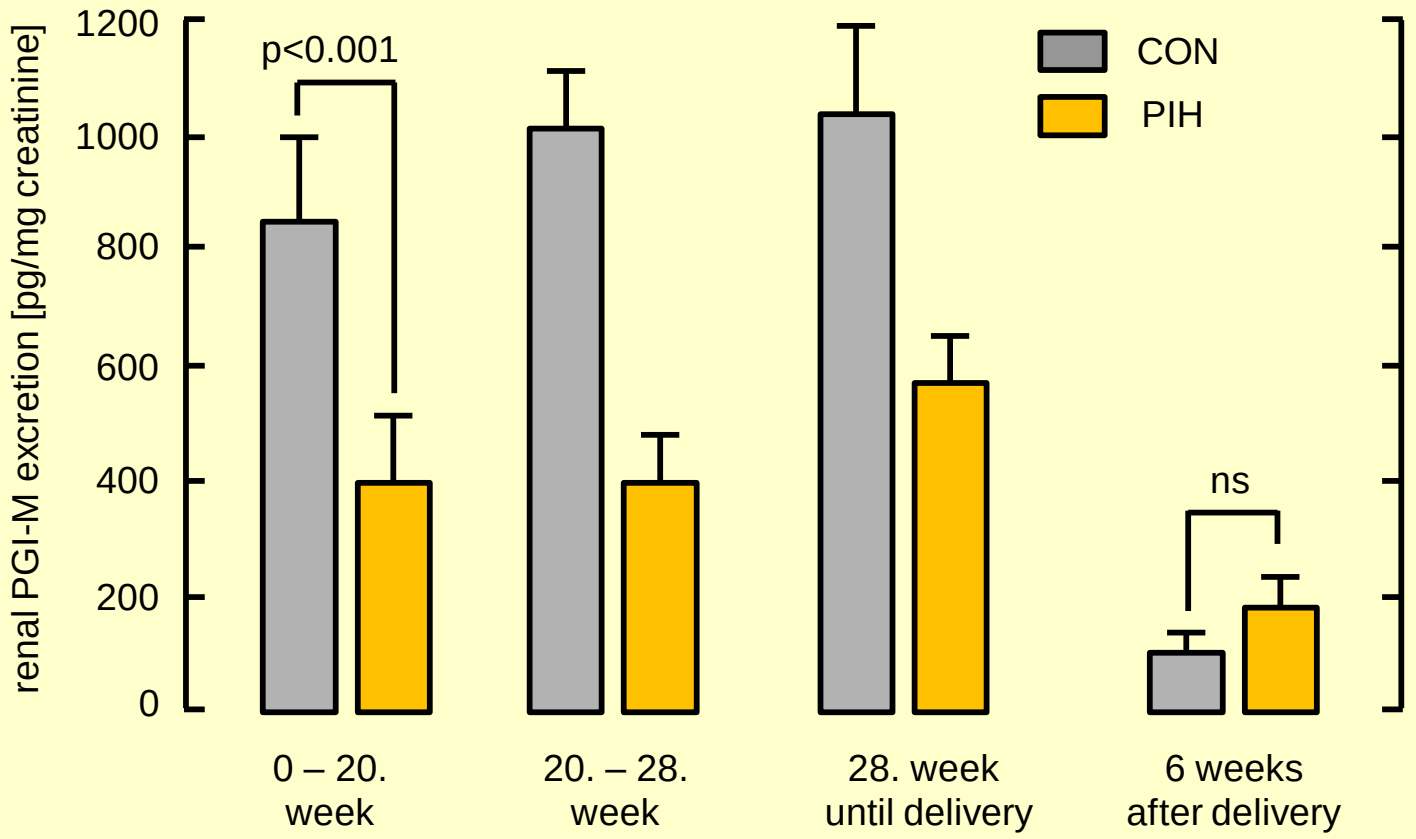
Plasmaspiegel und renale Ausscheidung von TX- und PGI_2 (Meta-boliten) bei Schwangeren (32.-36.W) vor und nach ASA-Einnahme





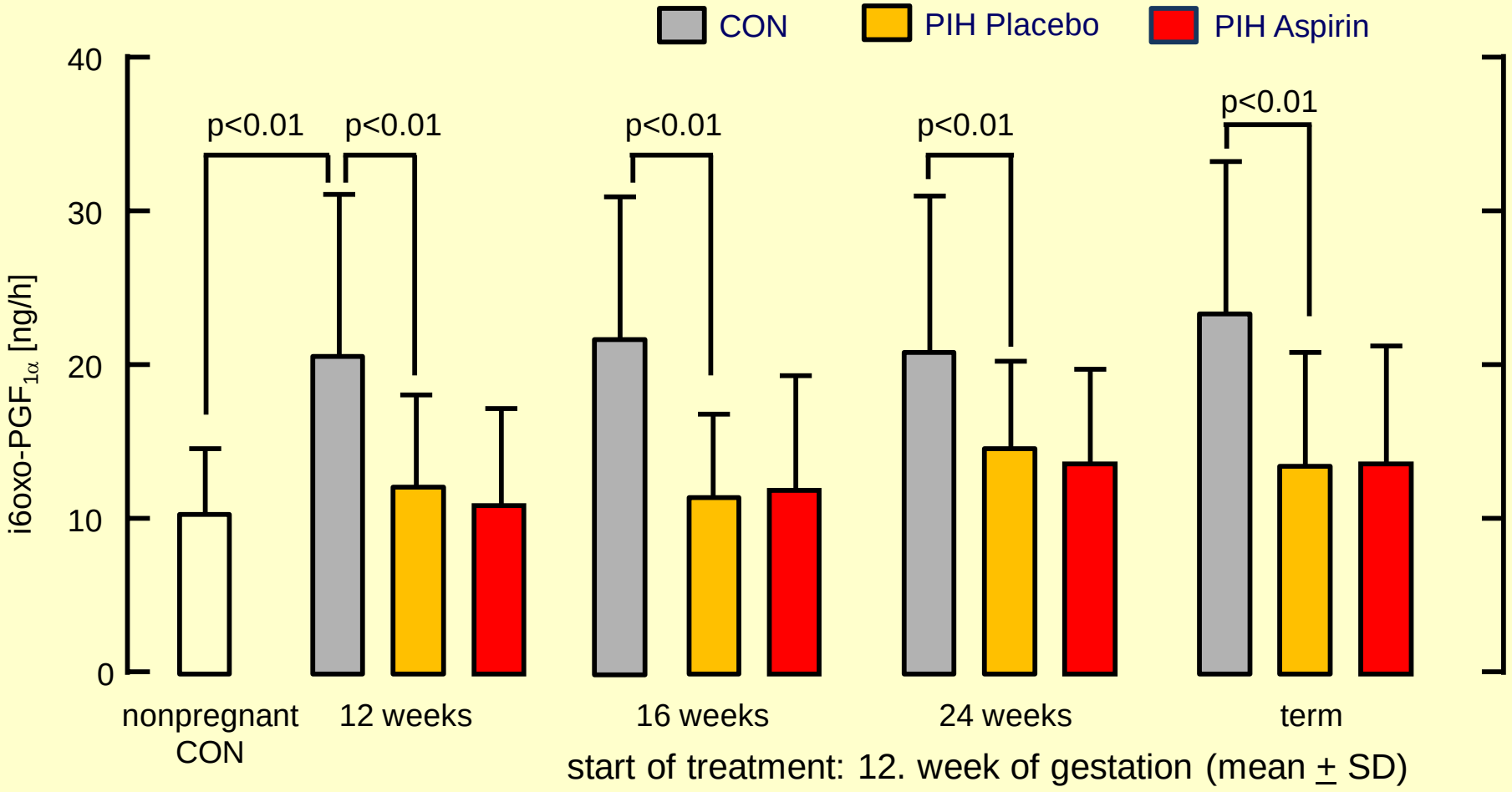
(Fitzgerald et al, Am J Obstet Gynecol 157:325-330; 1987)

Renal excretion of a prostacyclin metabolite (2,3-Dinor-6-keto-PGF1α (PGI-M) during and after gestation in normotensive women (CON) and women with pregnancy-induced hypertension (PIH)



(mod. after Fitzgerald, Circulation 75:956-963; 1987))

Renal excretion of immunoreactive 6-oxo-PGF1α (i6-oxo-PGF1α) during and after gestation in normotensive gravidae (CON) and gravidae at high risk of PIH treated with aspirin (60 mg/day) or placebo



(mod. after Benigni et al, NEJM 321:357-362; 1989)

