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Il Trauma nel Paziente in Terapia con Antiaggreganti

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Introduction

- In the last 10 yrs the use of antithrombotic therapy has grown, as an effect of international guidelines promoting their widespread use to prevent cardiovascular events in high-risk populations.
- This effect is particularly important, since the epidemiology of the trauma population has also changed, with a larger prevalence of older age-groups, where antiplatelet drugs are more prevalent.
- ≈10% of the Italian population is treated with antiplt agents, which increased to 24.7% in pts >65 yrs.

Introduction

- The effects of antiplatelets, mainly Aspirin and Clopidogrel, on traumatic bleeding are not clearly defined.
- Data from non-elective orthopaedic procedures show both increased peri-operative blood loss or no effects.
- In retrospective studies pre-injury use of antiPlts did not affect morbidity and mortality on pelvic trauma, as in hip fractures.

Introduction

Platelet function in trauma pts has been poorly investigated.

In pts with acute traumatic coagulopathy, plt. count does not decline to levels that might be expected to contribute significantly to coagulopathy [*Floccard, Injury* ***2012***].

The plt. count on admission, may be predictive of outcome as documented in massively transfused trauma pts, where plt count was inversely correlated with injury severity [*Hess JR, Transfusion* ***2009***], morbidity [*Schnuriger B, J Trauma* ***2010***] and mortality.

Severe injury increased platelet activation, along with decreased function as observed in TBI, was associated with increased mortality [*Jacoby RC J Trauma* ***2001***].

Antiplatelet Therapy Is Associated With Decreased Transfusion-Associated Risk of Lung Dysfunction, Multiple Organ Failure, and Mortality in Trauma Patients*

Objective: To determine whether prehospital antiplatelet therapy was associated with reduced incidence of acute lung dysfunction, multiple organ failure, and mortality in blunt trauma patients.

Design: Secondary analysis of a cohort enrolled in the National Institute of General Medical Sciences Trauma Glue Grant database.

Setting: Multicenter study including nine U.S. level-1 trauma centers.

Patients: A total of 839 severely injured blunt trauma patients at risk for multiple organ failure (age > 45 yr, base deficit > 6 mEq/L or systolic blood pressure < 90 mm Hg, who received a blood transfusion). Severe/isolated head injuries were excluded.

Measurements and Main Results: Primary outcomes were lung dysfunction (defined as grades 2–3 by the Denver multiple organ failure score), multiple organ failure (Denver multiple organ failure score >3), and mortality. Patients were documented as on antiplatelet therapy if taking acetylsalicylic acid, clopidogrel, and/or ticlopidine. Fifteen percent were taking antiplatelet therapy prior to injury. Median injury severity score was 30 (interquartile range 22–51), mean age 61 + 0.4 yr and median RBCs volume transfused was 1700 mL (interquartile range 800–3150 mL). Overall, 63% developed lung dysfunction, 19% had multiple organ failure, and 21% died. After adjustment for age, gender, comorbidities, blood products, crystalloid/12 hrs, presence of any head injury, injury severity score, and 12 hrs base deficit > 8 mEq/L, 12 hrs RBC transfusion was associated with a significantly smaller risk of lung dysfunction and multiple organ failure among the group receiving antiplatelet therapy compared with those not receiving it (lung dysfunction $p = 0.0116$, multiple organ failure $p = 0.0291$). In addition, antiplatelet therapy had a smaller risk (albeit not significant, $p = 0.06$) of death for patients receiving RBC compared to those not on antiplatelet therapy after adjustment for confounders,

Conclusions: Pre-injury antiplatelet therapy is associated with a decreased risk of lung dysfunction, multiple organ failure, and possibly mortality in high-risk blunt trauma patients who received blood transfusions. These findings suggest platelets have a role in organ dysfunction development and have potential therapeutic implications. (*Crit Care Med* 2013; 41:399–404)

Key Words: antiplatelet agents; blood transfusion; lung dysfunction; multiple organ failure; trauma

Harr Jeffrey, *et al*, ***Cri Care Med*** 2013

Antiplatelets and Head Injury

- In pts with head injury pre-injury anti-thrombotic therapy has been proposed as risk factor.
- The risk refers to an increased incidence of intracranial injury after CT scan, to a radiological worsening of lesions, to a risk of neurosurgical intervention and to unfavourable outcome at short- and long-follow up.

