

Sonotrombolisi: sperimentazione o pratica clinica?

Lavinia Dinia, Massimo Del Sette

**Hosp Vall d'Hebron, Barcelona
Ospedale S. Andrea, La Spezia**

Vantaggi del doppler transcranico nell'ictus acuto

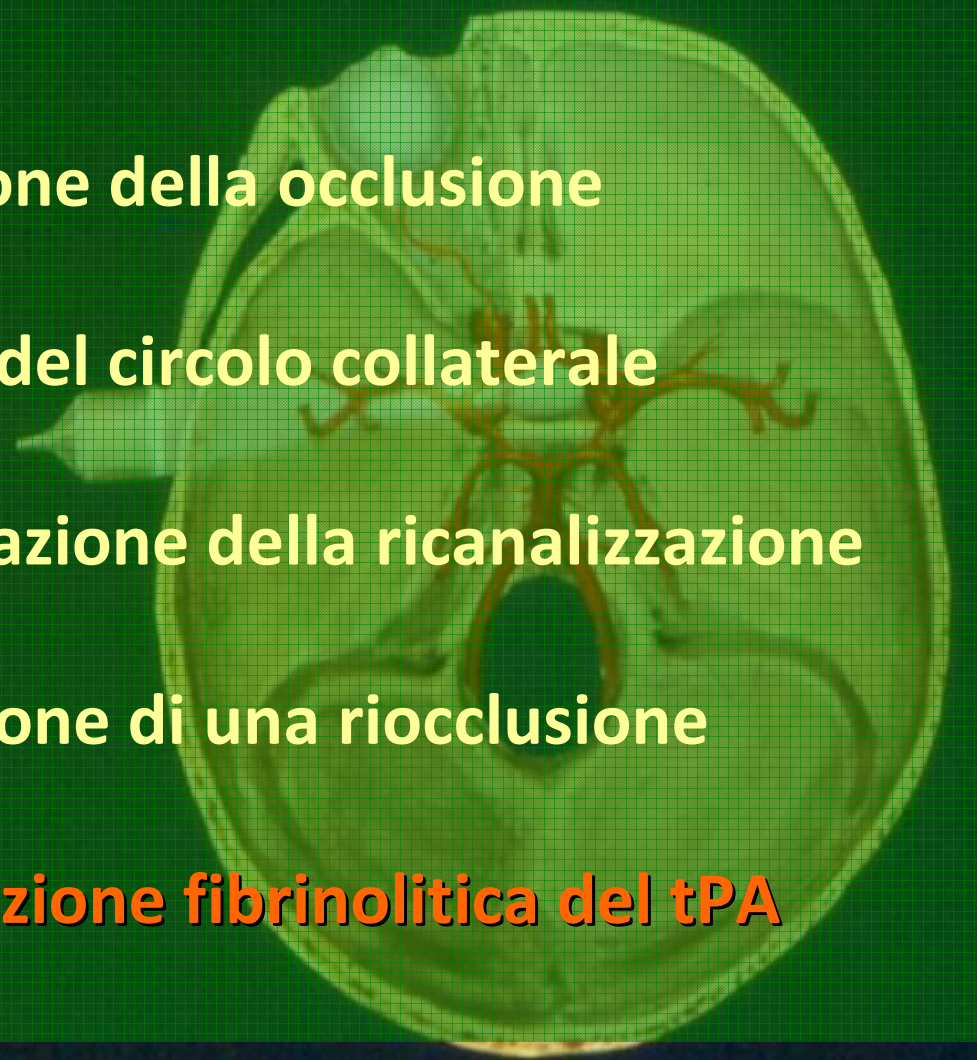
Localizzazione della occlusione

Condizioni del circolo collaterale

Monitorizzazione della ricanalizzazione

Identificazione di una riocclusione

Favorire l'azione fibrinolitica del tPA



Sonotrombolisi

Modificazioni reversibili nelle maglie di fibrina

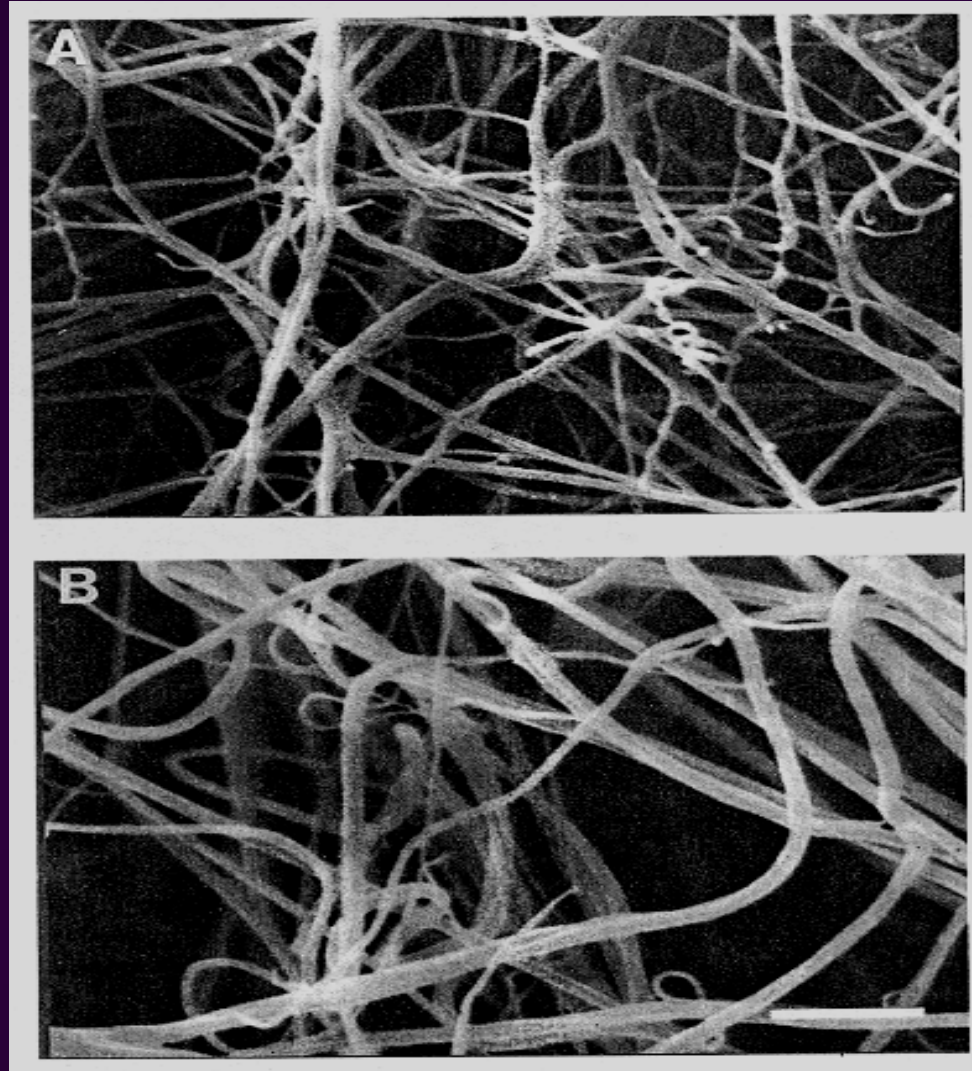
Before



During