LOW-DOSE ASPIRIN PREVENTS PREGNANCY-INDUCED HYPERTENSION (PIH) AND PRE-ECLAMPSIA IN ANGIOTENSIN-SENSITIVE PRIMIGRAVIDAE

H.C.S.Wallenburg, J.W.Makovitz, G.A.Dekker, P.Rotmans

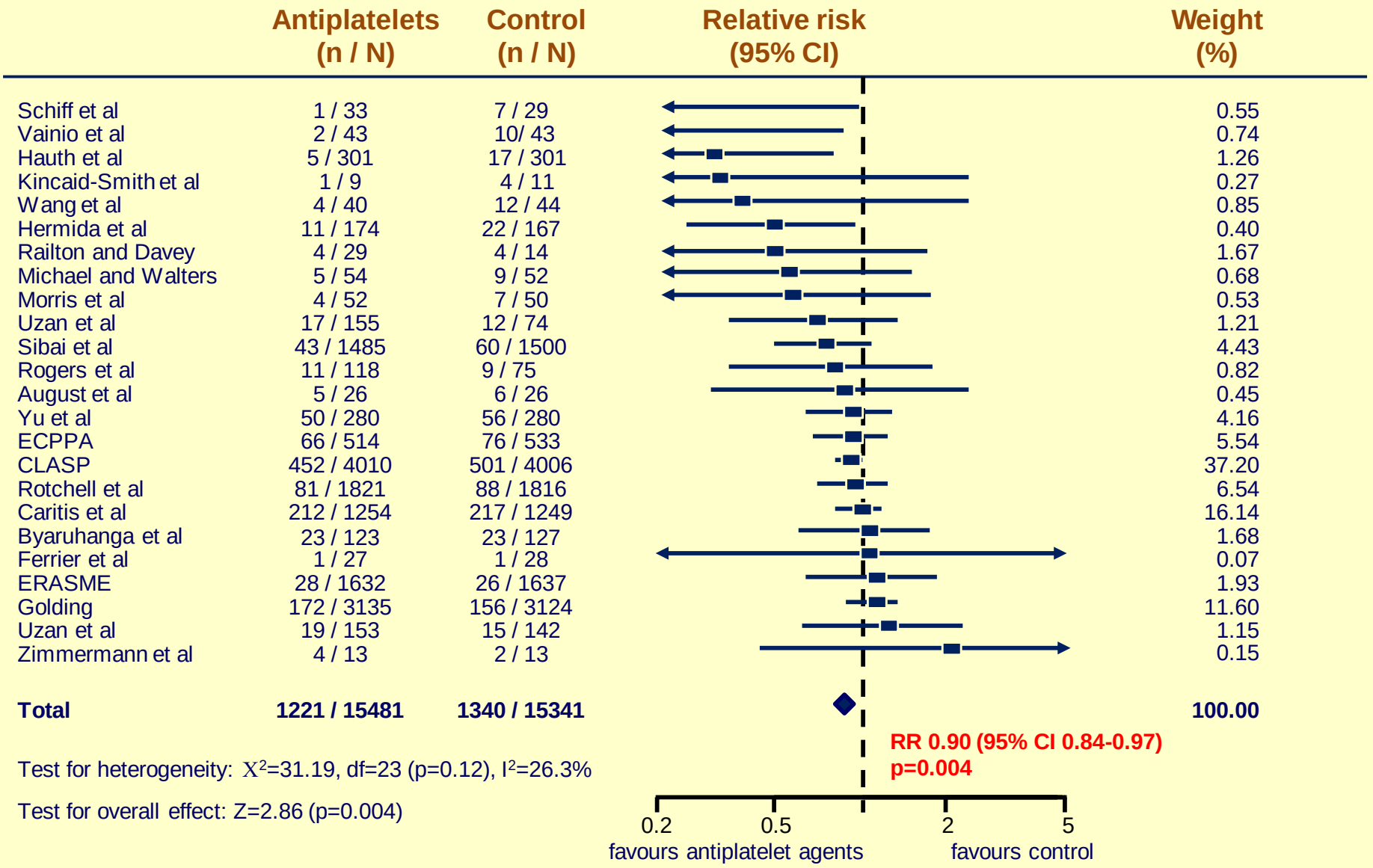
Abstract

The possibility of preventing pregnancy-induced hypertension (PIH) and pre-eclampsia in primigravidae by suppressing production of thromboxane A_2 with low-dose aspirin was investigated in a randomised, placebo-controlled, double-blind trial. 46 normotensive women at 26 weeks' gestation, judged to be at risk of PIH or pre-eclampsia because of an increased blood-pressure response to intravenously infused angiotensin II, were studied. 23 women received 60 mg aspirin daily, and the same number received matching placebo until delivery. In the placebo group PIH, pre-eclampsia, and eclampsia developed in 4, 7, and 1 cases, respectively, whereas only 2 women in the aspirin group had mild PIH. There were no adverse effects of treatment in mothers or infants.

Low-dose aspirin may restore prostacyclin/thromboxane imbalance, previously suggested as an important aetiological factor in PIH and pre-eclampsia.

(Wallenburg et al, Lancet 327; 1-3; 1986)

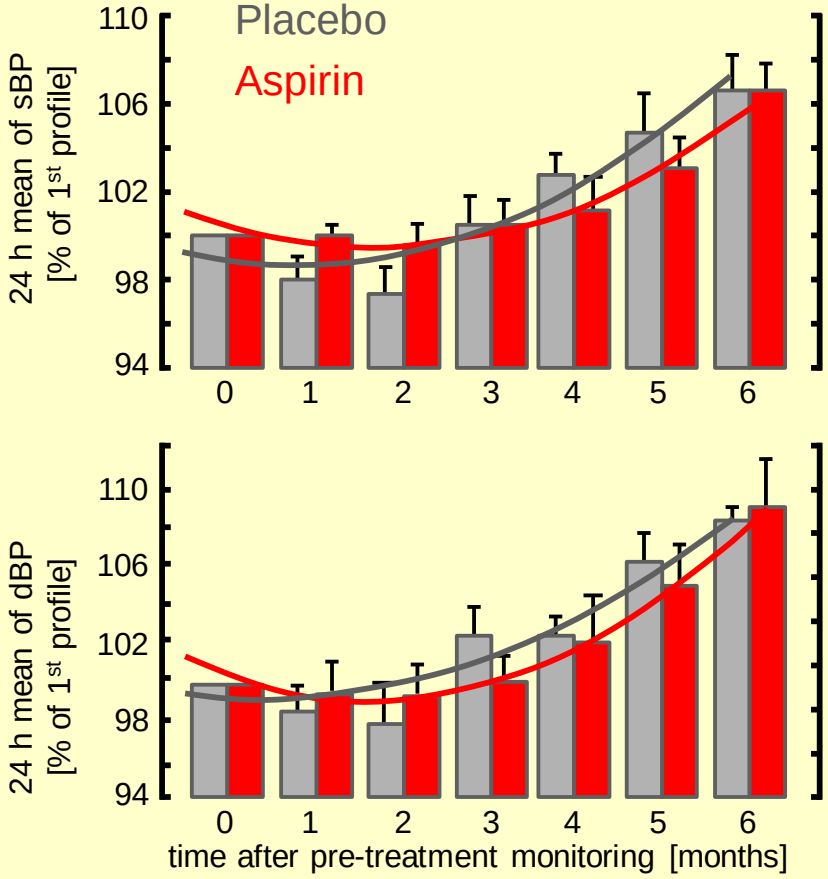
Maternal preeclampsia - ordered by effect size (PARIS group)



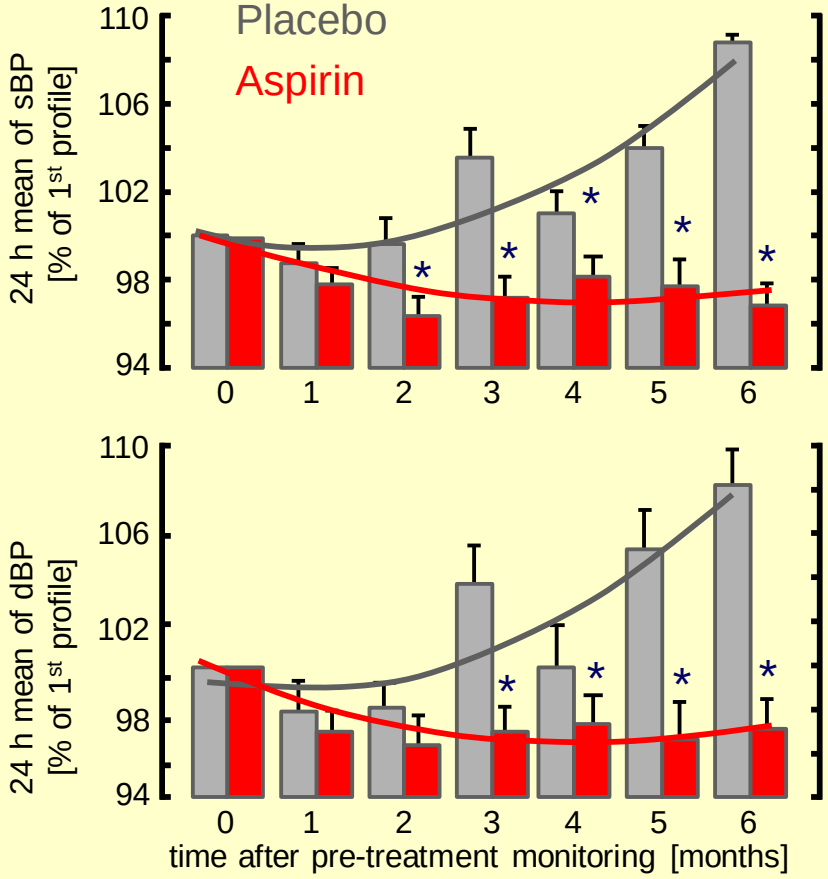
(mod. after Askie et al, Lancet, 369: 1791–98, 2007)