Antiplatelets and Risk of Intracranial Lesions after Head Injury

Author	Inclusion criteria	Antiplatelets	N. cases	Results
Spektor - **Israel** *J Neurosurg 2003*	Mild & Moderate, Age >60	Asp. 100 mg	110	ICH: Not increased
Jones - **USA** *Am J Surg 2006*	All TBI, Age >50	Asp. - Clop.	43	Neurosurg. & re-bleeds in Clop. increased
Tauber - **Austria** *J Trauma 2009*	Mild	Clop.	1,660	Incidence of ICH: increased
Fabbri – **Italy** *JNNP 2010*	Mild	Asp. - Ibuprofen.	10,288	ICH: increased (Asp + age>75)
Brewer – **USA** *J Trauma 2011*	Mild	Clop. - Warfarin	141	ICH: increased
Nishijima - **USA** *Acad Emerg Med 2013*	Mild	Clop. - Warfarin	958	ICH: increased
Levine - **USA** *Am J Emerg Med 2014*	Mild	Clop.	658	ICH: increased (OR 16.7; 95% CI 1.71-162.7).

Antiplatelet Therapy & Outcome in Head Injury

Author	Inclusion	Therapy	N. cases	Results
Mina, **USA** *J Trauma* ***2002***	ICH	Asp.	19	Mortality in Aspirin & Warfarin group: no difference
Ohm, **USA** *J Trauma* ***2005***	All ICH	Asp. Clop	90	Mortality: 3-fold increased
Jones, **USA** *Am J Surg* ***2006***	All TBI, Age >50	Asp. Clop.	43	Neurosurg. Interv. and re-bleeds: increased in Clop.
Wong- **Hawaii** *J Trauma* ***2008***	All TBI	Asp. Clop	111	Long-term disability and mortaliy: increased
Ivascu – **USA** *J Trauma* ***2006***	All TBI	Asp. Clop.	109	Mortality: increased
Major - **UK** *Emerg J Med* ***2009***	All TBI	Asp. Clop.	287	Mortality: 21% increased in Asp group
Fortuna - **USA** *Surgery* ***2009***	Mild	Asp.Clop. Warfarin	166	Mortality: no difference
Fabbri - **Italy** *JNNP* ***2010***	Mild	Asp. - Ibuprofen.	14,288	Death, vegetative state, severe disability: no difference
Boneville, **USA** *Surgery* ***2011***	All TBI	Asp. Clop.	271	Mortality or LOS: no difference
Bellal - **USA** *J Trauma ACS* ***2014***	All TBI	Clop	142	CT worsening, risk of neurosurg interv.: Increased