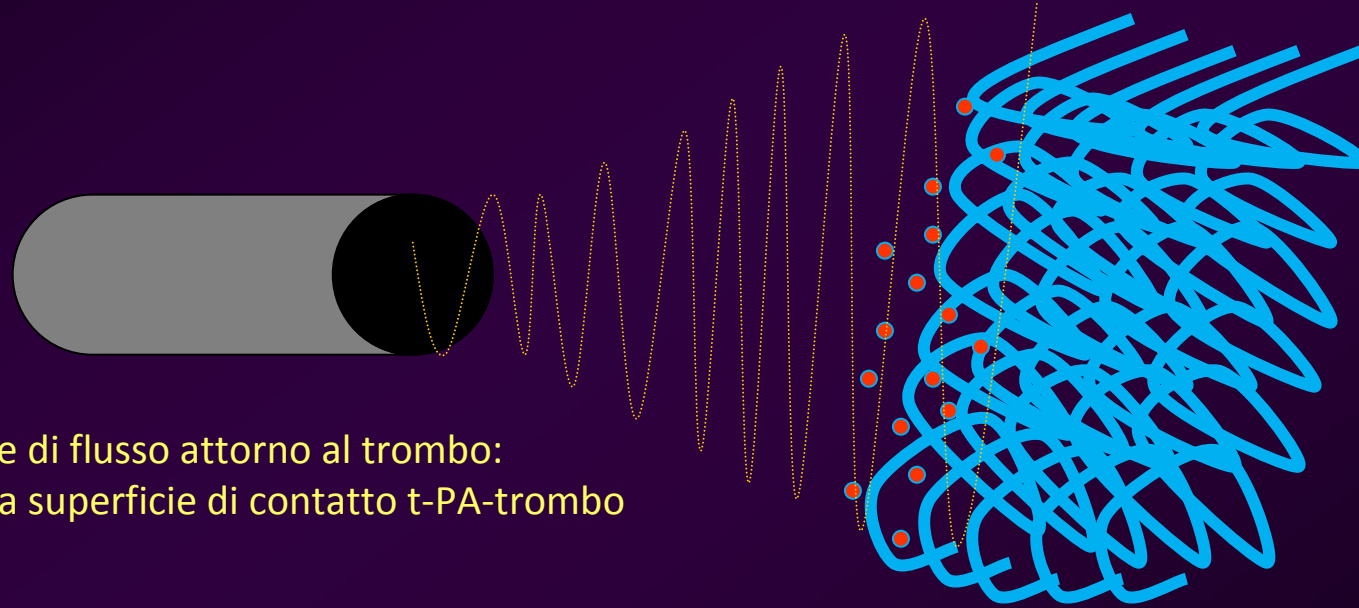
After



Braaten y coll Thromb Haemost 1997

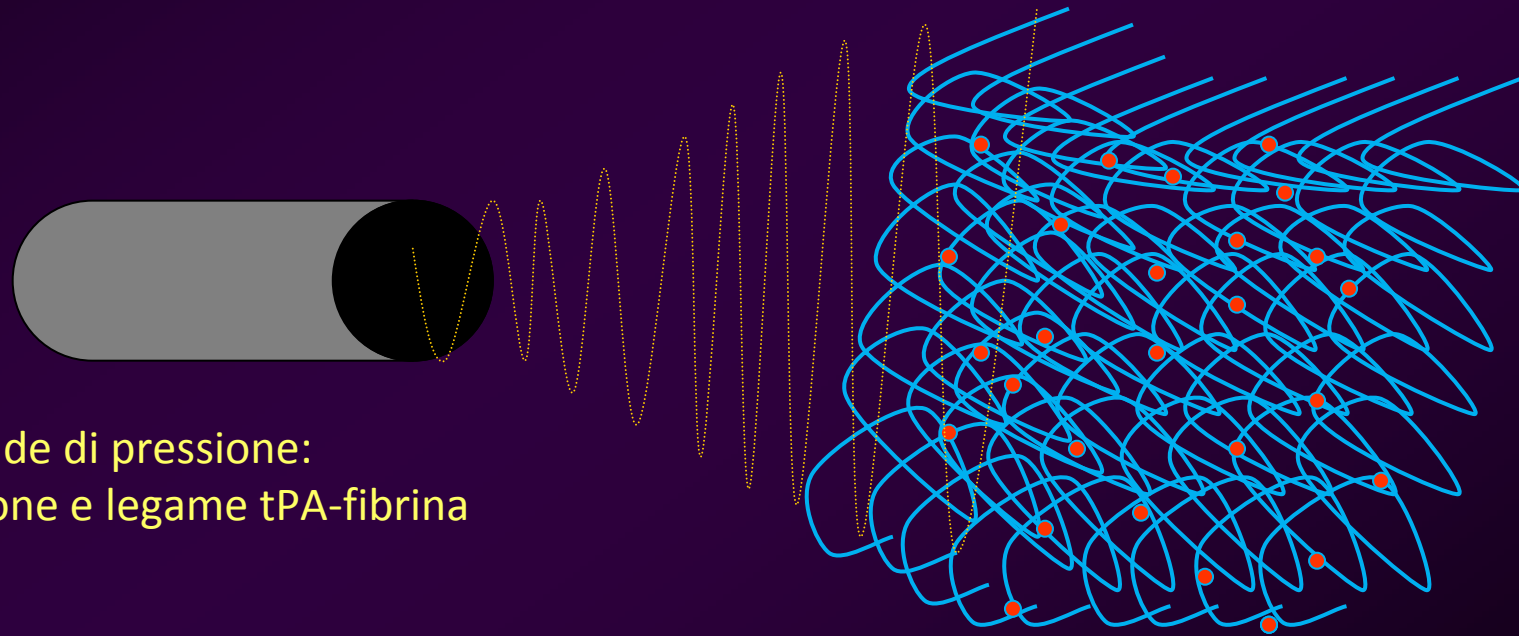
Sonotrombolisi

Migliora la penetrazione e la distribuzione del tPA



Sonotrombolisi

Migliora la penetrazione e la distribuzione del tPA

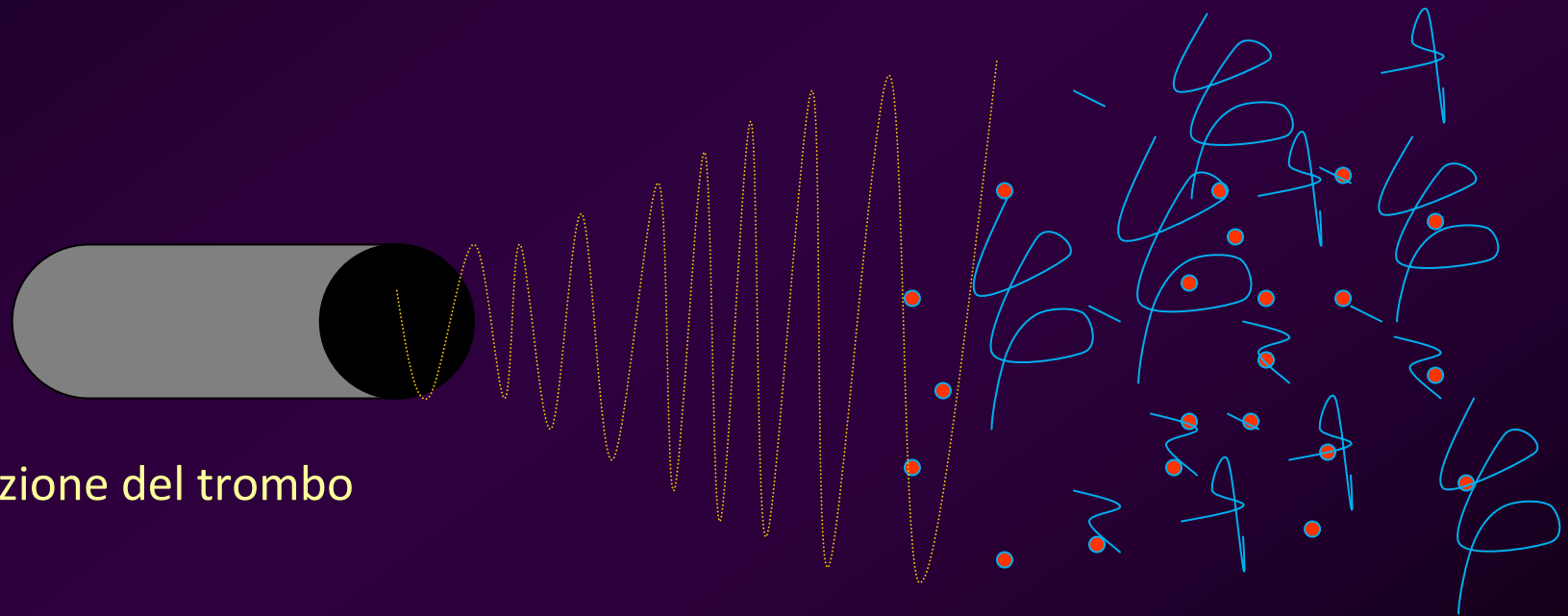


Onde di pressione:
penetrazione e legame tPA-fibrina

Sonotrombolisi

Migliora la penetrazione e la distribuzione del tPA

Dissoluzione del trombo



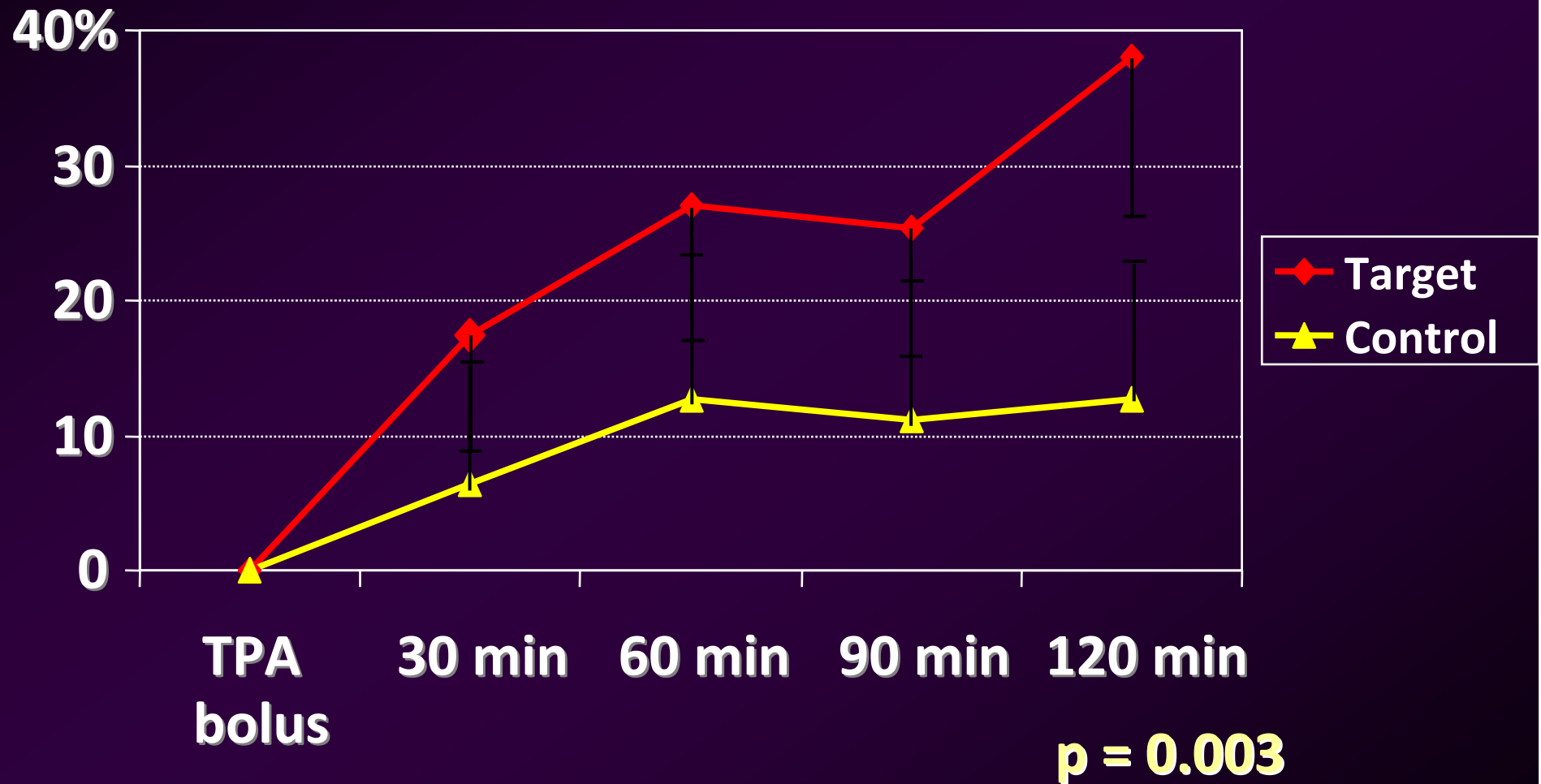
STUDI CLINICI

- tPA vs. tPA + U.S. (TCD)