Time-dependent alterations in arterial blood pressure in pregnant women and their modification by Aspirin

Morning



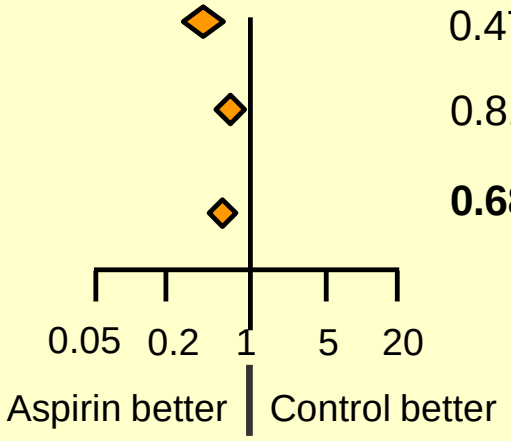
Evening



(Hermida et al, Hypertension, 30: 589-595, 1997)

Incidence of preeclampsia in aspirin-treated women at elevated risk in dependency on start of treatment. Metaanalysis of 34 randomized controlled trials, published between 1985 und 2005

Start of treatment	Number of patients (events / no events) Aspirin	Control	Relative Risk (RR)	RR	(95% CI)
≤ 16. week	36 / 389	80 / 375		0.47	(0.34-0.56)
> 16. week	387 / 5302	430 / 5282		0.81	(0.63-1.03)
total	**423 / 5691**	**510 / 5657**		**0.68**	**(0.54-0.86)**



(mod. after Bujold, Roberge et al, Obstet Gynaecol Can 31:818-826, 2009)

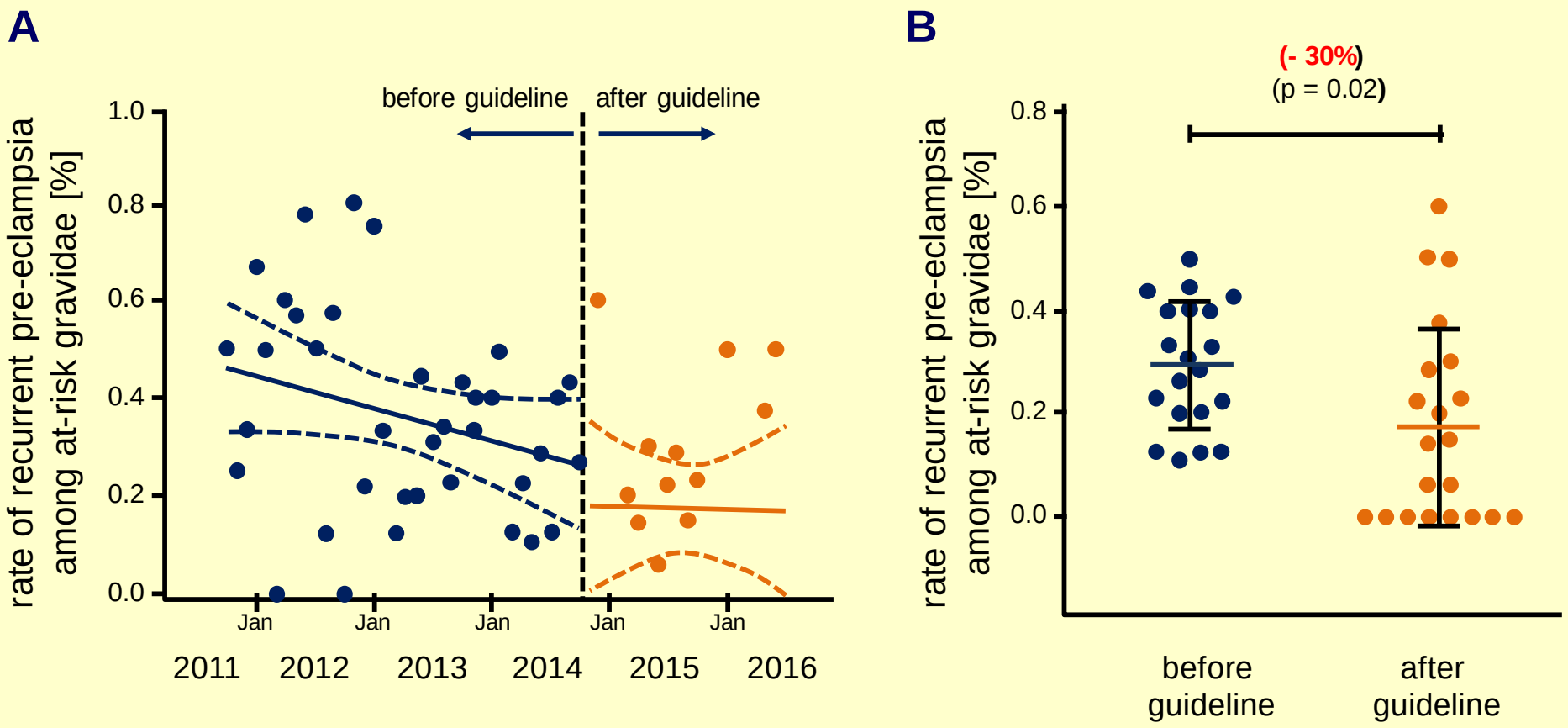
Effect of aspirin at a daily dose of ≤ or > 100 mg on placental abruption or antepartum hemorrhage. Metaanalysis of 20 studies on a combined total of 12,585 participants

Start of Treatment	daily Aspirin-dose	Number of patients (events / no events) Treatment	no Treatment	RR (95% CI)
≤ 16. week	< 100 mg	14/855	12/818	1.11 (0.52 - 2.36)
> 16. week	< 100 mg	51/3877	41/3911	1.32 (0.73 – 2.39)
total		**65 /4732**	**53/4729**	**1.20 (0.79 – 1.81)**
≤ 16. week	≥ 100 mg	12/1152	22/1166	0.62 (0.31-1.26)
> 16.week	≥ 100 mg	15/420	7/409	2.08 (0.86-5.06)
total		**27/1572**	**29/1575**	**0.99 (0.57-1.73)**

Significant differences in favor of ≥ 100 mg aspirin between ≤ 16. wk vs. > 16.wk (P = 0.04)

(mod. after Roberge et al, Am J Obstet Gynecol (in press) 2018)

Trends in rates of recurrent preeclampsia over 2 years before and 2 years after the USPSTF-recommendation on use of aspirin for prevention of recurrent preeclampsia



(Tolcher et al, Am J Obstet Gynecol, 217: 365;e1-365.e8, 2017)

The „ASpirin for evidence-based PREeclampsia prevention (ASPRE) Trial

Multicenter, doppelblind, randomisierte und Plazebo-kontrollierte Studie zur Untersuchung der Effektivität einer frühzeitigen ASA- Prophylaxe bei Hochrisiko-Schwangerschaften hinsichtlich Verhinderung einer präterminalenPräeklampsie (PIH), die Beendigung der Schwangerschaft vor der 37. Woche erforderte.