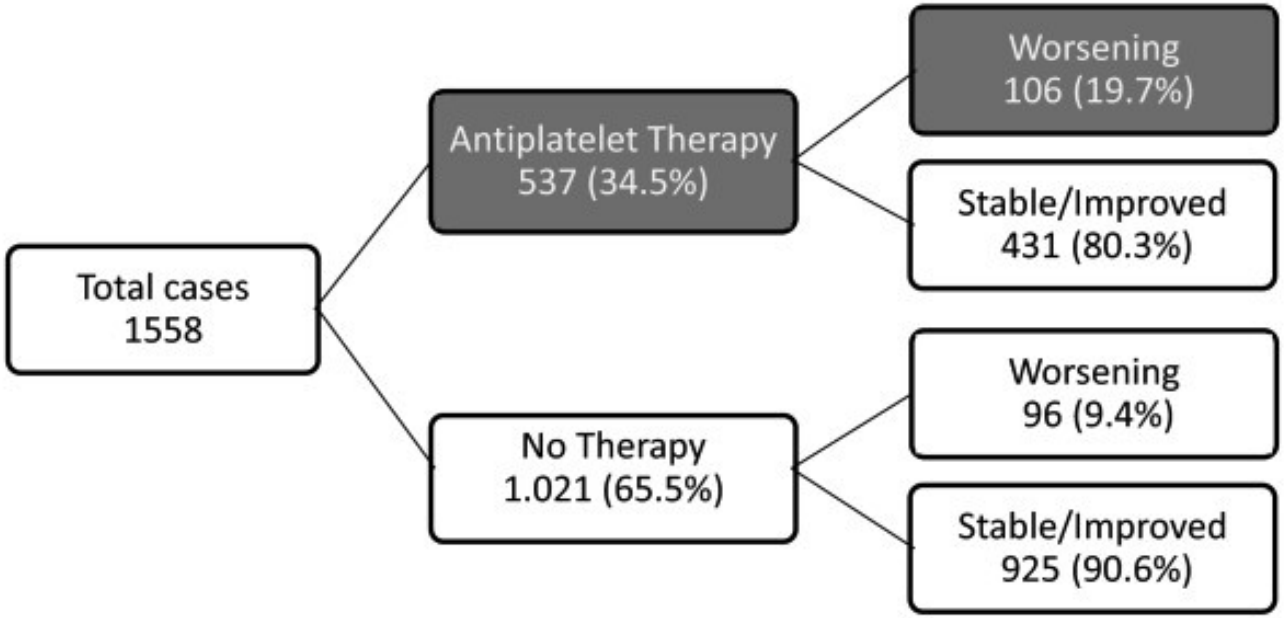
Antiplatelet therapy and the outcome of subjects with intracranial injury: the Italian SIMEU study

Introduction: We tested the potential risk of pre-injury antiplatelet drug use on short- and long-term outcome of head injured pts admitted to EDs.

Methods: 1,558 adult pts with mild, moderate and severe head injury included by 32 centres. In logistic analyses, the short-term outcome was assessed by an evaluation of head CT scan at 6 to 24 hours after trauma and the long-term outcome by the Glasgow outcome scale (GOS) at six months.

Fabbri A, *et al.* ***Crit*** **Care** 2013

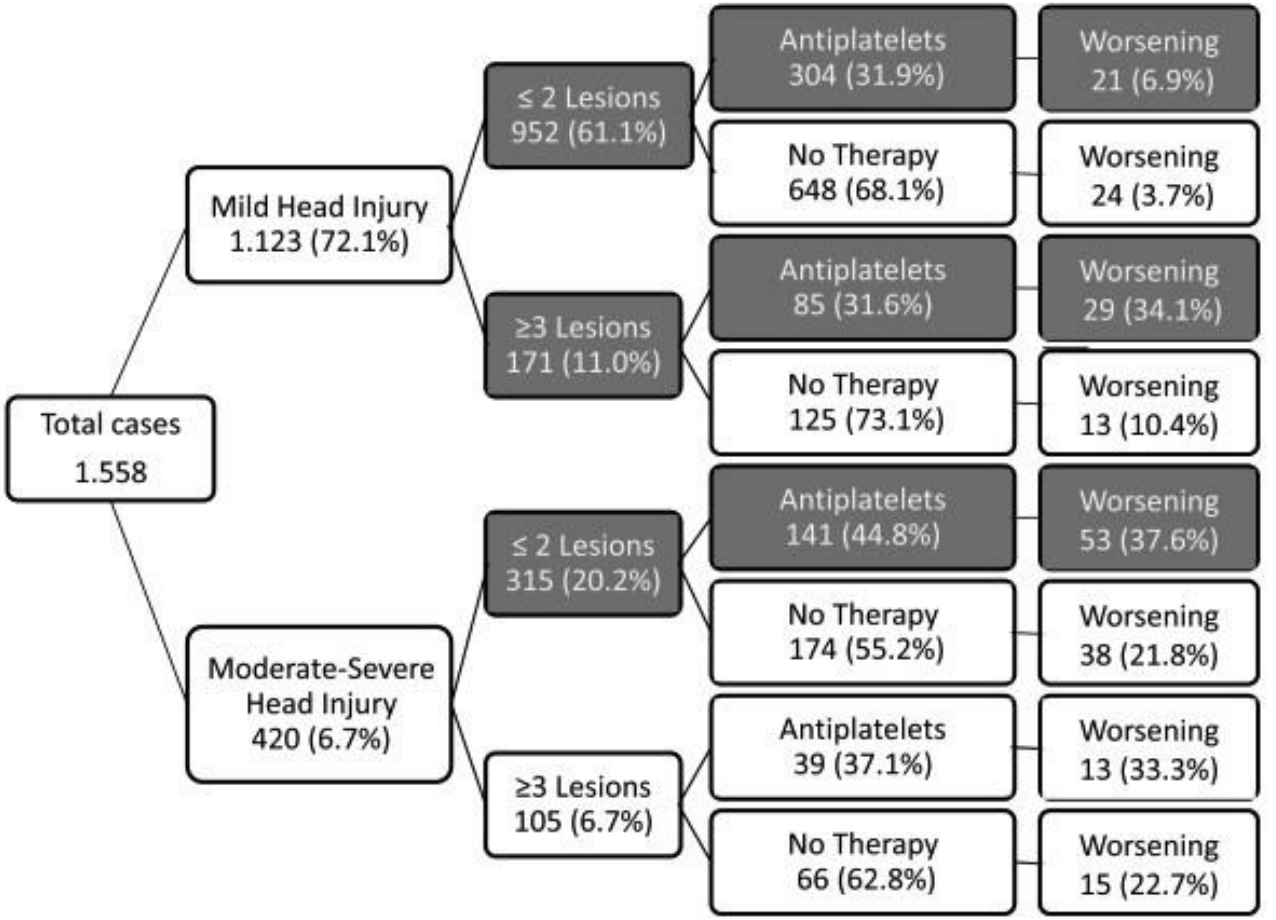
Antiplatelet therapy and the outcome of subjects with intracranial injury: the Italian SIMEU study