- tPA vs. tPA + U.S. (Bassa frequenza)
- tPA vs. tPA + U.S. (TCCD)
- Solo U.S. (TCCD)
- tPA vs tPA + U.S. (TCD) + Microbolle (Mb)


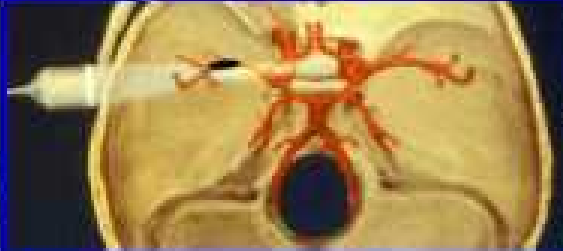

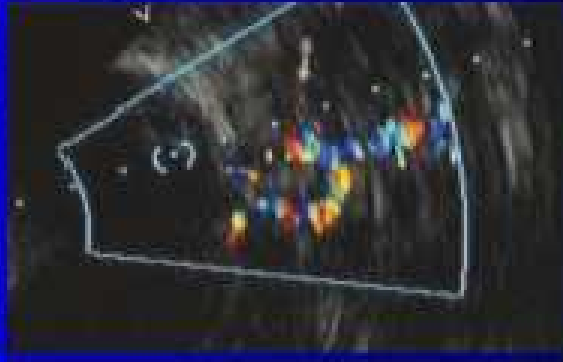

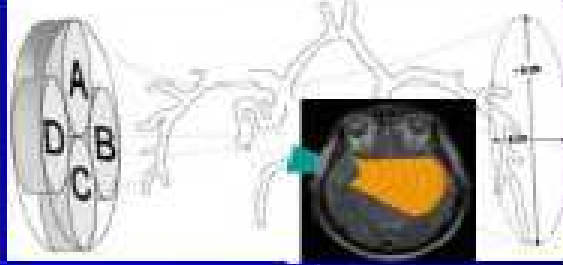
tPA vs tPA + US

Autore	anno	gruppi	Durata	Frequenza
Alexandrov (Clotbust)	2004	tPa (63) vs tPa+Us (63) RANDOM	120'	2 MHz (TCD)
Daffertshofer (Thrumbi)	2005	tPA (12) vs tPA+US (14) RANDOM	90'	30 KHz

Sustained Complete Recanalization: TCD TIBI 5 Flow at 30 min Intervals



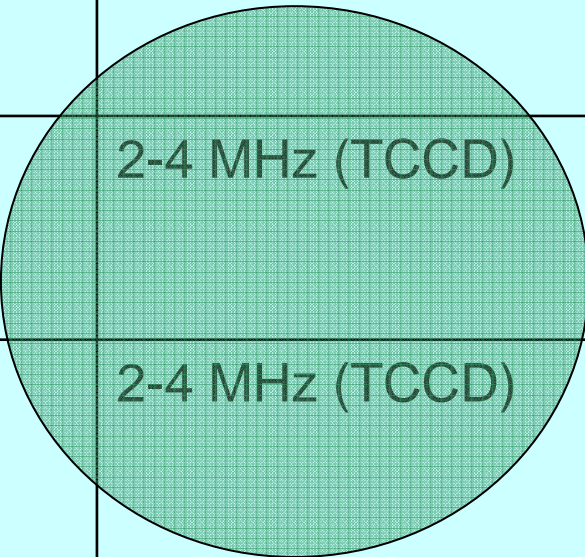