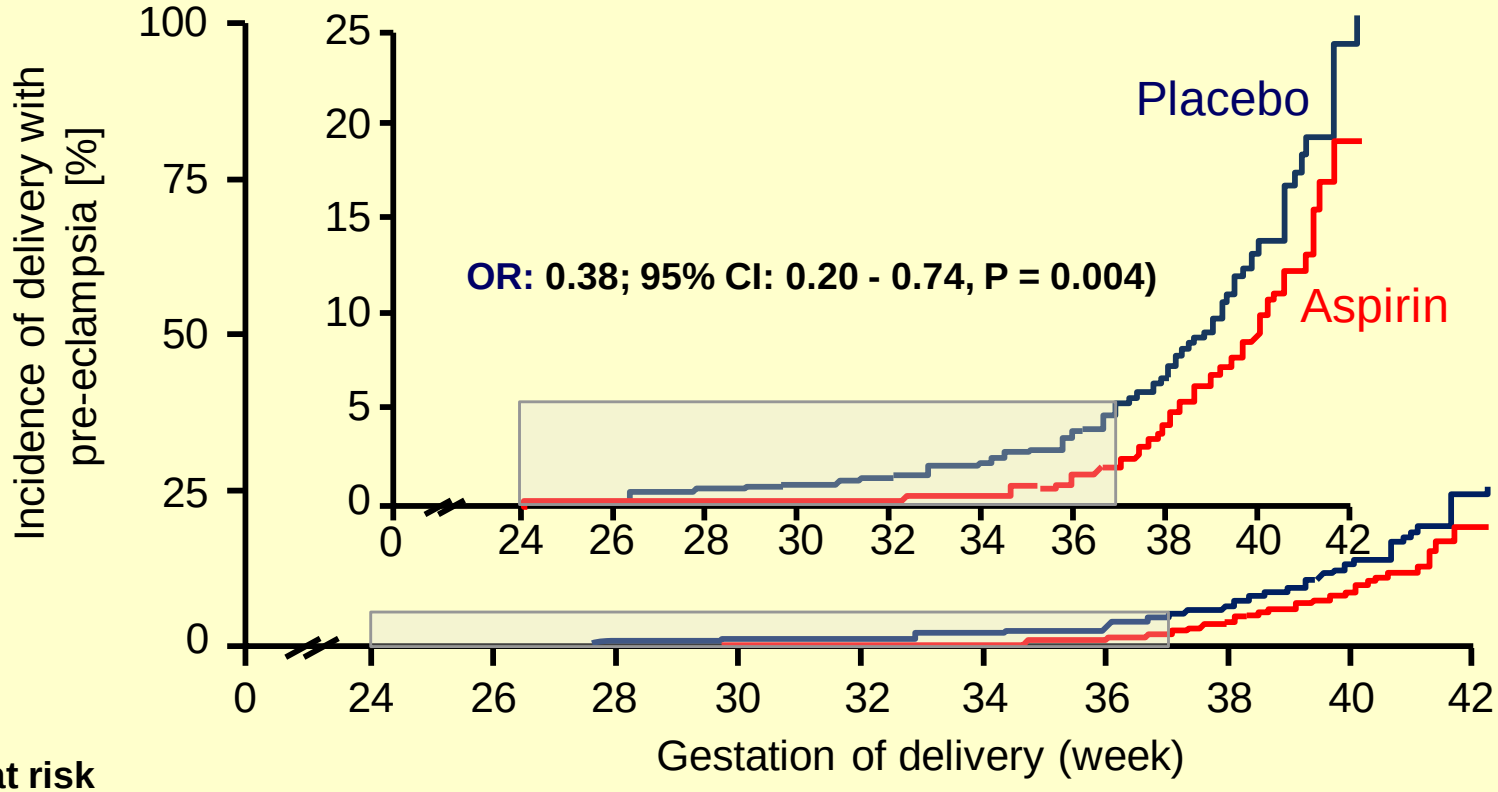
Intensives Screening-Programm in 11.-13. Schwangerschaftswoche mit Messung von laborchemischen („pregnancy-associated plasma protein“ (PAPP-A), PIGF), biophysikalischen (mAP, pulsatiler Index der Umbilikalarerie) und klinischen (aktueller Status, Vorerkrankungen, Medikationen) Parametern. Definition eines Risiko-Scores mit einer geschätzten Detektionsrate einer präterminalen PIH von 75% bei ca. 10% falsch positiven Ergebnissen (Akolekar et al, 2013)

1776 Risikoschwangerschaften. Therapiebeginn 11.-13. Schwangerschaftswoche, 150 mg/Tag beschichtete ASA-Tablette abends oder Placebo bis zur 36. Woche

Compliancekontrolle (Tablettenzählung)

(O´Gorman et al, BMJ Open 2016;6:e011801. doi:10.1136/bmjopen-2016-011801)

Incidence of delivery with preeclampsia in women at high risk for preterm eclampsia according to combined multimarker screening



 # at risk

Placebo	807	802	793	783	775	764	734	619	285	10
Aspirin	785	781	778	778	772	760	740	627	295	12

(Rolnik et al., N Engl J Med; 377: 613-622, 2017)

Offene Fragen zur medikamentösen Prophylaxe einer Präeklampsie mit Aspirin – Ziel: Erhöhung der Effizienz in Abhängigkeit vom individuellen Risiko

Bestätigung der ASPRE-Daten in weiteren Studien

Bessere Kenntnisse zur individuellen Ätiologie und Pathophysiologie der Erkrankung mit Option für Individualisierung der Therapie

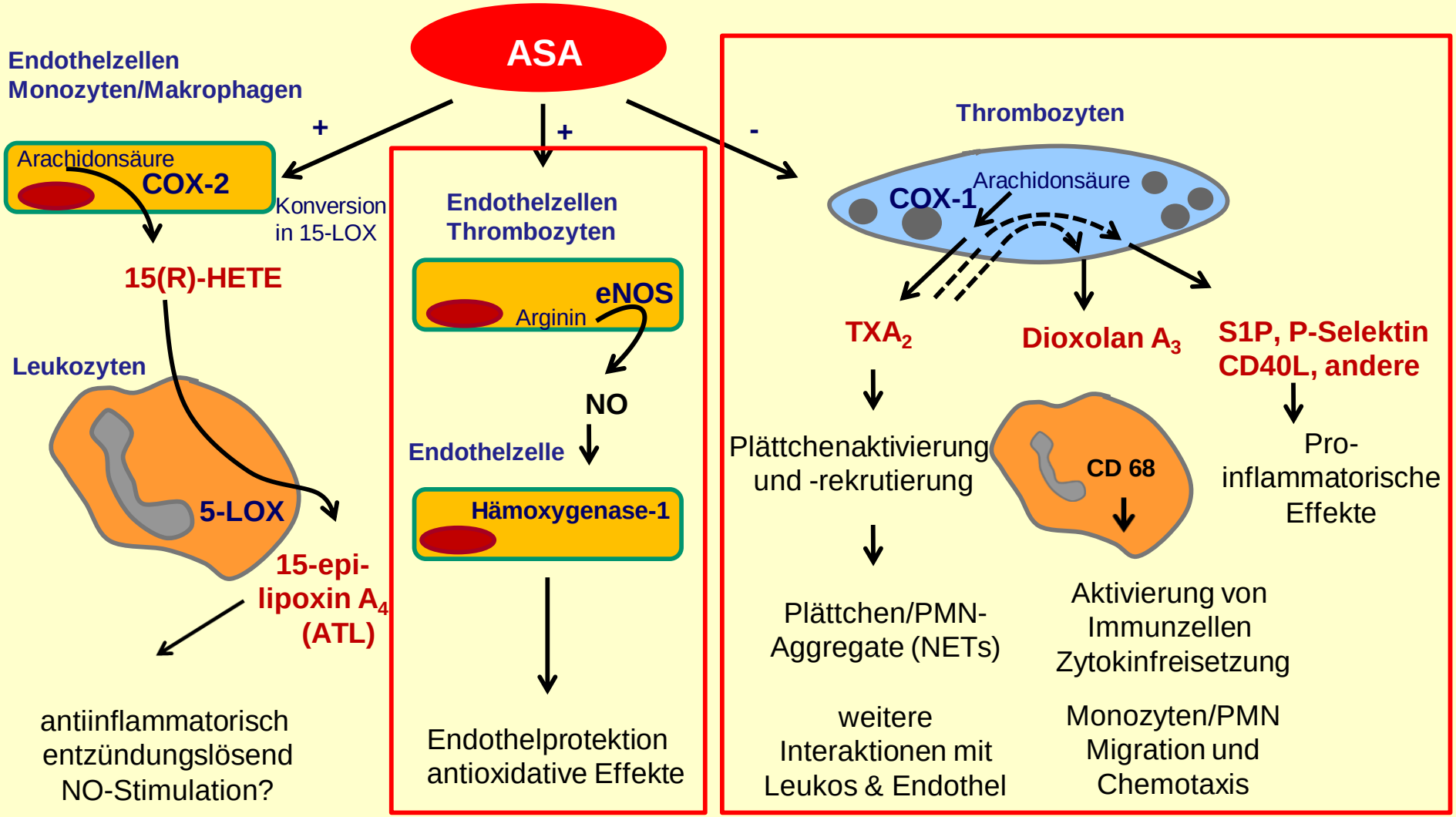
Standardisierung von klinischen und laborchemischen Risikomarkern. Entwicklung kombinierter klinisch/laborchemischer Profile

Festlegung von Risikoscores für Nutzen/Risiko-Kalkulation einer ASA-Prophylaxe

Medikamentöse Alternativen - neues mikronisiertes Aspirin? Thromboxanantagonisten?