In mild, moderate and severe head injury and positive CT scan, the short term outcome was studied in relation to antiplatelet therapy. The risk of short term outcome (TC worsening) 2-fold increased (19.7% treated vs. 9.3% untreated.The risk was higher in pts. on clopidogrel (RR 5.76, 95% CI 3.88 to 8.54).

Fabbri A, *et al.* ***Crit* Care** 2013

Antiplatelet therapy and the outcome of subjects with intracranial injury: the Italian SIMEU study



Short term worsening resulted particularly high, in relation to severity of head injury, n. of intracranial lesions and antiplatelet therapy.

Fabbri A, *et al.* ***Crit Care*** 2013

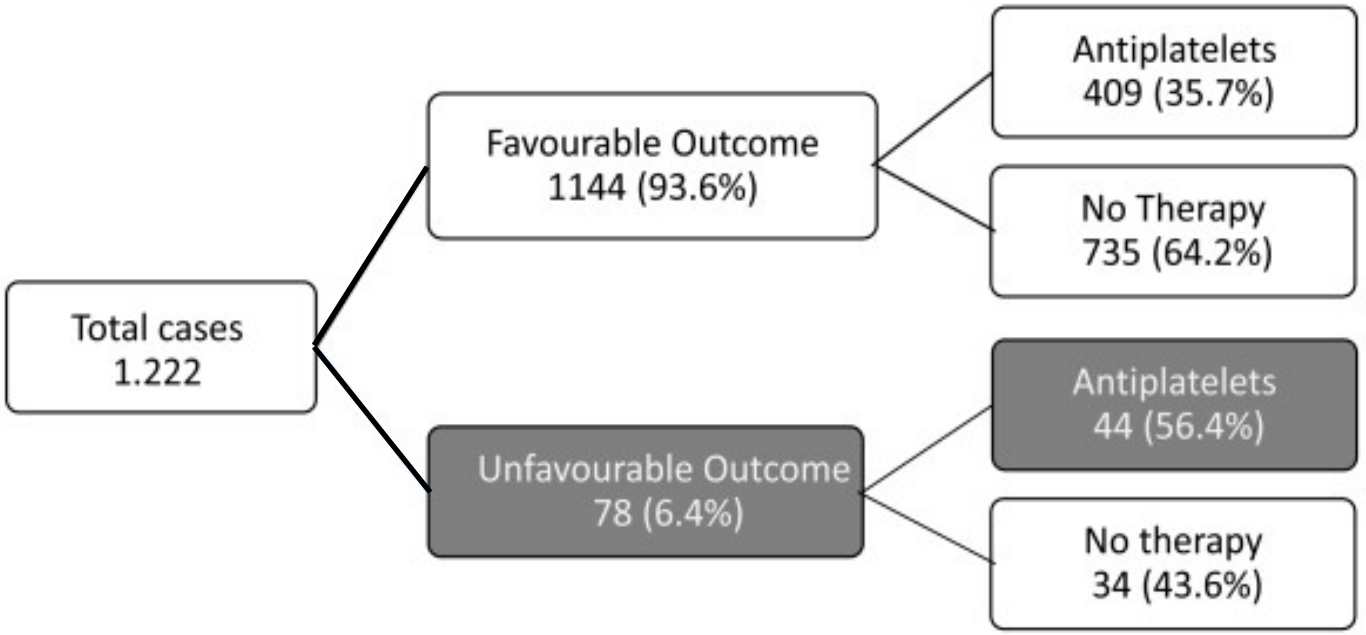
Antiplatelet therapy and the outcome of subjects with intracranial injury: the Italian SIMEU study