Sonotrombolisi sull'uomo

Trial	Transducer	Tissues Exposed	sICH	CR	mRS 0-1
CLOTBUST n = 126 2 MHz single beam			4.8%	38%	42%
			completed		
Eggers et al. n = 25 2-4MHz multi-beam			18%	27%	27%
			no pre-determined sample size		
TRUMBI n = 26 300 KHz multi-beam			36%	<22%	?
			terminated		

TCCD

(tPA vs tPA + US)

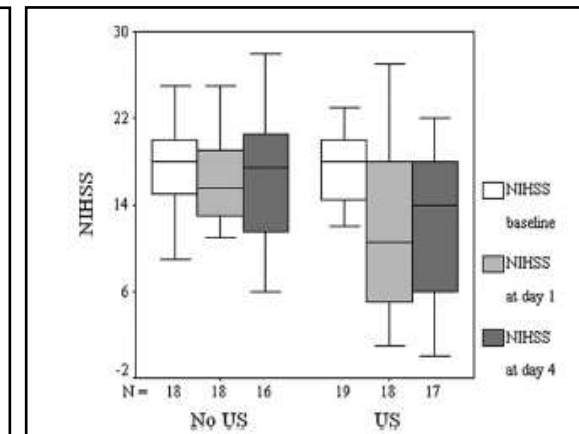
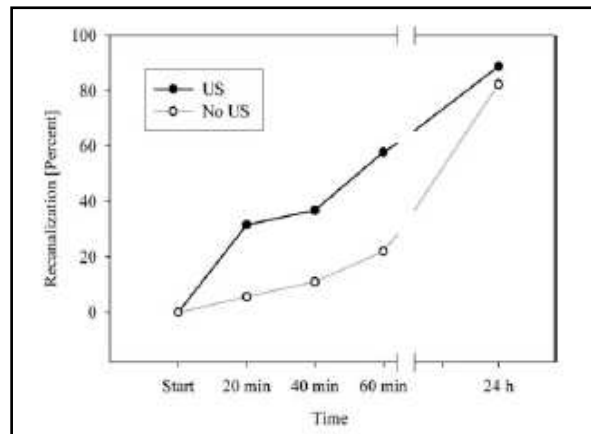
Autore	anno	gruppi	Durata	Frequenza
Eggers	2003	tPA (14) vs tPA+US (11) RANDOM	60'	2-4 MHz (TCCD)
Eggers	2008	tPA (18) vs tPA +US (19) RANDOM	60'	2-4 MHz (TCCD)



