

TERAPIA ANTIAGGREGANTE

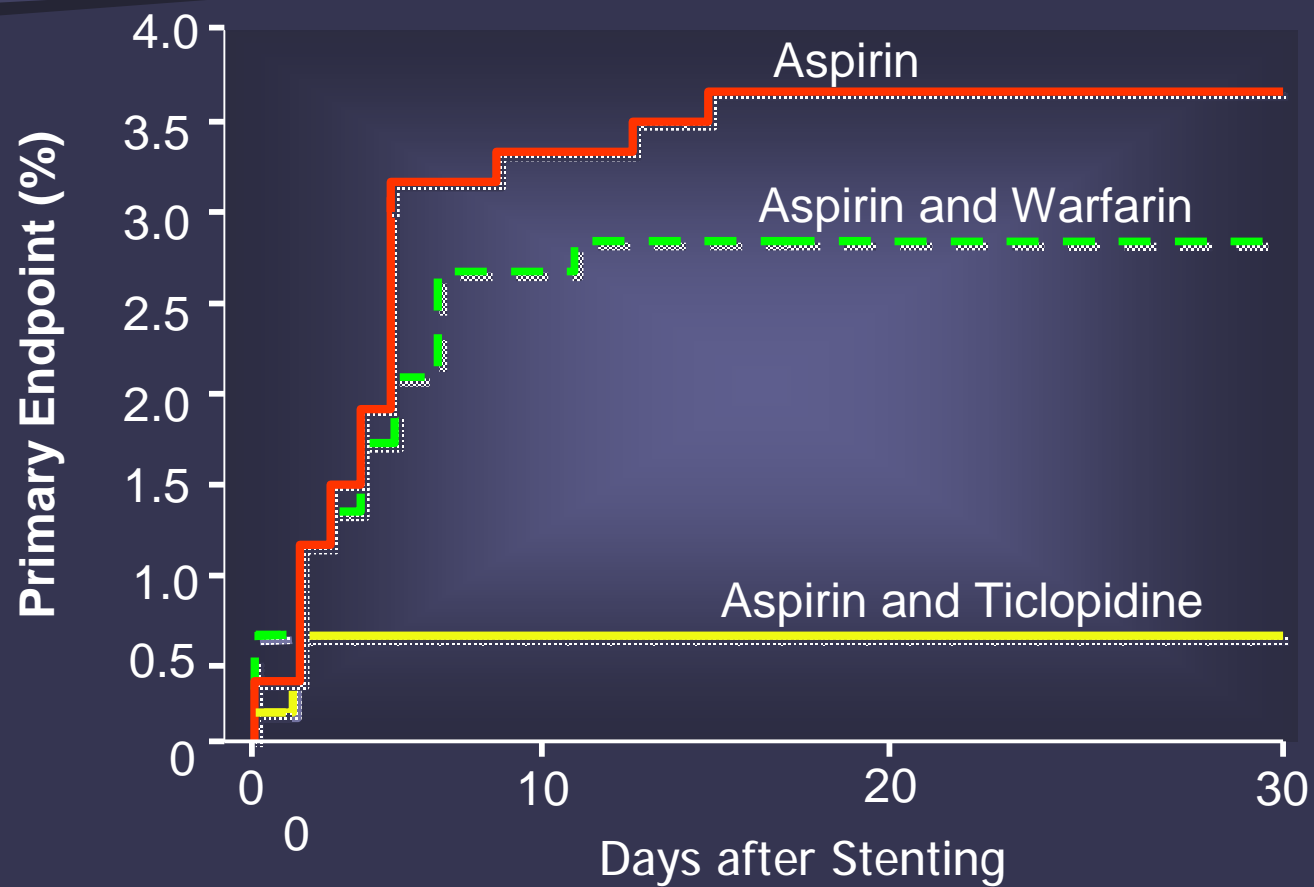
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**RIDUZIONE DEL
RISCHIO DI
TROMBOSI DI
STENT**