Covariates	Odds Ratio	95% CI	*P* value
Sex (males)	1.24	0.88 to 1.75	0.211
Age (decades)	0.91	0.83 to 1.01	0.065
Road accidents	1.03	0.70 to 1.52	0.874
Glasgow Coma Scale	4.59	3.23 to 6.51	< 0.001 ★
Basal skull fracture	1.20	0.72 to 1.99	0.480
Marshall category	1.43	1.09 to- 1.89	0.011 ★
Type of lesion			
Subdural hematoma	1.32	0.86 to 2.01	0.205
Epidural hematoma	1.13	0.65 to 1.98	0.656
Intracerebral hemorrhage/contusion	0.96	0.62 to 1.50	0.875
Traumatic subarachnoid hemorrhage	0.80	0.51 to 1.24	0.322
Intraventricular hemorrhage	0.37	0.17 to0.775	0.008
Depressed skull fracture	1.03	0.60 to 1.78	0.903
Number of lesions (≥ 2)	2.56	1.46 to 4.51	0.001 ★
Anticoagulant therapy	1.17	0.65 to 2.10	0.606
Antiplatelet therapy	2.87	1.94 to 4.23	< 0.001 ★

Logistic analysis with variables tested in the predictive model for short-term outcome (CT worsening) after head injury.

Fabbri A, *et al*. ***Crit Care*** 2013

Antiplatelet therapy and the outcome of subjects with intracranial injury: the Italian SIMEU study



The risk of unfavorable outcome at six month (death, vegetative state and permanent severe disability) increased by 50% in the group treated with antiplatelet therapy (RR 1.58, 95% CI 1.28 to 1.95; $P < 0.001$).

Fabbri A, *et al*. ***Crit Care*** 2013

A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet medication-associated intracranial haemorrhage.

- Six studies were found to be suitable for the meta-analysis (two studies for spontaneous ICH and the remaining four were traumatic intracranial haemorrhage).
- The pooled OR showed no benefit in survival following a platelet transfusion (OR=0.773, 95% CI 0.414 to 1.442).