EXTRA

Die multiplen pharmakologischen Wirkungen von Aspirin in Antiplättchendosen (75 – 325 mg)



(Schrör, K; „Acetylsalicylsäure“, S. 131 (2018)

Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. The ASPRE trial.

Abstract

BACKGROUND:

Does low-dose aspirin during pregnancy reduce the risk of preterm preeclampsia.

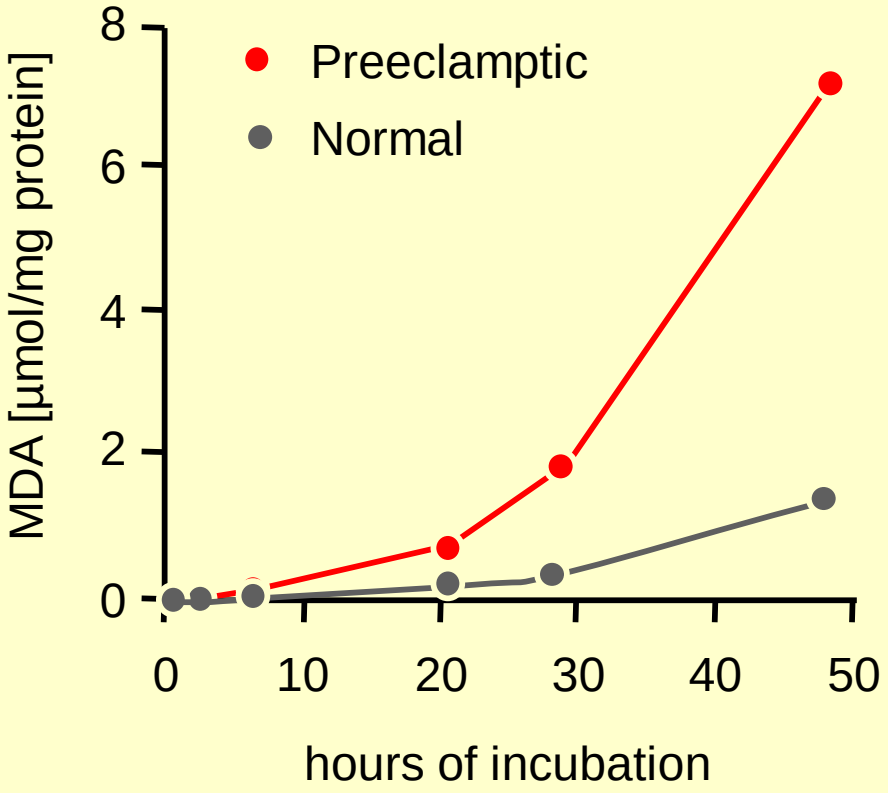
METHODS:
In this multicenter, double-blind, placebo-controlled trial, we randomly assigned 1776 women with singleton pregnancies who were at high risk for preterm preeclampsia to receive aspirin, at a dose of 150 mg per day, or placebo from 11 to 14 weeks of gestation until 36 weeks of gestation. The primary outcome was delivery with preeclampsia before 37 weeks of gestation.

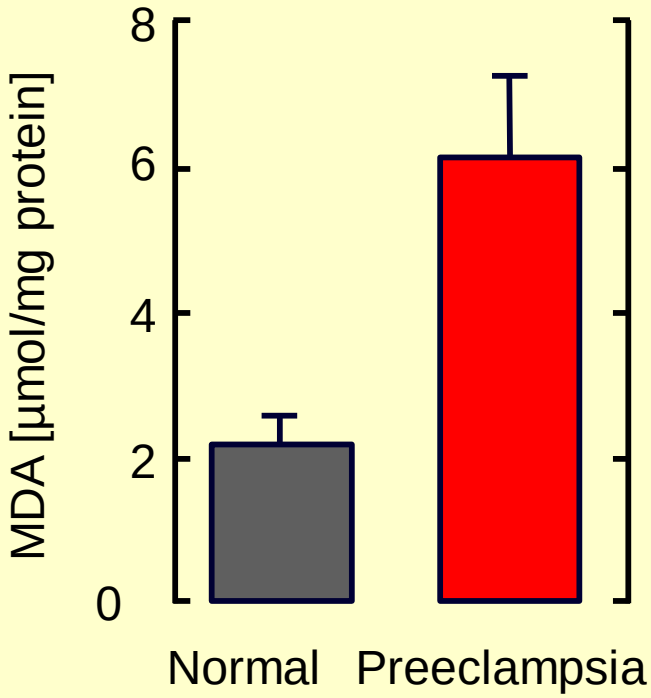
RESULTS:
A total of 152 women withdrew consent during the trial, and 4 were lost to follow up, which left 798 participants in the aspirin group and 822 in the placebo group. Preterm preeclampsia occurred in 13 participants (1.6%) in the aspirin group, as compared with 35 (4.3%) in the placebo group (odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74; P=0.004). Results were materially unchanged in a sensitivity analysis that took into account participants who had withdrawn or were lost to follow-up. Adherence was good, with a reported intake of 85% or more of the required number of tablets in 79.9% of the participants. There were no significant between-group differences in the incidence of neonatal adverse outcomes or other adverse events.

CONCLUSIONS:
Treatment with low-dose aspirin in women at high risk for preterm preeclampsia resulted in a lower incidence of this diagnosis than placebo.

Rolnik et al, (N Engl J Med; 377:613-622, 2017)

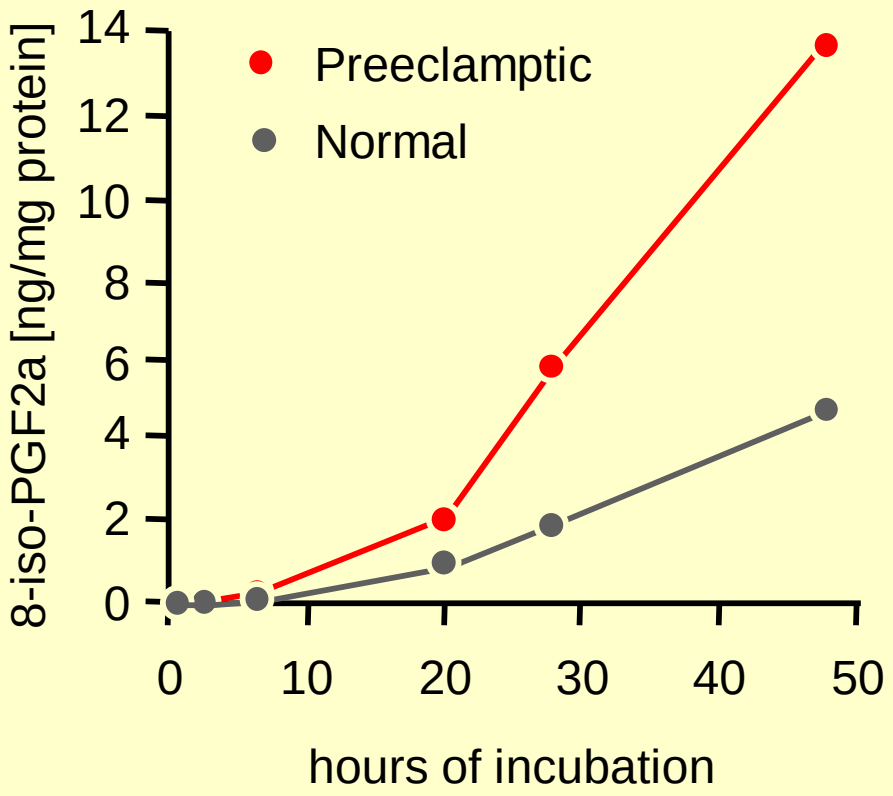
Release of malondialdehyde (MDA) (left) and MDA - levels (right) in placenta explantants of women with normal pregnancy (n =7) and preeclampsia (n = 7) at delivery