**RISCHIO DI
COMPLICANZE
EMORRAGICHE**

Duplice terapia antiaggregante - cenni storici -

STARS



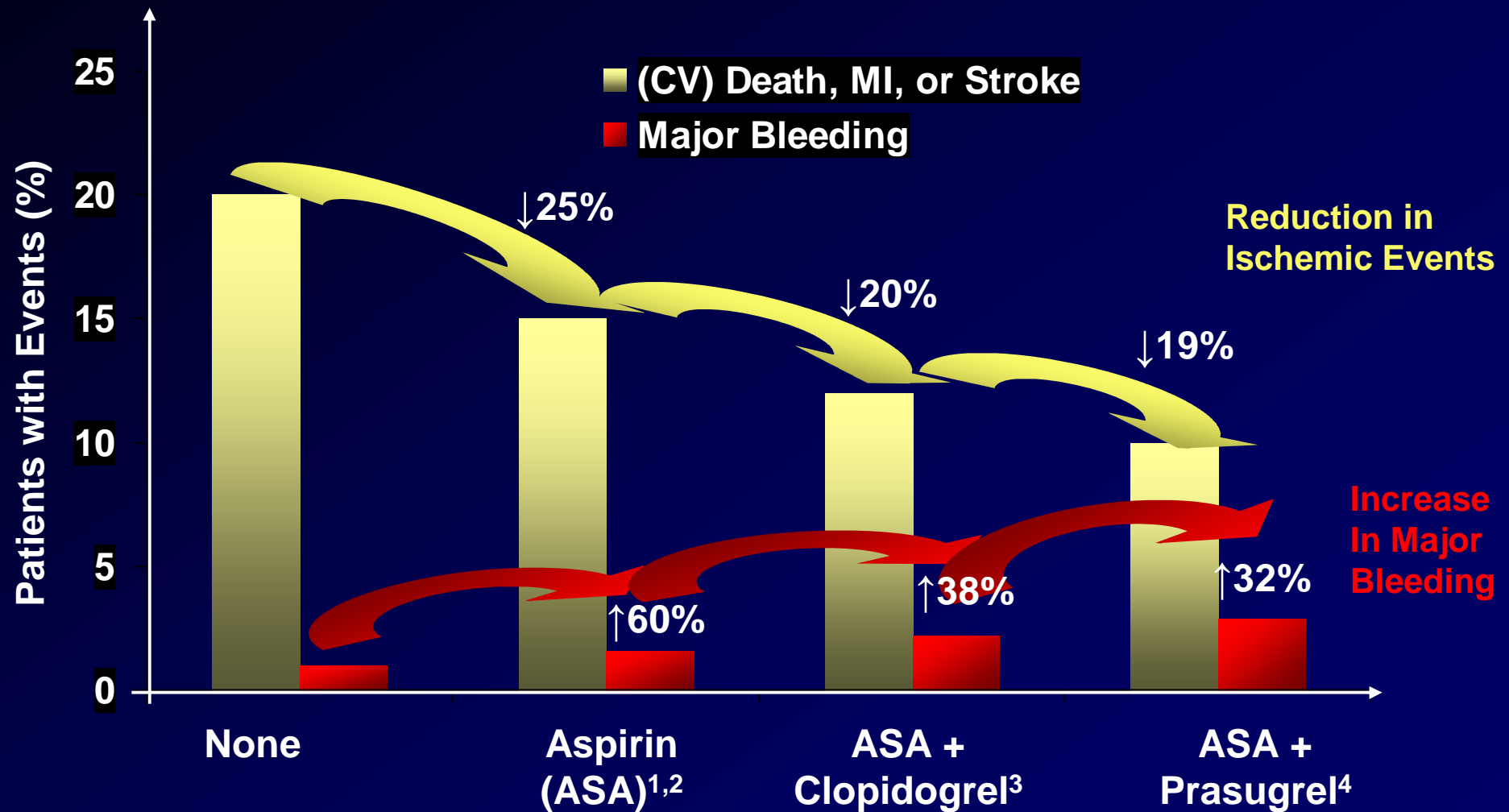
Duplice terapia antiaggregante - cenni storici -

STARS

TABLE 3. PRIMARY AND SECONDARY EVENTS IN THE FIRST 30 DAYS AFTER STENTING.*

EVENT	ASPIRIN ALONE (N=557)	ASPIRIN AND WARFARIN (N=550)	ASPIRIN AND TICLOPIDINE (N=546)	P VALUE†
	number (percent)			
Primary end point	20 (3.6)	15 (2.7)	3 (0.5)	0.001
Death	1 (0.2)	0	0	
Revascularization of target lesion	19 (3.4)	14 (2.5)	3 (0.5)	0.002
CABG	3 (0.5)	1 (0.2)	1 (0.2)	0.63
PTCA	17 (3.1)	14 (2.5)	3 (0.5)	0.003
Angiographically evident thrombosis	16 (2.9)	15 (2.7)	3 (0.5)	0.005
Recurrent myocardial infarction	15 (2.7)	11 (2.0)	3 (0.5)	0.01
Q-wave	8 (1.4)	8 (1.5)	1 (0.2)	0.04
Non-Q-wave	7 (1.3)	3 (0.5)	2 (0.4)	0.27
Other clinical events				
Procedure-related myocardial infarction	16 (2.9)	23 (4.2)	23 (4.2)	0.41
Q-wave	4 (0.7)	0	0	0.04
Non-Q-wave	12 (2.2)	23 (4.2)	23 (4.2)	0.10
Hemorrhagic complications	10 (1.8)	34 (6.2)	30 (5.5)	<0.001
Vascular surgical complications	2 (0.4)	11 (2.0)	11 (2.0)	0.02
Neutropenia or thrombocytopenia	1 (0.2)	1 (0.2)	3 (0.5)	0.46
Cerebrovascular accident	2 (0.4)	1 (0.2)	0	0.78

Antiplatelet Therapy



**Complicanze
Emorragiche
Gastrointestinali**

Complicanze emorragiche - cenni di base -

Sono in modo imprescindibile legate alla terapia antiaggregante

La loro incidenza incrementa con il progressivo incremento dell'aggressività della duplice antiaggregazione

Esistono diversi fattori predisponenti che rendono un paziente più prono a complicanze emorragiche