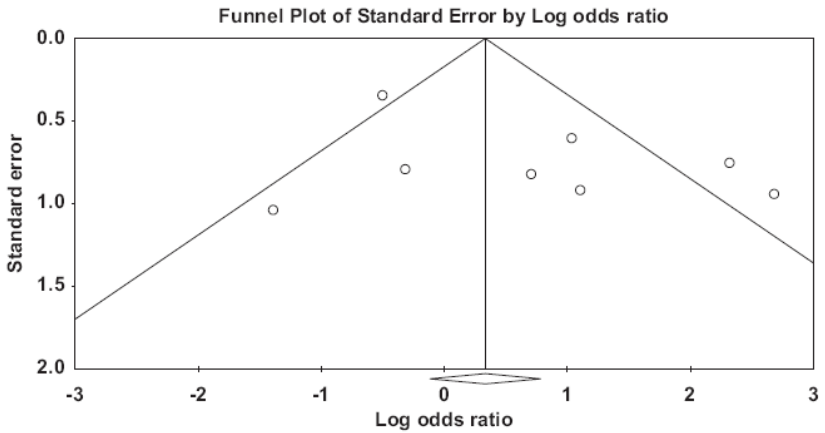


Fig. 4. Funnel plot including both the aspirin and clopidogrel studies.

Table I. The five studies included in the meta-analysis.

Author	Type of study	CAG* (n =)	NCAG** (n =)
Fortuna et al	Nested Case Control [A]*	91	250
Fortuna et al	Nested Case Control [C]**	17	250
Ivascu et al	Case Control Study [A]*	61	42
Ivascu et al	Case Control Study [C]**	17	42
Wong et al	Case Control Study [A]*	90	178
Wong et al	Case Control Study [C]**	21	178
Jones et al	Case Control Study [C]**	43	43
Mina et al	Case Control Study [A]*	19	37

CAG* (Clopidogrel or Aspirin Group) n = total number of patients.
NCAG** (Non Clopidogrel, non Aspirin Group) n = total number of patients.
[A]* = Aspirin group [C]** = Clopidogrel group.

Strengths and limitations of this study

- The studies were small, unpowered and not randomised.
- Mortality is a relatively crude marker of effect in the cohort of patients with either spontaneous or traumatic haemorrhage.
- Significant bias may have been introduced in view of the fact that in all but one study, the platelet transfusions were given at the discretion of the attending physician.

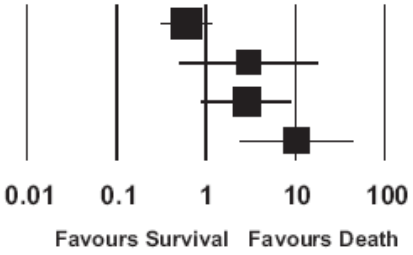
BMJ open accessible medical research

Batchelor JS, *et al* ***Br J Neurosurg*** 2012

A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet medication-associated intracranial haemorrhage.

Aspirin

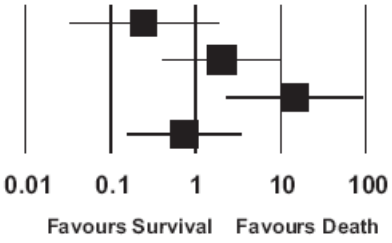
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Fortuna et al	0.608	0.307	1.201	–1.432	0.152
Wong et al	3.034	0.498	18.496	1.204	0.229
Ivascu et al	2.830	0.860	9.308	1.712	0.087
Mina et al	10.200	2.311	45.021	3.066	0.002



Random effects model: pooled OR = 2.435 (95% CI: 0.637 - 9.314)

Clopidogrel

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Fortuna et al	0.250	0.032	1.930	–1.329	0.184
Ivascu et al	2.036	0.404	10.261	0.861	0.389
Wong et al	14.667	2.297	93.630	2.839	0.005
Jones et al	0.731	0.154	3.482	–0.393	0.694



Random effects model: pooled OR = 1.554, (95% CI: 0.320 -7.536)

Batchelor JS *et al.*; **Br J Neurosurg** 2012

REVIEW

Clinical review: Traumatic brain injury in patients receiving antiplatelet medication

Christopher Beynon*, Daniel N Hertle, Andreas W Unterberg and Oliver W Sakowitz

CRITICAL CARE

Conclusion

Options to (partially) restore platelet activity include transfusion of platelets and application of haemostatic drugs such as desmopressin, TXA and FVII-a. Guidelines regarding their use are missing, since these agents have not been subject to controlled trials in TBI so far.