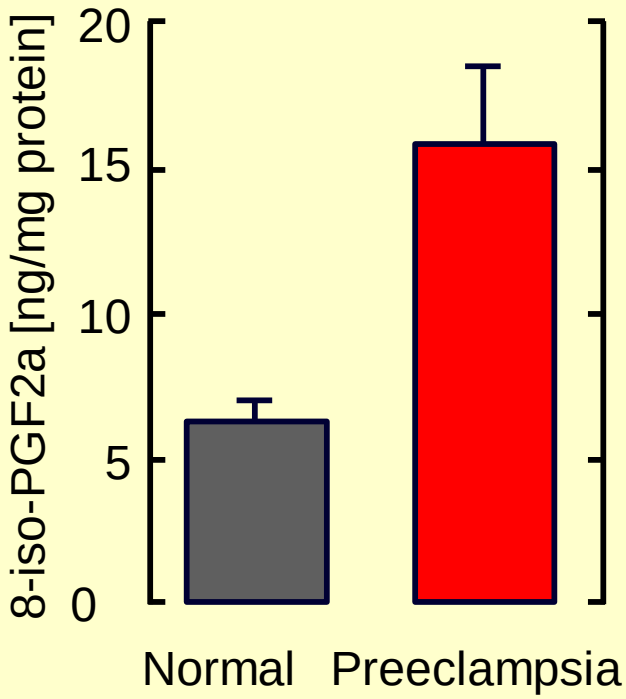




(Walsh et al, FASEB J. 14: 1289–1296, 2000)

Release of 8-iso-PGF2$_a$ (left) and 8-iso-PGF2$_a$ levels (right) in placenta explantants of women with normal pregnancy (n =7) and preeclampsia (n = 7) at delivery





(Walsh et al, FASEB J. 14: 1289–1296, 2000)

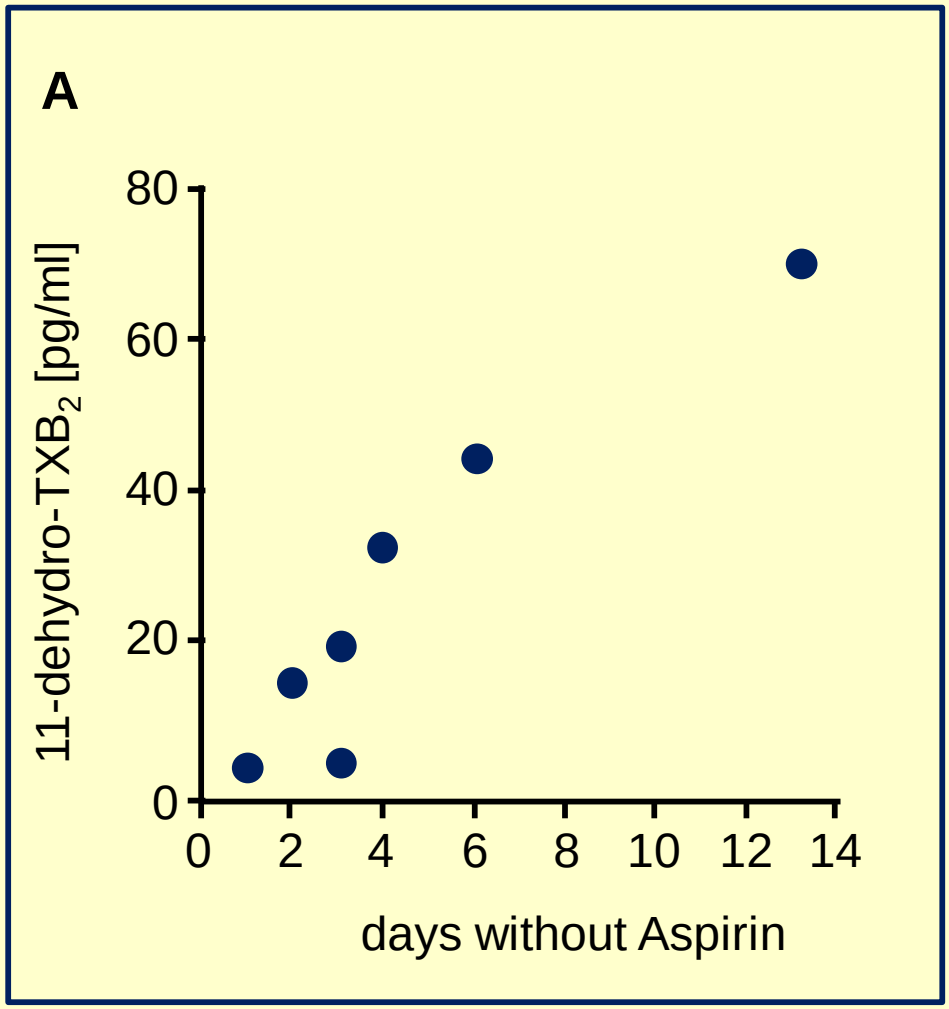
Course and outcome of pregnancy

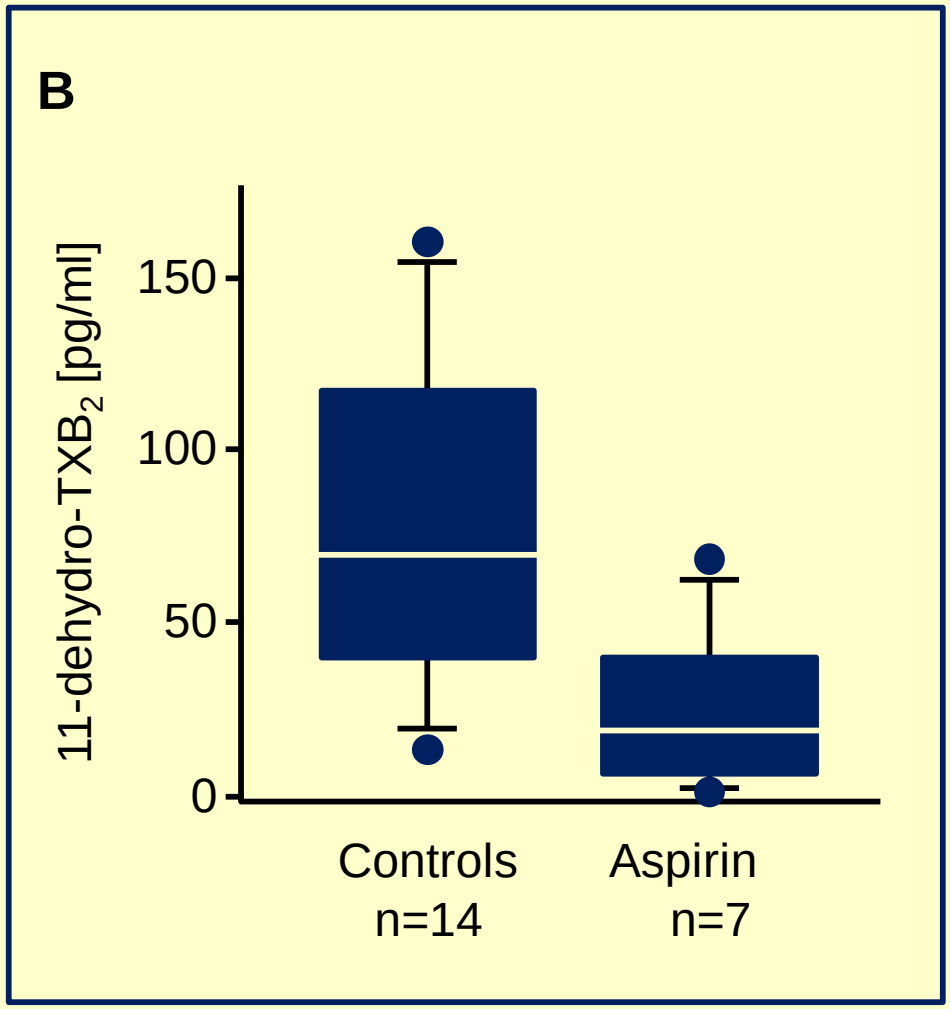
Women with	Aspirin (n=21)	Placebo (n=23)
Mild PIH*	2	1
Severe PIH**	0	3
Pre-eclampsia	0	7
Eclampsia	0	1
Week of delivery	40 (37-42)	39 (30-43)
No or deliveries <37 weeks	0	4
Malondialdehyde (nmol/10^9 platelets)	4.6 ± 1.1	0.51 ± 0.3

diastolic blood pressure: *): 95-100 mm Hg **): ≥105 mm Hg **): ≥95 mm Hg mit Proteinurie

(Wallenburg et al, Lancet 327; 1-3; 1986)

Levels of 11-DH-TXB2 in umbilical cord blood of newborns after maternal Aspirin prophylaxis (100 mg/day) as compared to controls. Discontinuation 1-13 days prior to delivery





(Leonhardt et al, Pediatrics, 111 - 1: e77-81, 2003)

015/018 – S1-Leitlinie der AWMF: Diagnostik und Therapie hypertensiver Schwangerschaftserkrankungen (aktueller Stand 12/2013) (Wikipaedia 02/18)

……Die derzeit einzige effektive Prävention der Präeklampsie bei Frauen mit Risikofaktoren (z.B. schwere Präeklampsie in der Anamnese) besteht in einer ab der Frühschwangerschaft (bis spätestens 16. SSW) beginnenden oralen Einnahme von niedrig dosierter Acetylsalicylsäure (ASS: 75-150 mg/Tag).