Le complicanze emorragiche hanno un impatto prognostico negativo

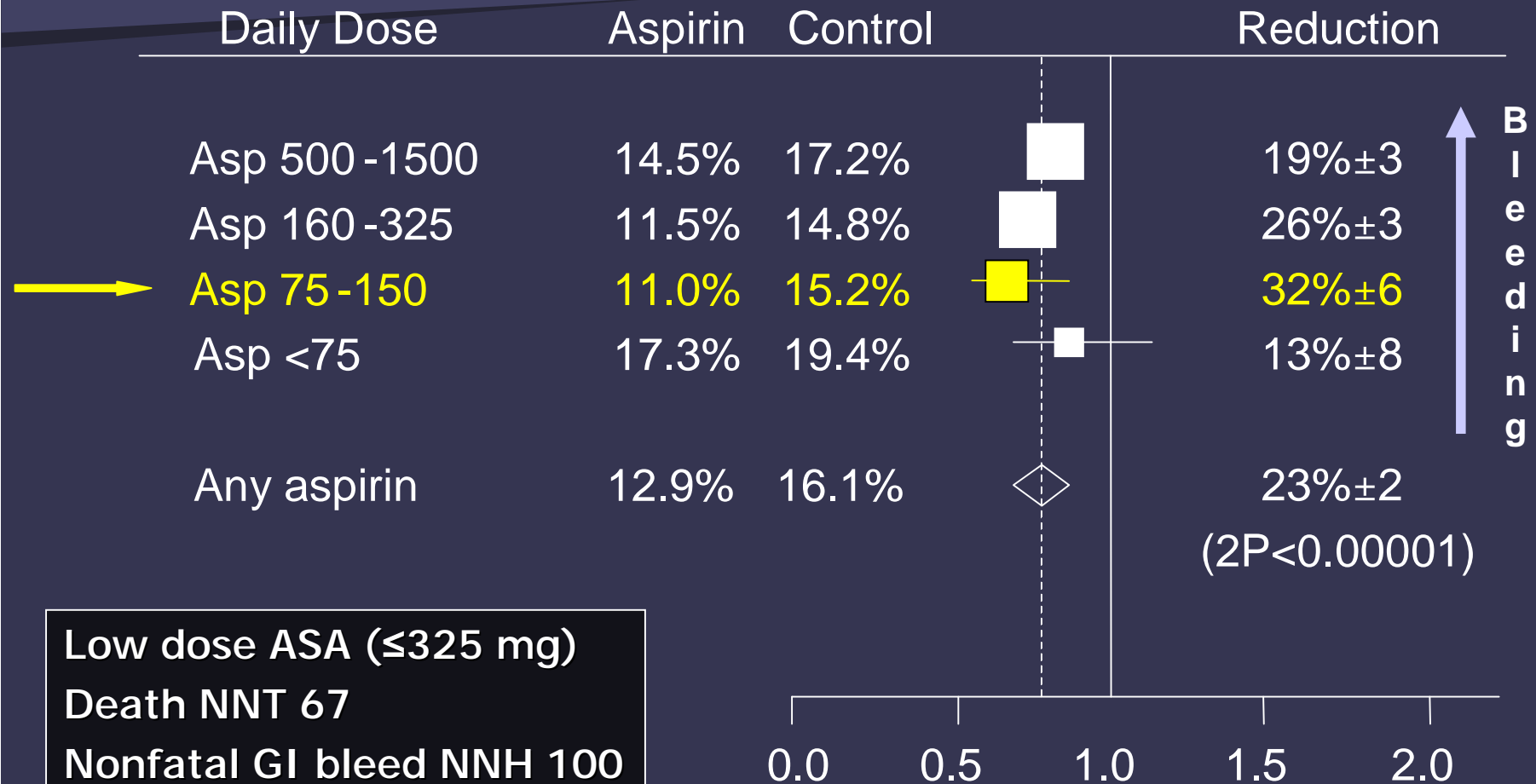


ASPIRINA



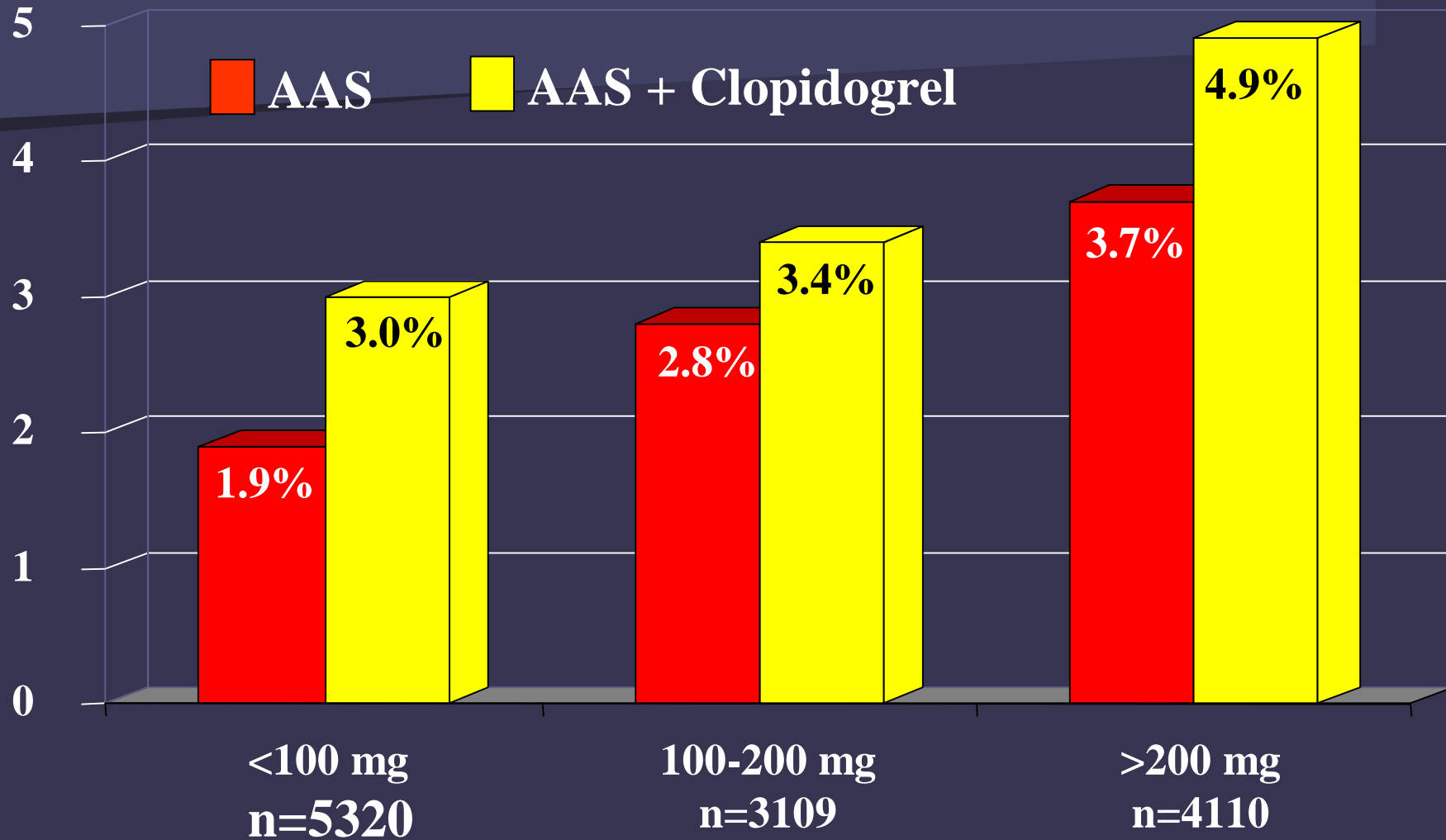
Antithrombotic Trialists' Collaboration

Different Doses of Aspirin vs Control



Insights from CURE

Aspirin Dose and Incidence of Major Bleedings



BRAVO: Bleeding By ASA dose

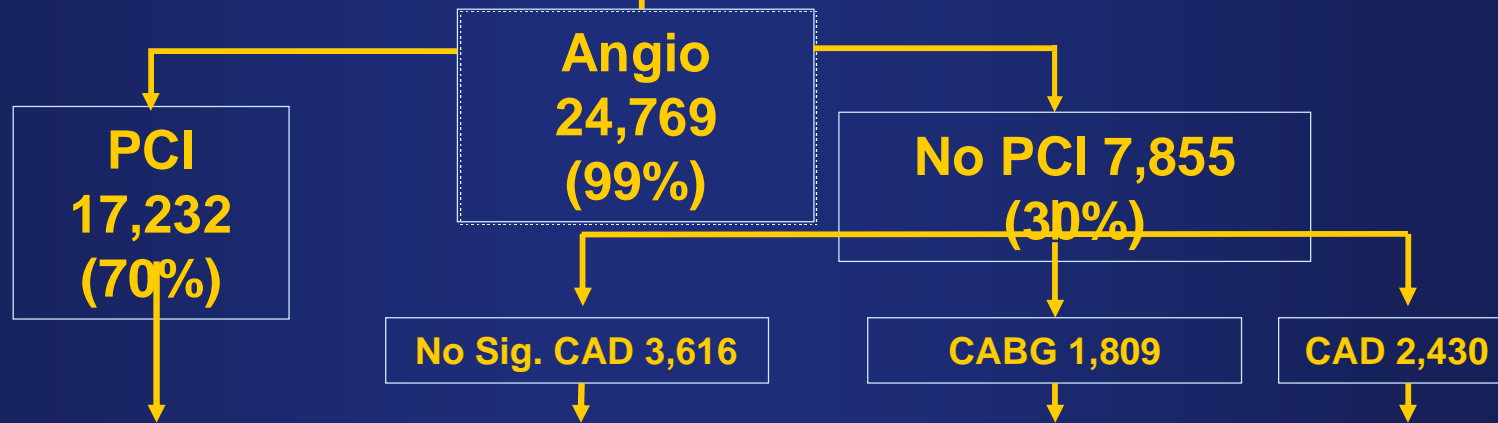
Outcomes by Aspirin Dose in Placebo Study Drug Patients

	Low Dose, 75-162 mg/d (n=2410)	Higher Dose, 162-326 mg/d (n=2179)
Primary end point	16.4	18.6
Death, MI, stroke	6.2	6.1
Death	2.8	1.7
MI	2.0	2.1
Stroke	2.1	2.8
Internal bleeding	2.4	3.3
Any bleeding	11.1	15.4