Eggers J et al, Stroke 2008

- **Maggiore tasso di Ricanalizzazione (completa o parziale) alla fine di 1 ora di esposizione agli US:**
⇒ **58% vs 22%**
- **Miglioramento clinico a 1 e 4 giorni**
- **Trend verso un migliore outcome a 3 mesi.**

- **Ma ↑Emorragie Cerebrali sintomatiche:**
15.8% vs 5.6%



SONOTROMBOLISI **con TCCD + t-PA**

Accelerazione della Trombolisi con rt-PA + Ultrasuoni

È in corso uno Studio Multicentrico



TRUST

Transcranial Ultrasound enhanced Thrombolysis

SONOTROMBOLISI

in pazienti non eleggibili al t-PA

Accelerazione della Trombolisi con la sola energia degli Ultrasuoni?

È in corso uno Studio Multicentrico (registro)



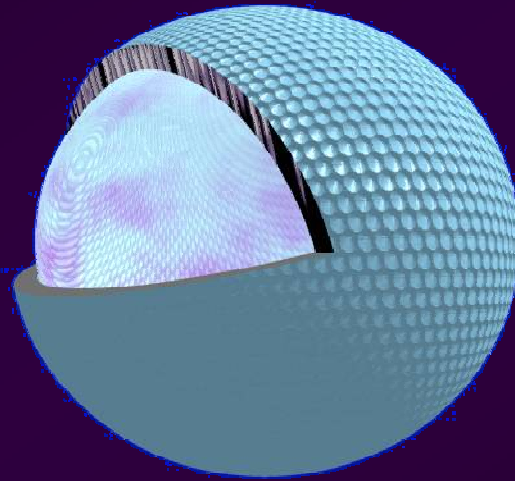
TRUSCA

Thrombolysis with Ultrasound in Contraindication for Alteplase

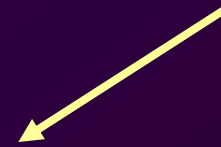
Microbolle



Gas / aria



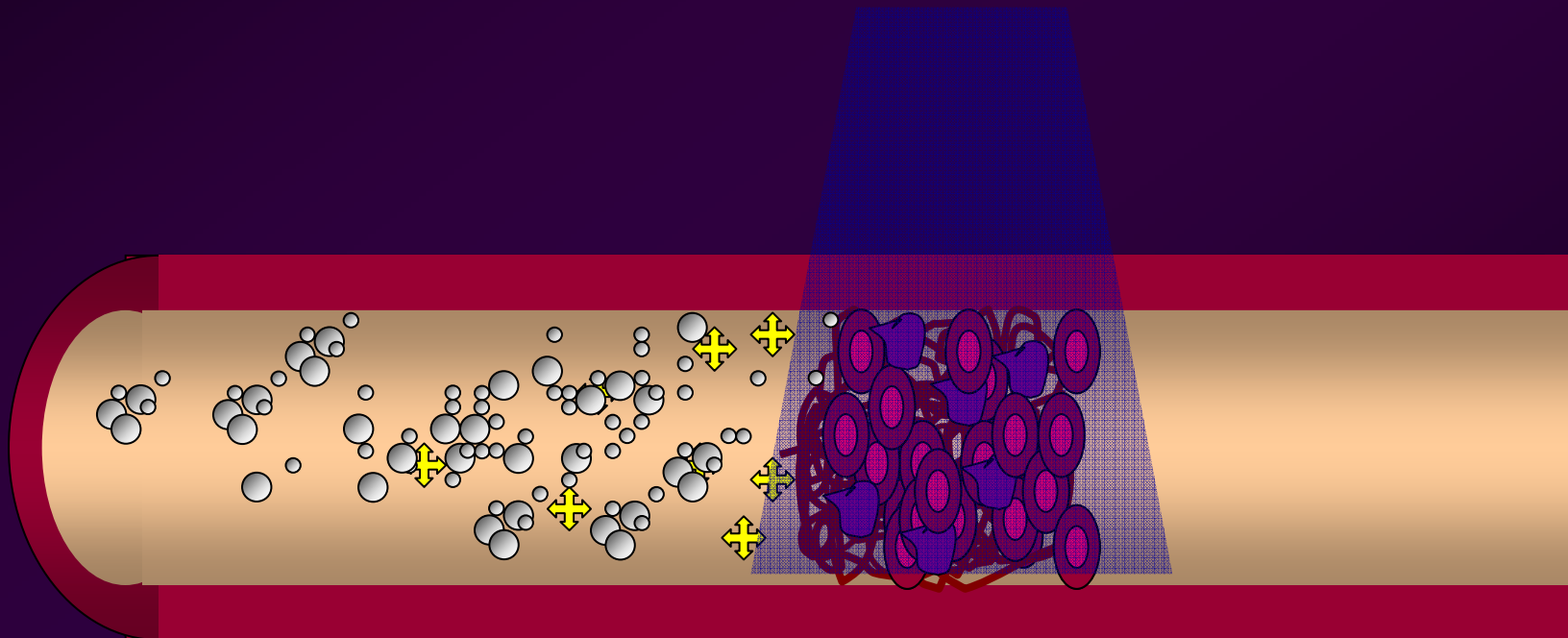
shell



MB-enhanced sonothrombolysis

Ultrasound-accelerated thrombolysis may be further enhanced by MB

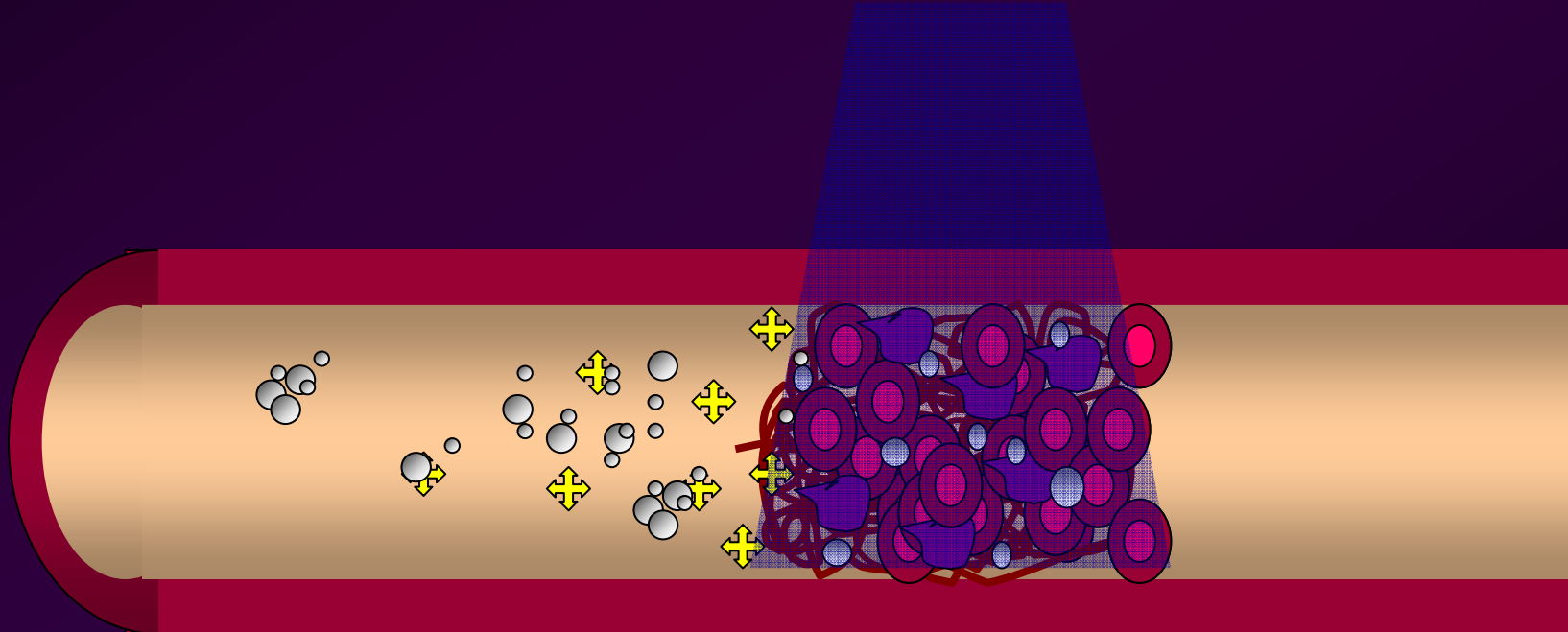
- lowering the threshold for cavitation
- Providing a nucleus for cavitation



MB-enhanced sonothrombolysis

Ultrasound-accelerated thrombolysis may be further enhanced by MB

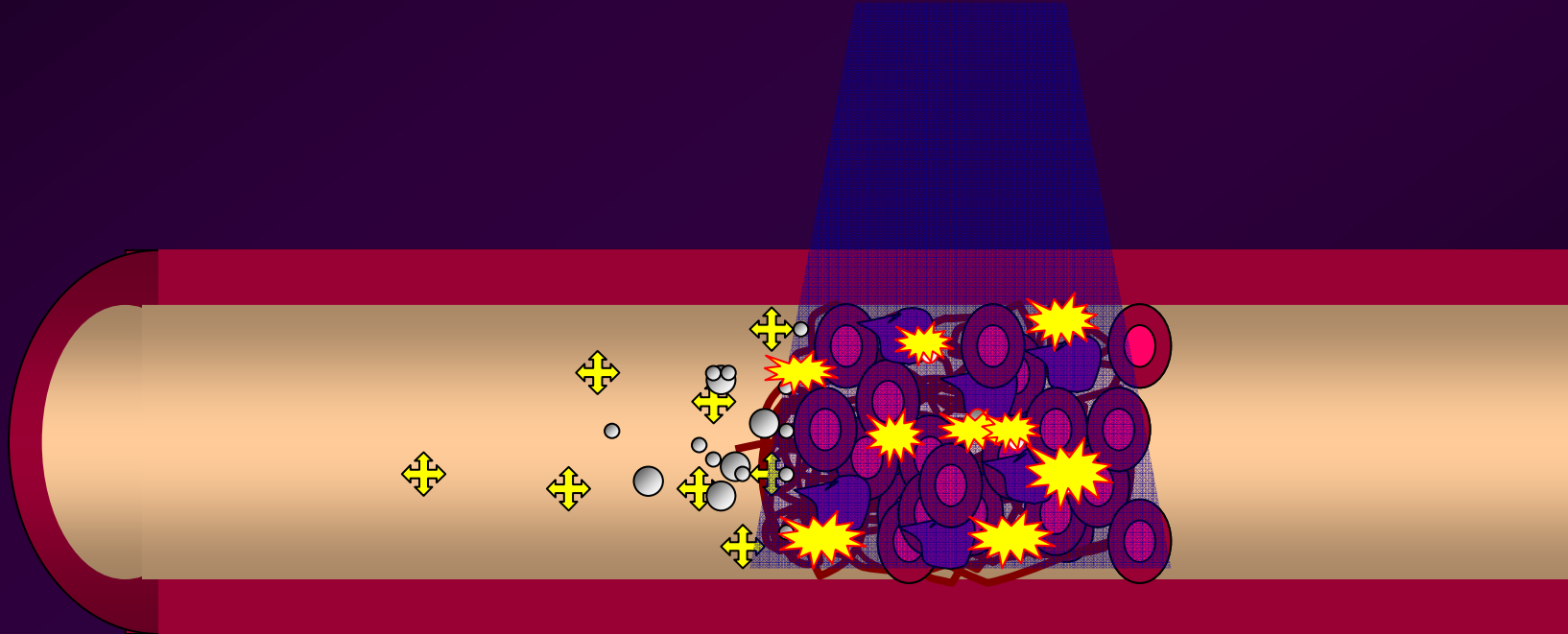
- lowering the threshold for cavitation
- Providing a nucleus for cavitation