Dieses Vorgehen senkt signifikant das Risiko für eine Präeklampsie vor der 37. SSW, nicht aber in Terminnähe, sowie das Risiko für eine (schwere) Präeklampsie, Gestationshypertonie und IUGR bei pathologischem Dopplerbefund der Aa. uterinae.

Incidence (event) of preeclampsia in aspirin-treated women at elevated risk in dependency on start of treatment. Metaanalysis of 34 randomized controlled trials, published between 1985 und 2005

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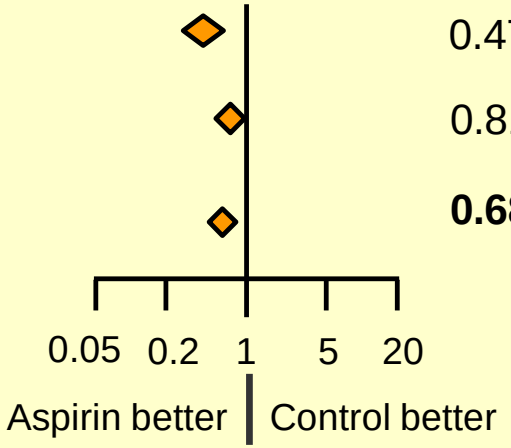
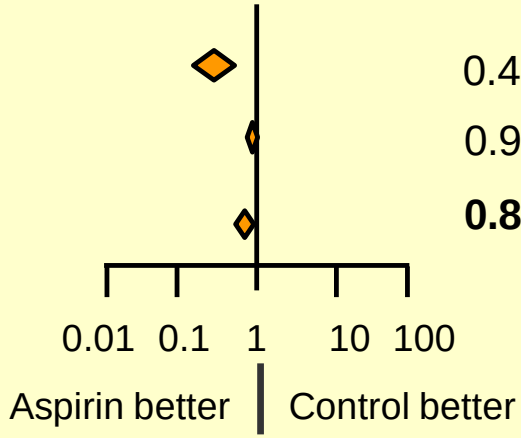


(mod. after Bujold, Roberge et al, Obstet Gynaecol Can 31:818-826)

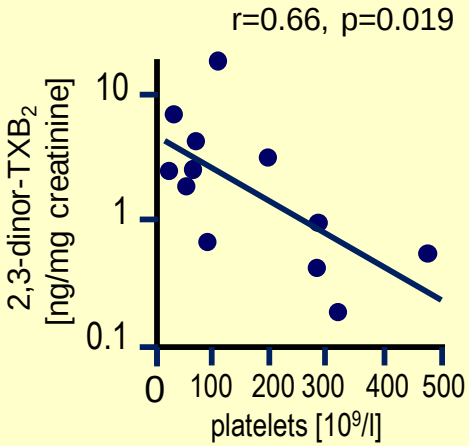
Incidence (event) of IUGR in aspirin-treated women at elevated risk in dependency on start of treatment. Metaanalysis of 34 randomized controlled trials, published between 1985 und 2005

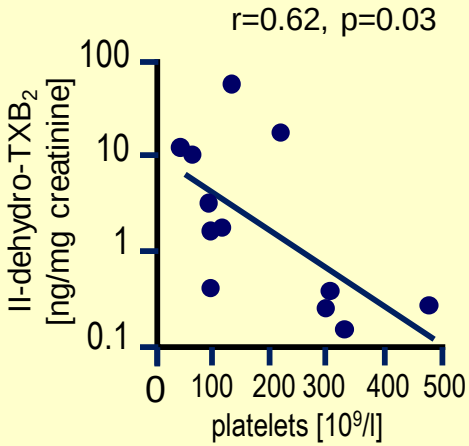
Start of treatment	Number of patients (events / no events) Aspirin	Control	Relative Risk (RR)	RR	(95% CI)
≤ 16. week	31 / 437	68 / 416		0.44	(0.30-0.65)
> 16. week	362 / 3528	369 / 3499		0.98	(0.87-1.10)
total	**393 / 3965**	**437 / 3915**		**0.85**	**(0.72-1.00)**

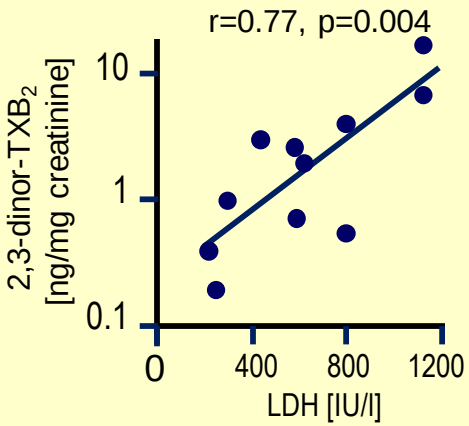


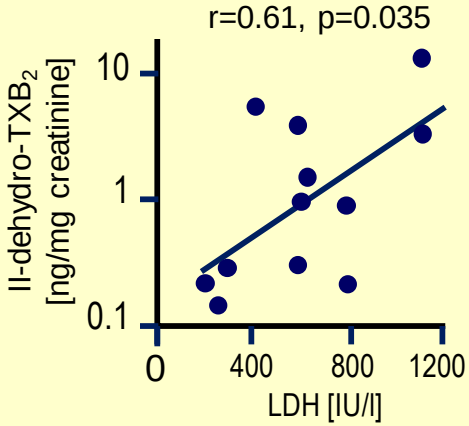
(mod. after Bujold, Roberge et al, Obstet Gynaecol Can 31:818-826)

Korrelation zwischen TX-Ausscheidung, (niedrigstem) Plättchencount, und LDH-Ausscheidung (unvollständig!)