Transfusion	1.0	2.0

Study Design, Flow and Compliance

25,087 ACS Patients (UAINSTEMI 70.8%, STEMI 29.2%)
 ü Planned Early (<24 h) Invasive Management with **intended PCI**
 ü Ischemic ECG Δ (80.8%) or ↑ cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):
CLOPIDOGREL: Double-dose (600 mg then 150 mg/d x 7d then 75 mg/d) **vs Standard dose** (300 mg then 75 mg/d)
ASA: High Dose (300-325 mg/d) **vs Low dose** (75-100 mg/d)



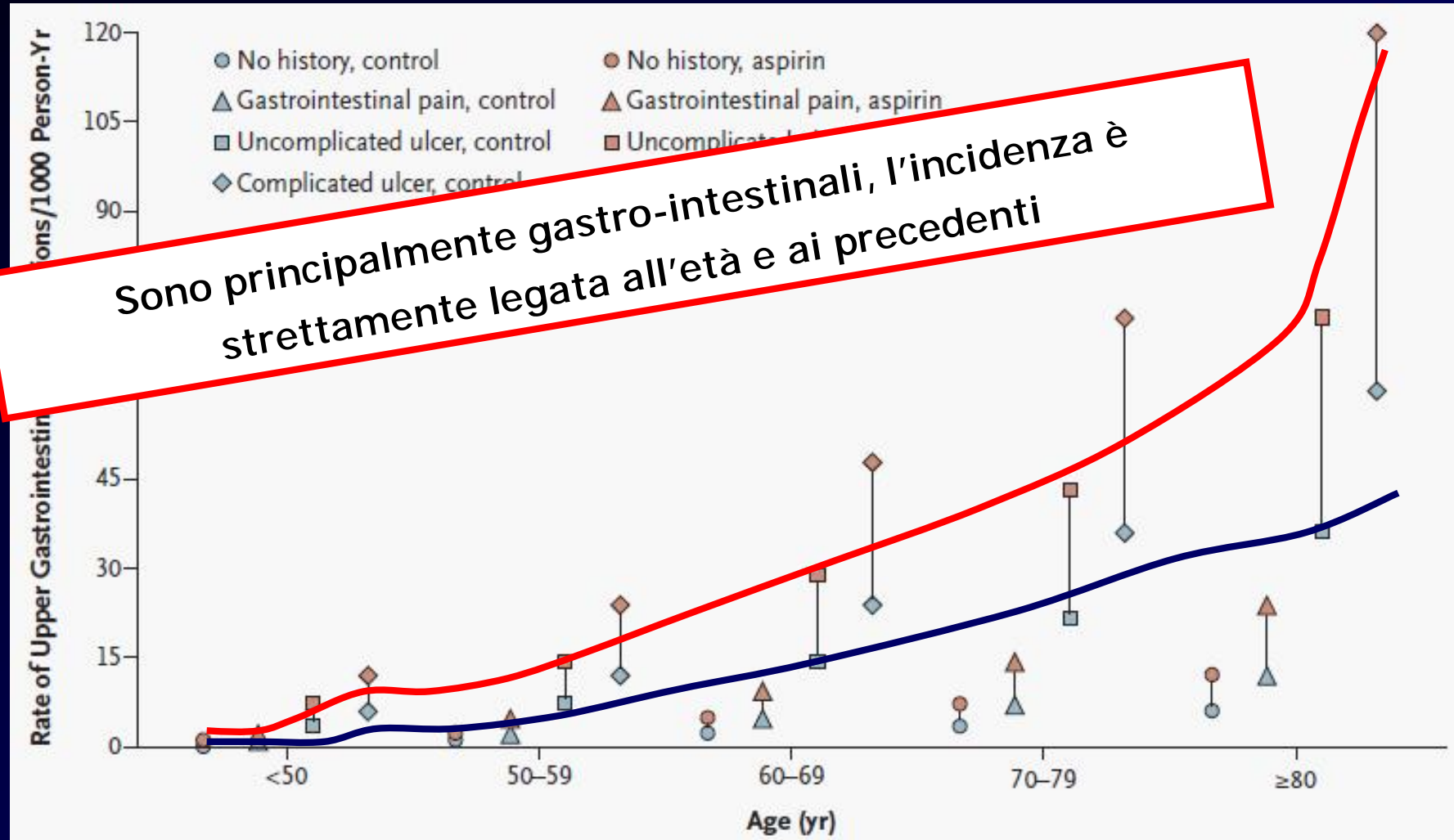
Efficacy Outcomes: CV Death, MI or stroke at day 30
 Stent Thrombosis at day 30
Safety Outcomes: Bleeding (CURRENT defined Major/Severe and TIMI Major)
Key Subgroup: PCI v No PCI