MB-enhanced sonothrombolysis

Ultrasound-accelerated thrombolysis may be further enhanced by MB

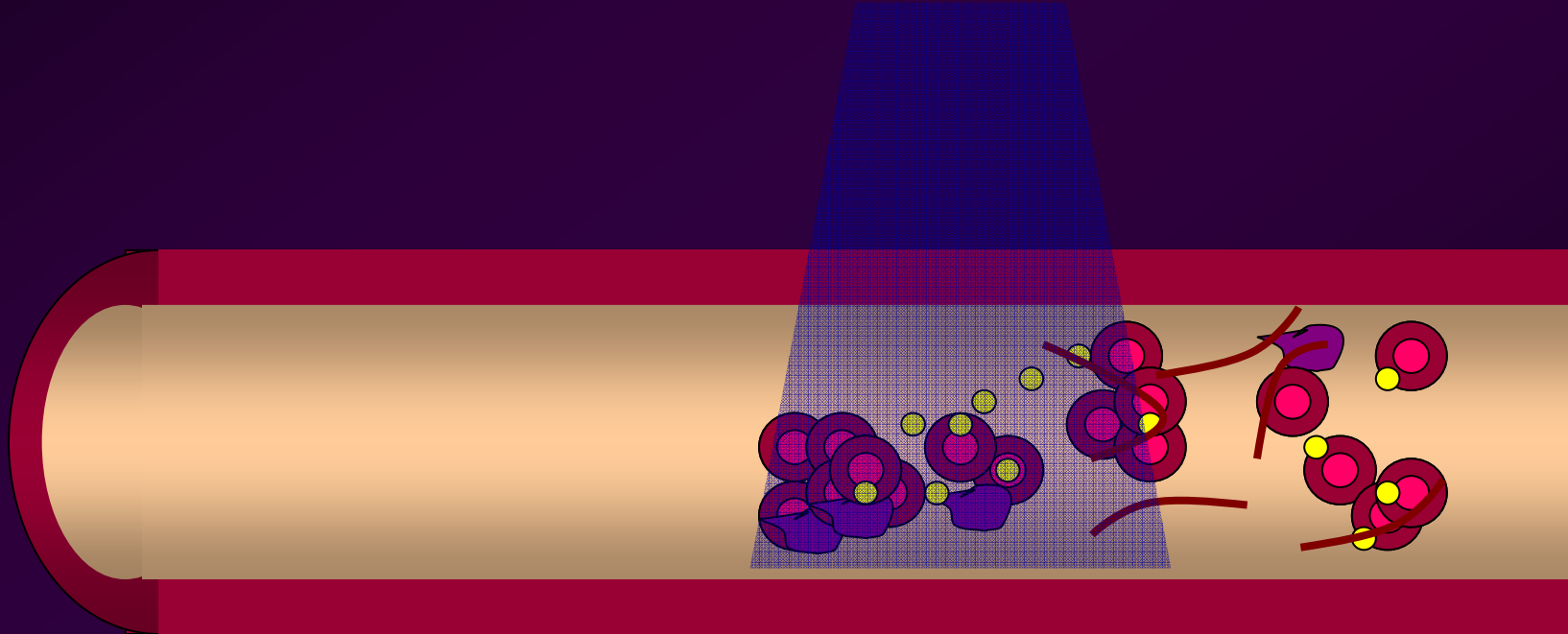
- lowering the threshold for cavitation
- Providing a nucleus for cavitation



MB-enhanced sonothrombolysis

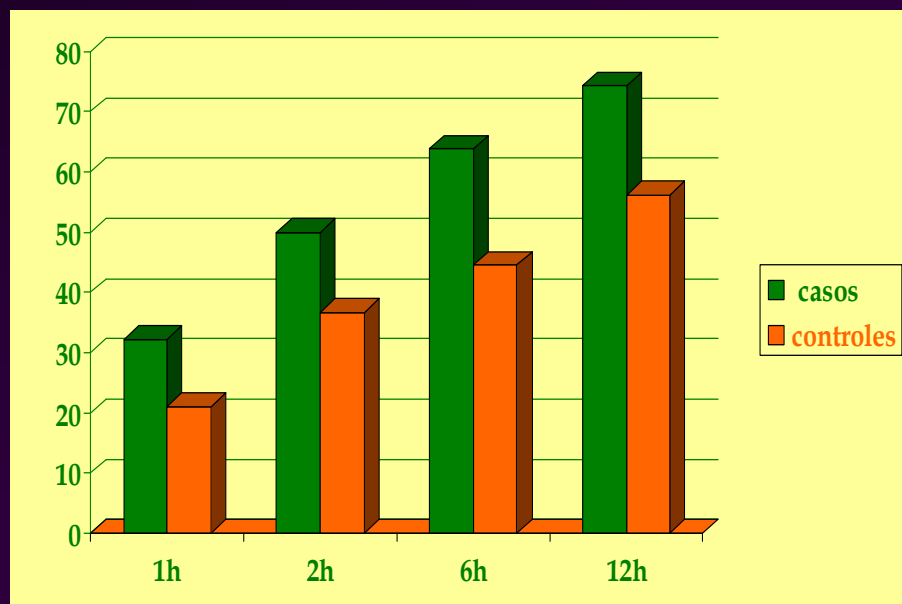
Ultrasound-accelerated thrombolysis may be further enhanced by MB

- lowering the threshold for cavitation
- Providing a nucleus for cavitation



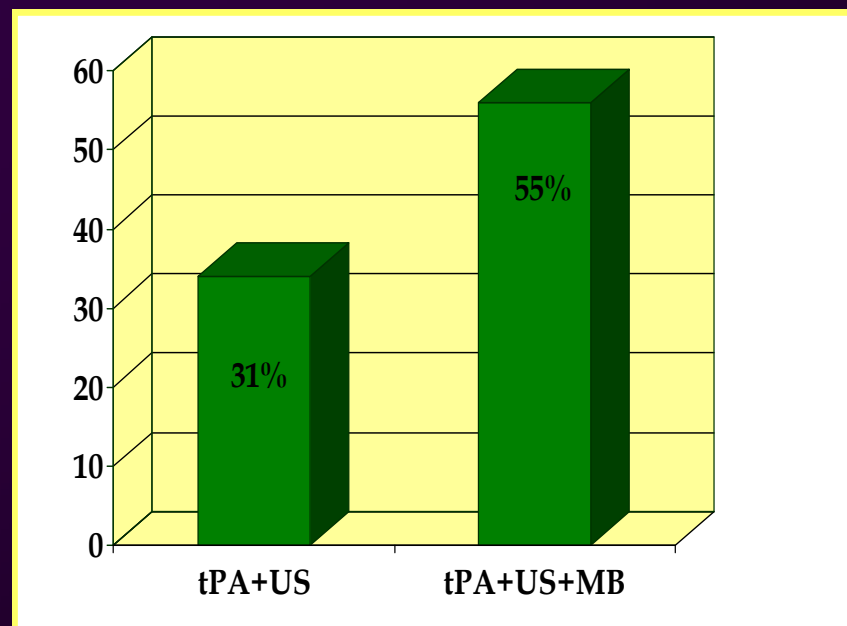
Sonotrombolisi con microbolle

timing della ricanalizzazione



$P > 0.05$

miglioramento clinico



STUDI con Microbolle

Autore	anno	gruppi	Durata	Frequenza
Larrue	2007	tPA vs (11) tPA+US+Mb (9) RANDOM	?	2 MHz (TCCD)
Molina	2006	tPa (73) vs tPa+Us+Mb (38) NO RANDOM	120'	2 MHz (TCD)
Perren	2008	tPA + US (15) vs tPA+US+ Mb (11) NO RANDOM	60'	2 MHz (TCCD)
Dinia	2009	tPA(98) vs tPA+US+Mb (188) NO RANDOM	120'	2 MHz (TCD)