Withdrawal of antiplatelet agents may carry high risks for patients, so treatment has to consider co-morbidities and an interdisciplinary approach should be chosen. Further trials needed …

Beynon C. *et al,* ***Crit Care*** 2012

bjh
British Journal of Haematology

Guideline on the management of bleeding in patients on antithrombotic agents

Recommendations

Decisions to withhold antiplatelet drugs or to administer pro-haemostatic agents should be made after a careful multidisciplinary assessment of the risks and benefits of intervention. (1C)

Bleeding in pts during treatment with aspirin, P2Y12 antagonists or GP IIa/IIIb inhibitors should be managed in the first instance with general haemostatic measures. If necessary, drug cessation and reversal of the effect of co-prescribed anticoagulants should also be considered (2C).

Platelet transfusion (2–3 adult doses) should be considered as an additional measure for critical bleeding or prevention of bleeding before emergency surgery (2C).

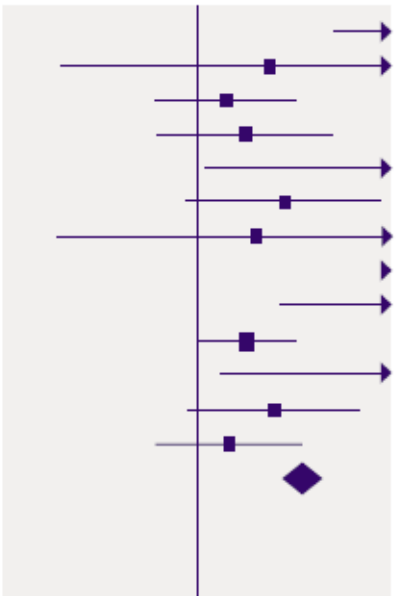
Platelet transfusion should be considered to prevent bleeding in severe thrombocytopenia caused by abciximab (2C).

Makris, *et al.* ***Br J Haematol*** 2012

Aspirin "resistance" and risk of cardiovascular morbidity: systematic review and meta-analysis

BMJ

Study	No with event/ No of aspirin resistant patients	No with event/ No of aspirin sensitive patients	Odds ratio (fixed) (95% CI)	Weight (%)	Odds ratio (fixed) (95% CI)
Aspirin					
Grotemeyer et al[w13]	24/60	5/114		2.66	14.53 (5.16 to 40.89)
McCabe et al[w9]	2/22	1//25		1.09	2.40 (0.20 to 28.45)
Buchanan et al[w6]	15/158	9/131		11.46	1.42 (0.60 to 3.36)
Andersen et al[w5]	9/25	11/46		6.38	1.79 (0.62 to 5.17)
Grundmann et al[w3]	12/12	23/41		0.55	19.68 (1.09 to 354.69)
Gum et al[w7]	4/17	30/309		3.08	2.86 (0.88 to 9.33)
Cotter et al[w2]	1/9	3/52		1.01	2.04 (0.19 to 22.13)
Stejskal et al[w4]	61/73	1/30		0.30	147.42 (18.28 to 1188.69
Borna et al[w1]	17/20	15/44		1.81	10.96 (2.77 to 43.40)
Hobikoglu et al[w8]	42/69	62/135		21.11	1.83 (1.02 to 3.30)
Yilmaz et al[w12]	7/8	7/20		0.64	13.00 (1.32 to 128.11)
Poston et al[w11]	7/49	9/146		4.99	2.54 (0.89 to 7.22)
Pamukcu et al[w14]	8/52	20/182		9.68	1.47 (0.61 to 3.57)
Subtotal (95% CI)	574	1275		64.76	3.53 (2.66 to 4.68)
Test for heterogeneity: χ^2=39.83, df=12, P<0.001, I^2=69.9%					
Test for overall effect: z=8.75, P<0.001					



In a meta-analysis (20 studies, 2,930 pts), most of these used aspirin regimens, 75-325 mg daily, **28% of pts. were classified as aspirin resistant.**

Krasopoulos G, *et al*, ***BMJ*** 2008

Clopidogrel Resistance: World Experience

(Courtesy of Paul Gurbel MD)