ASA Dose Comparison Primary Outcome and Bleeding

	ASA 75-100 mg	ASA 300-325 mg	HR	95% CI	P
CV Death/MI/Stroke					
PCI (2N=17,232)	4.2	4.1	0.98	0.84-1.13	0.76
No PCI (2N=7855)	4.7	4.4	0.92	0.75-1.14	0.44
Overall (2N=25,087)	4.4	4.2	0.96	0.85-1.08	0.47
Stent Thrombosis	2.1	1.9	0.91	0.73-1.12	0.37
TIMI Major Bleed	1.03	0.97	0.94	0.73-1.21	0.71
CURRENT Major Bleed	2.3	2.3	0.99	0.84-1.17	0.90
GI Bleeds:	0.24%	0.38%		P=0.051	
CURRENT Severe Bleed	1.7	1.7	1.00	0.83-1.21	1.00

Aspirina e complicanze emorragiche





CLOPIDOGREL

Clopidogrel e complicanze emorragiche

Adverse experience	Patients ever reporting		Severe	
	Clopidogrel	Aspirin	Clopidogrel	Aspirin
Rash	578 (6.02%)	442 (4.61%)*	25 (0.26%)	10 (0.10%)*
Diarrhoea	428 (4.46%)	322 (3.36%)*	22 (0.23%)	11 (0.11%)
Indigestion/nausea/vomiting	1441 (15.01%)	1686 (17.59%)*	93 (0.97%)	118 (1.23%)
Any bleeding disorder	890 (9.27%)	890 (9.28%)	132 (1.38%)	149 (1.55%)
Intracranial haemorrhage	34 (0.35%)	47 (0.49%)	30 (0.31%)	41 (0.43%)
Gastrointestinal haemorrhage	191 (1.99%)	255 (2.66%)*	47 (0.49%)	68 (0.71%)*
Abnormal liver function	285 (2.97%)	302 (3.15%)*	11 (0.11%)	9 (0.09%)

*Statistically significant, $p < 0.05$.

Clopidogrel e complicanze emorragiche

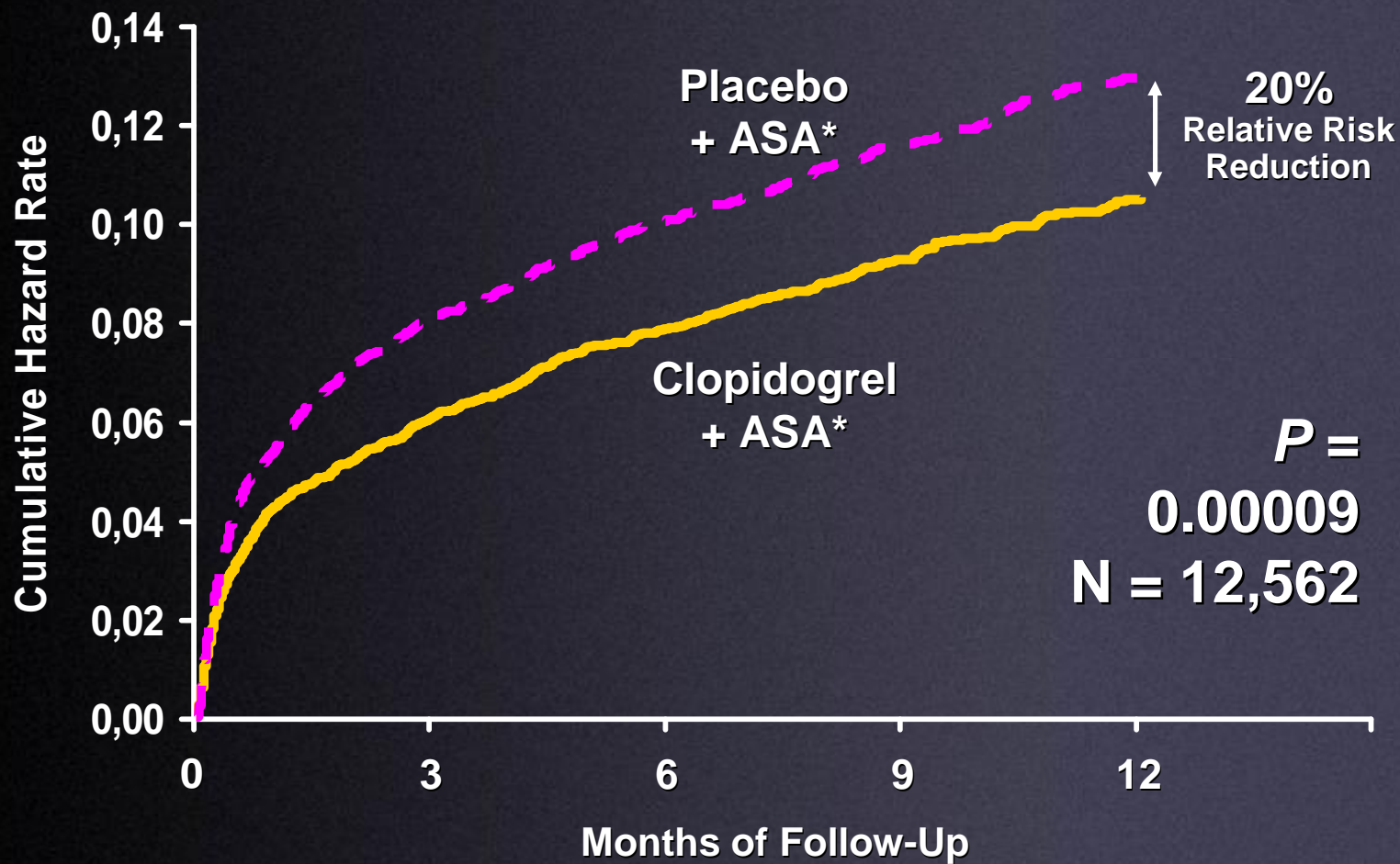
	UGIB Cases (n=2049), n (%)	Controls (n=20 000), n (%)	RR (95% CI)	Adjusted RR (95% CI)
Low-dose ASA (with or without clopidogrel)				
Nonuse	1319 (64.4)	15 584 (77.9)	1.00	1.00
Current use	631 (30.8)	3778 (18.9)	2.13 (1.91–2.38)	1.80 (1.59–2.03)
Past use	99 (4.8)	638 (3.2)	1.54 (1.55–2.43)	1.33 (1.05–1.70)