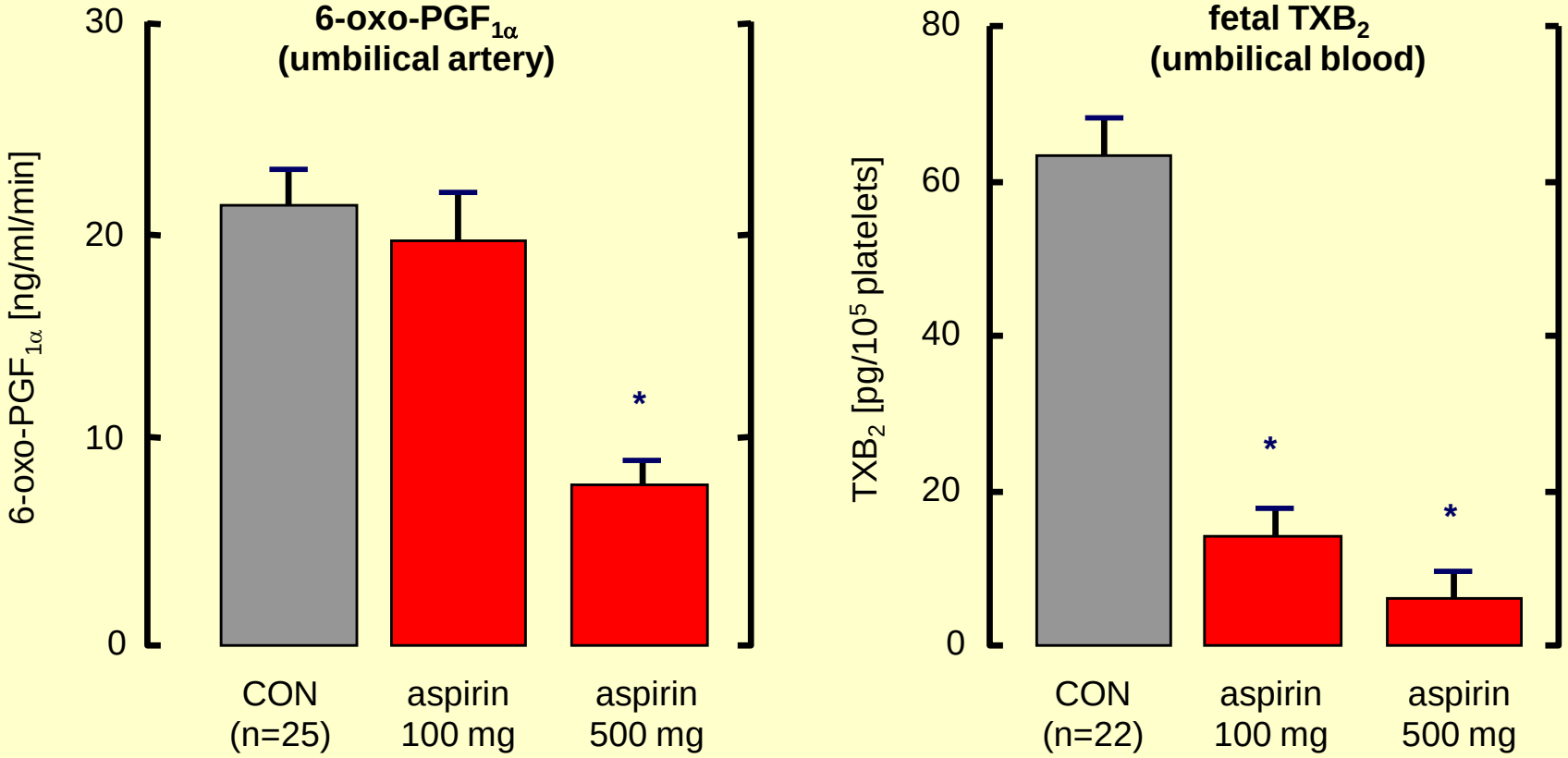






(Fitzgerald et al, Lancet, 335: 751-754, 1990)

Dose-dependent inhibition of prostacyclin (6-oxo-PGF1a) and thromboxane ($_{TXB2}$) formation by 100 and 500 mg oral aspirin in healthy women during labour at term. 100 mg aspirin cause a marked reduction of (platelet-dependent) TXB_2 in spontaneous clotting cord blood but leave prostacyclin formation by umbilical artery (in vitro) unaffected. The high dose of 500 mg aspirin markedly reduced both thromboxane and prostacyclin formation



*): $p < 0.001$ vs. CON

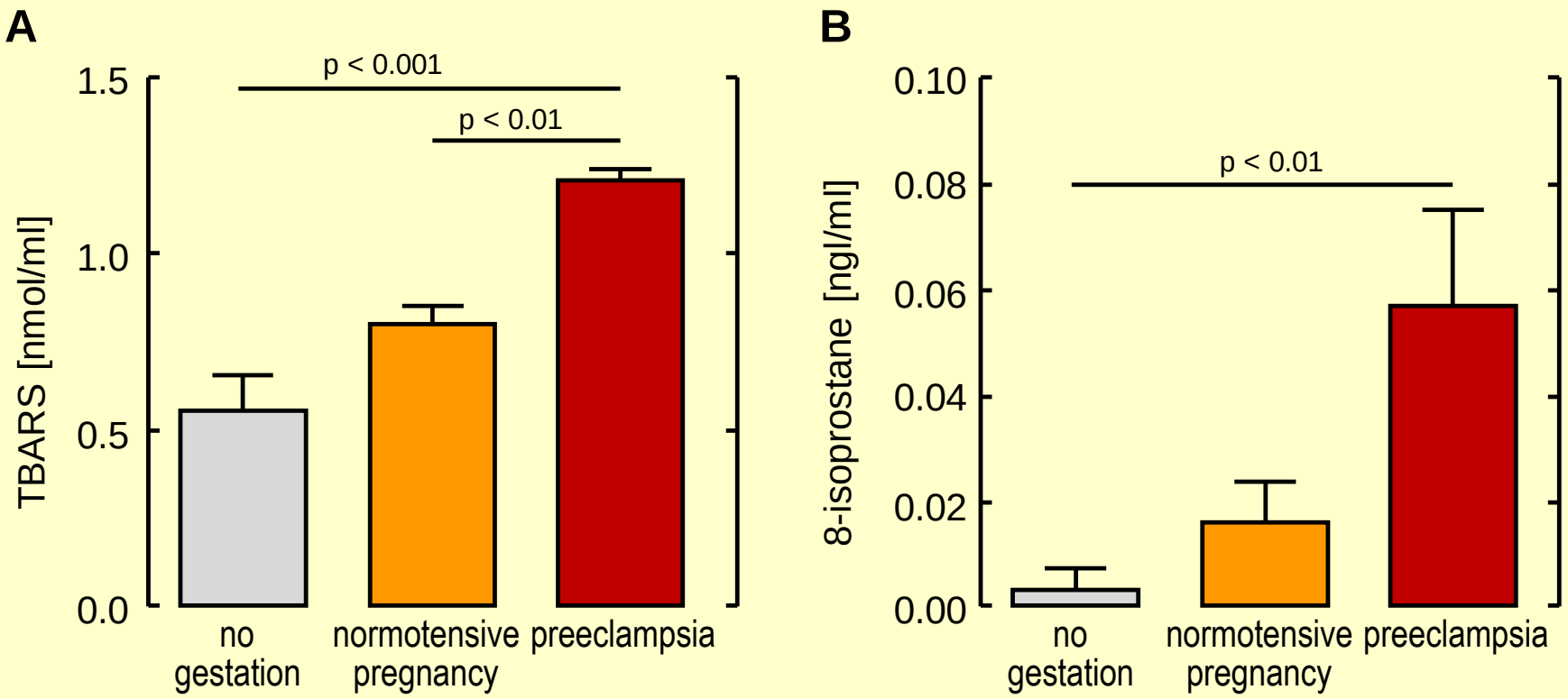
(Ylikorkala et al, 1986)

Effect of aspirin at a daily dose of ≤ or > 100 mg/day on placental abruption or antepartum hemorrhage. Metaanalysis of 20 studies on a combined total of 12,585 participants

Start of treatment	Aspirin-Dose	Number of patients (events / no events) Treatment	Control	RR (95% CI)
≤ 16. week	< 100 mg	14/855	12/818	1.11 (0.52 - 2.36)
> 16. week	< 100 mg	51/3877	41/3911	1.32 (0.73 – 2.39)
total		**65 /4732**	**53/4729**	**1.20 (0.79 – 1.81)**
≤ 16. week	≥ 100 mg	12/1152	22/1166	0.62 (0.31-1.26)
> 16.week	≥ 100 mg	15/420	7/409	2.08 (0.86-5.06)
total		**27/1572**	**29/1575**	**0.99 (0.57-1.73)**

(mod. after Roberge et al, Am J Obstet Gynecol (in press) , 2018)

Lipid peroxidation levels as measured by thiobarbituric acid-reactive substance (TBARS) (A) and isoprostane (B) in plasma of women with preeclampsia but without preexisting clinical conditions as opposed to normotensive pregnant women and non-pregnant women. This was associated with elevated levels of antiangiogenic protein (sFtl-1) and TNFα



((not shown) [?])

Benigni

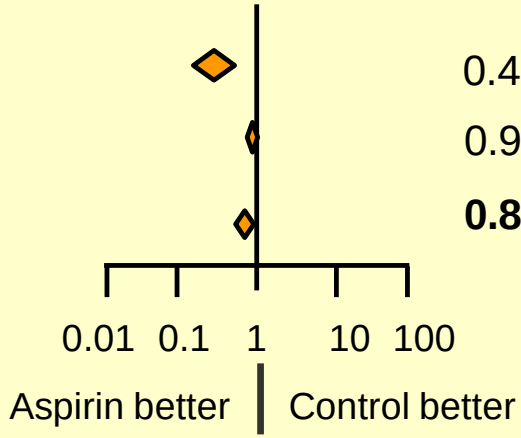
Urinary excretion of i6oxo-PGF1a (ng/hour) in normal pregnant women and women at risk for Preeclampsia

Group	12 wk	16 wk	24 wk	term
Normal pregnancy	20.7 + 10.4	21.9+ 9.0	21.0 + 10.0	23.5+9.8
Preeclampsia placebo	12.2 + 5.8	11.5 + 5.3	14.7+5.5	13.6 +7.2
Preeclampsia aspirin	11.0 + 6.1	12.0 + 7.3	13.7 + 6.0	13.7+ 7.6

Nonpregnant women: 10.3 + 4.6 (als Text darunter)

Incidence (event) of IUGR in aspirin-treated women at elevated risk in dependency on start of treatment. Metaanalysis of 34 randomized controlled trials, published between 1985 und 2005

Start of treatment	Number of patients (events / no events) Aspirin	Control	Relative Risk (RR)	RR	(95% CI)
≤ 16. week	31 / 437	68 / 416		0.44	(0.30-0.65)
> 16. week	362 / 3528	369 / 3499		0.98	(0.87-1.10)
total	**393 / 3965**	**437 / 3915**		**0.85**	**(0.72-1.00)**



(mod. after Bujold, Roberge et al, Obstet Gynaecol Can 31:818-826, 2009)