Investigators	n	Patients	Clopidogrel Dose (mg Load)	Resistance
Jaremo *et al.* [6]	18	PCI	300	28%
Gurbel *et al.*[3]	92	PCI	300	31%
Muller *et al.* [7]	105	PCI	*600*	*5-11%*
Mobley *et al.*[8]	50	PCI	300	30%
Lepantalo *et al.*[9]	50	PCI	300	40%
Angiolillo *et al.*[4]	48	PCI	300	44%
Matetzky *et al.*[10]	60	PCI	300	25%
Dziewierz *et al.*[11]	31	Stable angina	300	23%
Gurbel *et al.*[12]	190	PCI	300/*600*	*8*-32%
Lev *et al.*[13]	150	PCI	300	24%
Total	**794**			**5-44%**

Clop. resistance definitions are different: ***Gurbel et al.*** Change in inhibition of platelet aggregation (IPA) of <10% using light transmittance aggregometry (LTA)**,** ***Angiolillo et al***: IPA <40% by LTA), ***Lau et al***: Platelet aggregation ≥70% by LTA.

Subjects treated with Clop showed large response variability and resistance in some cases **(study range from 5% to 44%).**

Gurbel P, *et al*. ***Thrombosis Res*** 2007

Analysis of transfusion reactions associated with prestorage-pooled platelet components

PLT component reaction rates, total and by study site

PLT component	Total components infused		Aggregate reaction rate†
	Site A	Site B	
PSPPs	4,014	717	0.89% (42/4731)
SDPs	3,316	683	0.75% (30/3999)
RDPs	987	534	1.38% (21/1521)
Total	10,251		

Platelet transfusions reactions has been reported in approx. **1-2% of cases.**

There were no statistical differences in aggregate reaction rates between PSPPs and SDPs ($p = 0.56$) or between PSPPs and RDPs ($p = 0.13$).

Tormey CA, *et al* ***Transfusion*** 2009

Functional measures of platelet activity are needed ?

Early Platelet Transfusion Improves Platelet Activity and May Improve Outcomes After Intracerebral Hemorrhage

Assessment of Platelet Activity

We routinely measured platelet activity on admission and an hour after platelet transfusion. The VerifyNow-ASA (Accumetrics, CA) uses an optical detection system that measures platelet-induced aggregation as an increase in light transmittance. Citrated whole blood is exposed to lyophilized human fibrinogen-coated beads. Cationic propyl gallate is used to induce platelet activation without fibrin formation. The results are reported as aspirin reaction units (ARU), with $\leq$550 ARU indicative of reduced platelet activity due to aspirin.

Functional optical detection systems to test the real functional activity of platelet aggregation are coming in the ED in particular in pts. with ICH haemorrhage, where Physician must decide whether or not to transfuse.

Naidech AM, *et al*. ***Neurocrit Care*** 2012

Conclusions:
Trauma and Antiplatelet Therapy

Studies on severe trauma not available.

Studies on head injury not conclusive, no guidelines available.

Platelet transfusion still "*investigational*", (Class 2B, Evidence Lev.B)

Consider risk/benefit ratio in individual pts (*CT scan, drug and clinical-anamnestic profile*).

- Pre-injury antiplt. therapy is a risk factor for intracranial lesions: Asp. lower-risk, Clop. higher-risk.
- Pre-injury antiplt. therapy in pts. with positive CT scan increases the risk of worsening. Asp. low-risk, Clop. high risk.
- The effect of antiplts on long-term outcome is uncertain.

Conclusions:
Trauma and Antiplatelet Therapy

- Results of a multi-centre RCT on platelet transfusion in pts. with severe trauma are awaited
- The suggested dose for normalising plt activity in healthy volunteers given aspirin alone or a combination of aspirin and clopidogrel was 5 and 10 to 15 platelet units
- Reverse therapy with platelets transfusions:
  1. Indicated in head injury, positive CT scan, need for neurosurgical intervention, any therapy (Asp. and/or Clop).
  2. Indicated in head injury, positive CT scan and therapy with Clop.
  3. Not indicated in head injury, positive CT scan and therapy with Asp, but a risk /benefit evaluation in individual subjects is needed.