Clopidogrel as antiplatelet monotherapy

Nonuse of clopidogrel or ASA	1285 (62.7)	15 401 (77.0)	1.00	1.00
Current use (all doses)	30 (1.5)	170 (0.9)	2.55 (1.72–3.80)	1.48 (0.96–2.27)
Treatment duration 0–365 d	8 (0.4)	45 (0.2)	2.43 (1.15–5.24)	1.46 (0.65–3.26)
Treatment duration >365 d	22 (1.1)	125 (0.6)	2.58 (1.62–4.09)	1.46 (0.89–2.39)



Primary Outcome – MI/Stroke/CV Death



* In addition to other standard therapies.
CURE Investigators. *N Engl J Med.* 2001;345:494

Aspirina + Clopidogrel e complicanze emorragiche

TABLE 3. BLEEDING COMPLICATIONS.*

VARIABLE	CLOPIDOGREL GROUP (N= 6259)	PLACEBO GROUP (N= 6303)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
Major bleeding	231 (3.7)	169 (2.7)	1.38 (1.13–1.67)	0.001
Necessitating transfusion of ≥ 2 units of blood	177 (2.8)	137 (2.2)	1.30 (1.07–1.57)	0.005
Life-threatening	127 (2.0)	97 (1.5)	1.70 (1.22–2.35)	0.002
Fatal	57 (0.9)	47 (0.7)		
Causing ≥ 5 days of disability	83 (1.3)	47 (0.7)		
Retroperitoneal	8 (0.1)	5 (0.1)		
Urinary (hematuria)	4 (0.1)	5 (0.1)		
Arterial puncture site	36 (0.6)	22 (0.3)		
Surgical site	56 (0.9)	53 (0.8)		
Minor bleeding	322 (5.1)	153 (2.4)	2.12 (1.75–2.56)	<0.001
Total with bleeding complications	533 (8.5)	317 (5.0)	1.69 (1.48–1.94)	<0.001

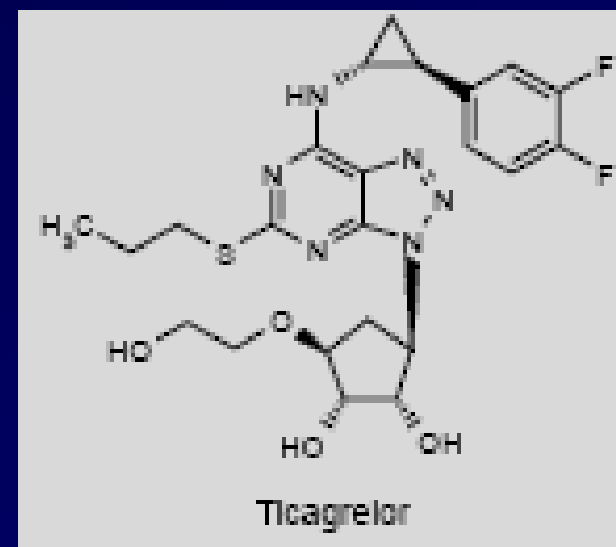
Rispetto alla sola aspirina la duplice terapia con asa e clopidogrel incrementa in modo significativo la complicanze emorragiche maggiori, minori. Non c'è un impatto significativo sulle emorragie life-threatening

Aspirina + Clopidogrel e complicanze emorragiche

Table 2. Risk of Upper Gastrointestinal Bleeding Associated With Antiplatelet Therapy

	UGIB Cases (n=2049), n (%)	Controls (n=20 000), n (%)	RR (95% CI)	Adjusted RR (95% CI)
Dual antiplatelet therapy with clopidogrel and low-dose ASA				
Nonuse of clopidogrel or ASA	1285 (62.7)	15 401 (77.0)	1.00	1.00
Current use (all doses)	32 (1.6)	101 (0.5)	4.65 (3.10–6.99)	3.71 (2.38–5.76)
Treatment duration for ASA and clopidogrel 0–365 d	10 (0.5)	32 (0.2)	4.43 (2.16–9.08)	3.06 (1.40–6.69)
Treatment duration for ASA and clopidogrel >365 d	8 (0.4)	32 (0.2)	3.76 (1.72–8.23)	3.28 (1.45–7.43)

OPZIONI FUTURE



Aspirina + Prasugrel e complicanze emorragiche

Table 3. Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6741) <i>no. of patients (%)</i>	Clopidogrel (N=6716) <i>no. of patients (%)</i>	Hazard Ratio for Prasugrel (95% CI)	P Value
Non-CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)		0.45
Spontaneous	92 (1.6)	73 (1.1)		0.01
Related to trauma				0.51
Life-threatening				0.01
Intracranial				0.14
Major or minor TIMI bleeding			0.70 (0.27–1.84)	0.47
Bleeding requiring transfusion§		5 (0.1)	4.19 (1.58–11.11)	0.002
CABG-related TIMI major bleeding¶	64 (1.1)	51 (0.9)	1.25 (0.87–1.81)	0.23
Major or minor TIMI bleeding	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

L'aggiunta in terapia di prasugrel comporta un incremento significativo delle complicanze emorragiche maggiori, fatali, spontanee (soprattutto gastrointestinali e cerebrali) e quelle post-cardiochirurgia

Aspirina + Ticagrelor e complicanze emorragiche

Table 4. Safety of the Study Drugs.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI) [†]	P Value
Primary safety end points — no./total no. (%)				
Major bleeding, study criteria	961/9235 (11.6)	929/9186 (11.2)	1.04 (0.95–1.13)	0.43
Major bleeding, TIMI criteria [‡]	657/9235 (7.9)	638/9186 (7.7)	1.03 (0.93–1.15)	0.57
Bleeding requiring red-cell transfusion	818/9235 (8.9)	809/9186 (8.9)		0.96
Life-threatening or fatal bleeding, study criteria	491/9235 (5.3)	477/9186 (5.2)		0.70
Fatal bleeding	10/9235 (0.1)	10/9186 (0.1)		0.66
Nonintracranial fatal bleeding	38/9235 (0.4)	38/9186 (0.4)		0.03
Intracranial fatal bleeding	12/9235 (0.1)	9/9186 (0.1)		0.06
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)		0.02
Major or minor bleeding, TIMI criteria [‡]	946/9235 (11.4)	906/9186 (10.9)		0.69
Secondary end points				
Non-CABG-related major bleeding, study criteria	562/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non-CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria [‡]	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33

Anche se meno rispetto al prasugrel anche l'introduzione in terapia di ticagrelor comporta un incremento del rischio di complicanze emorragiche. Paradossalmente la sede meno interessata è quella gastrointestinale

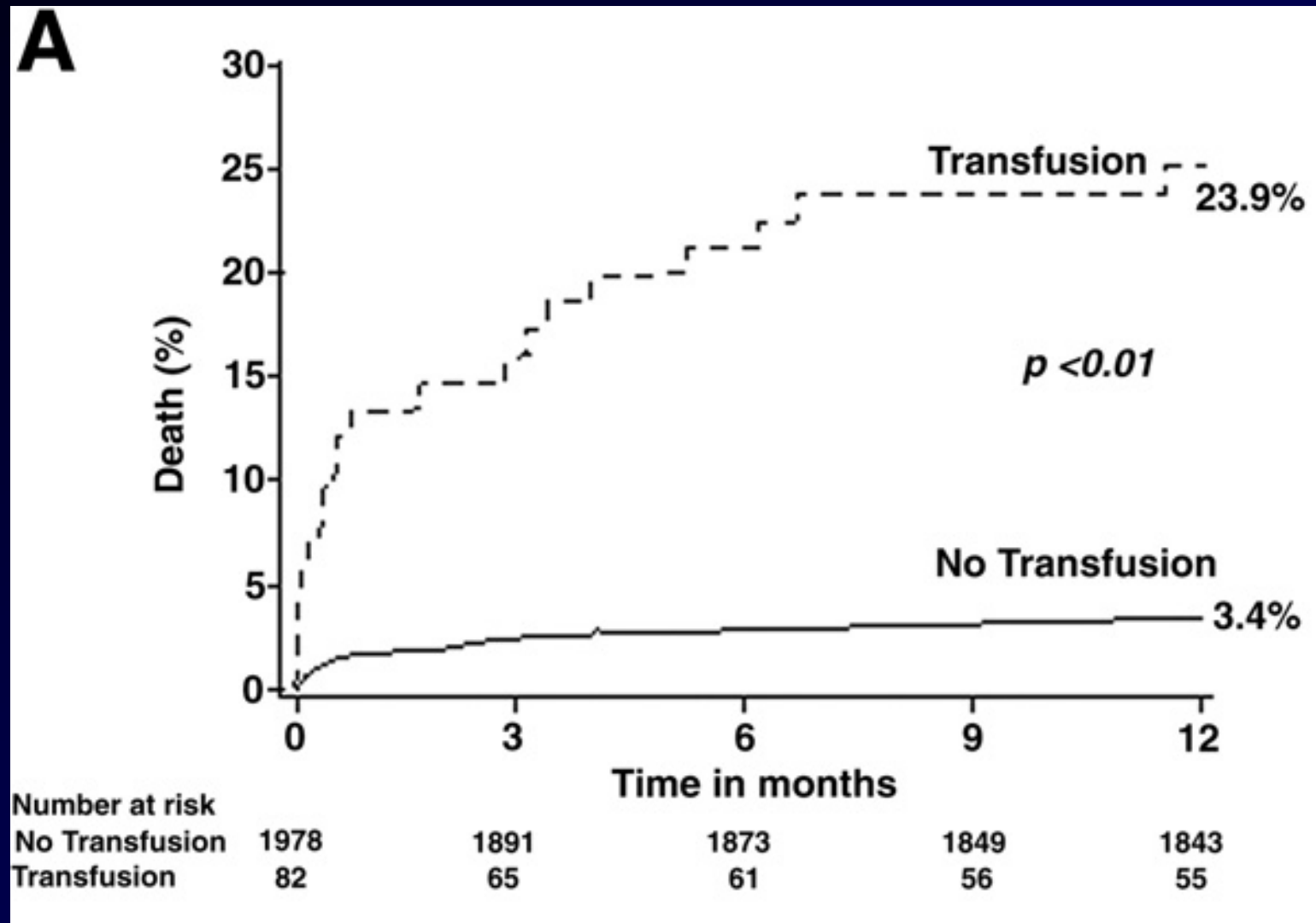
Impatto prognostico degli eventi emorragici

Come detto gli eventi emorragici hanno un impatto prognostico importante e negativo.

Questa azione è principalmente mediata da due fattori:

- **SOSPENSIONE PREMATURA TERAPIA ANTIAGGREGANTE**
 - **RICORSO ALLE TRASFUSIONI**

Impatto prognostico delle trasfusioni

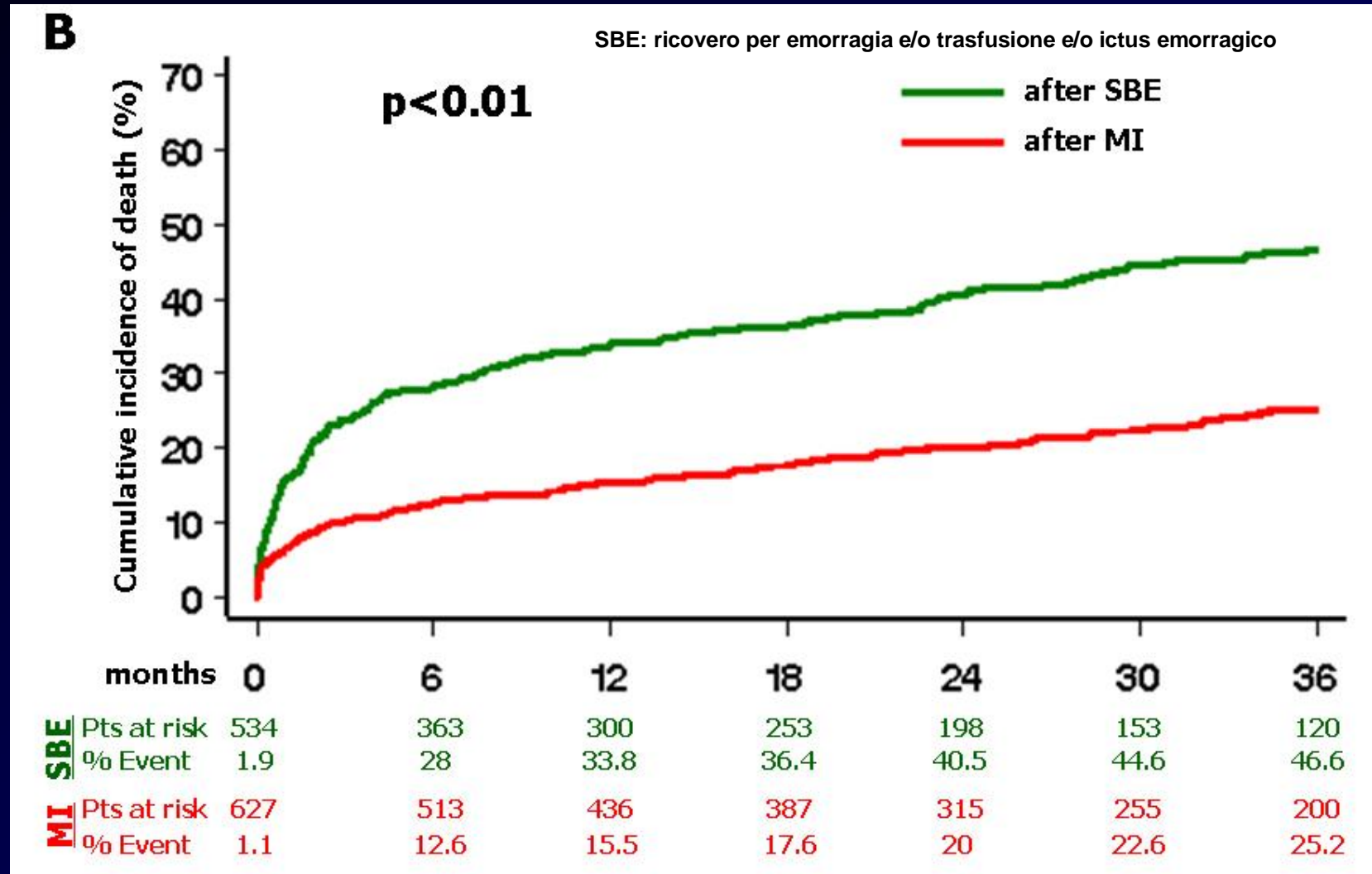


Impatto prognostico delle trasfusioni

Table 4. Multivariable Predictors of Mortality at 30 Days and 1 Year

	Hazard Ratio (95% Confidence Interval)	p Value
30-day mortality		
Renal insufficiency	5.96 (2.73–13.03)	<0.0001
Left anterior descending artery infarct vessel	5.06 (2.32–11.02)	<0.0001
Blood transfusion	4.71 (1.97–11.26)	0.0005
Propensity to transfusion	1.60 (1.04–2.45)	0.032
Hypertension	2.91 (1.24–6.81)	0.014
1-year mortality		
Blood transfusion	3.16 (1.66–6.03)	0.0005
Left anterior descending artery infarct vessel	2.41 (1.47–3.96)	0.0005
Renal insufficiency	2.60 (1.42–4.74)	0.002
Killip class 2 or 3	2.28 (1.30–4.02)	0.004
Baseline minimal luminal diameter	0.44 (0.24–0.81)	0.0008
Age	1.03 (1.01–1.06)	0.015
Propensity to transfusion	1.43 (1.03–1.99)	0.033

Impatto prognostico delle emorragie maggiori



CONCLUSIONI ??!???