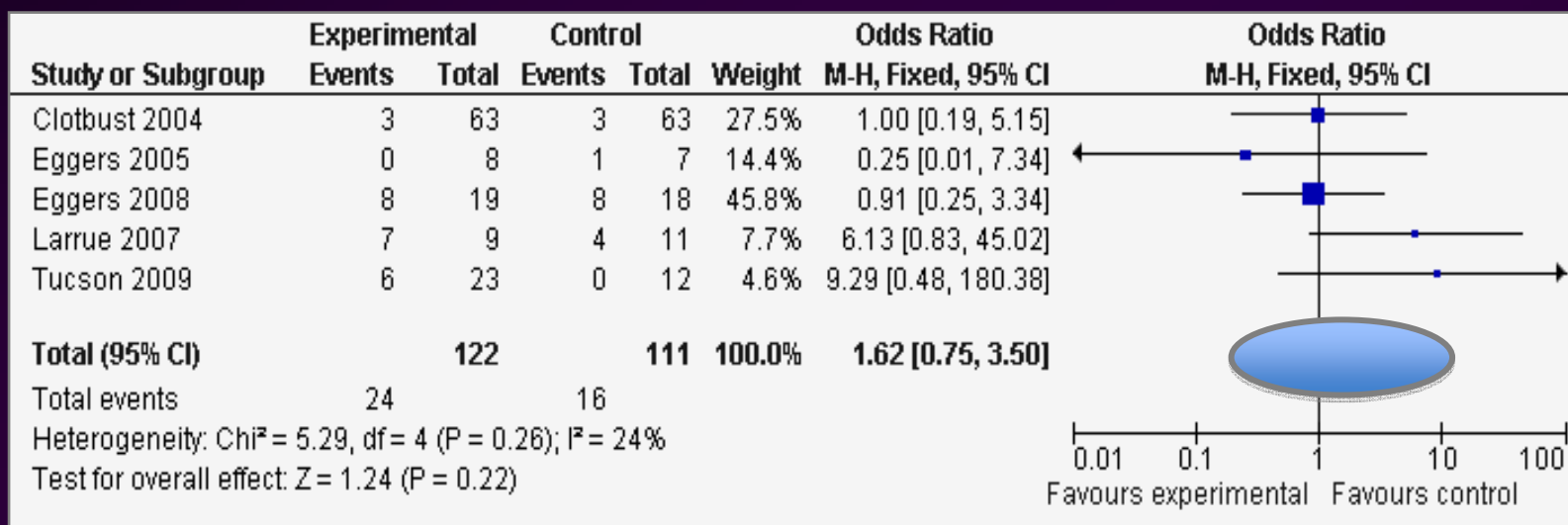
STUDI CON NANOBOLLE

tPA vs tPA + US + nanobolle (Perflutren)

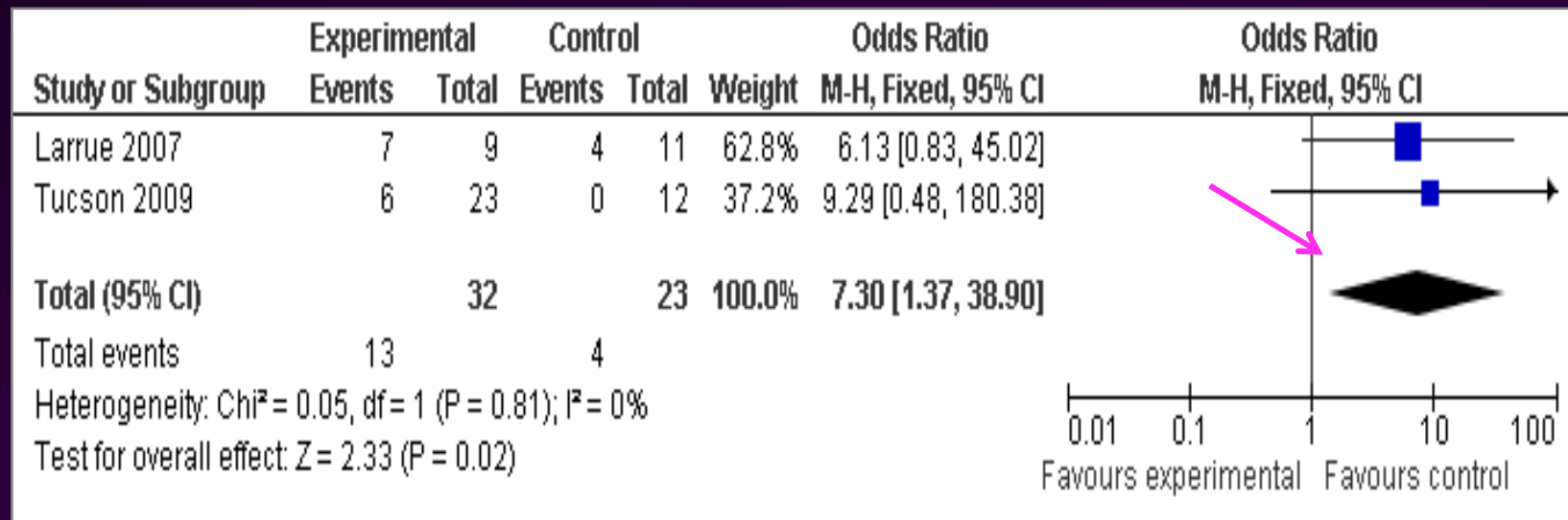
Autore	anno	gruppi	Durata	Frequenza
Alexandrov	2008	tPa (12) vs tPa+Us + Nb (3) RANDOM	90'	2 MHz (TCD)
Molina (Tucson)	2009	tPA+US + Nb diffenti dosi (35) RANDOM	90'	2 MHz (TCD)

REVISIONE SISTEMATICA COCHRANE

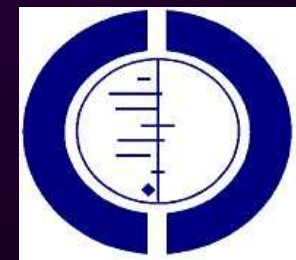
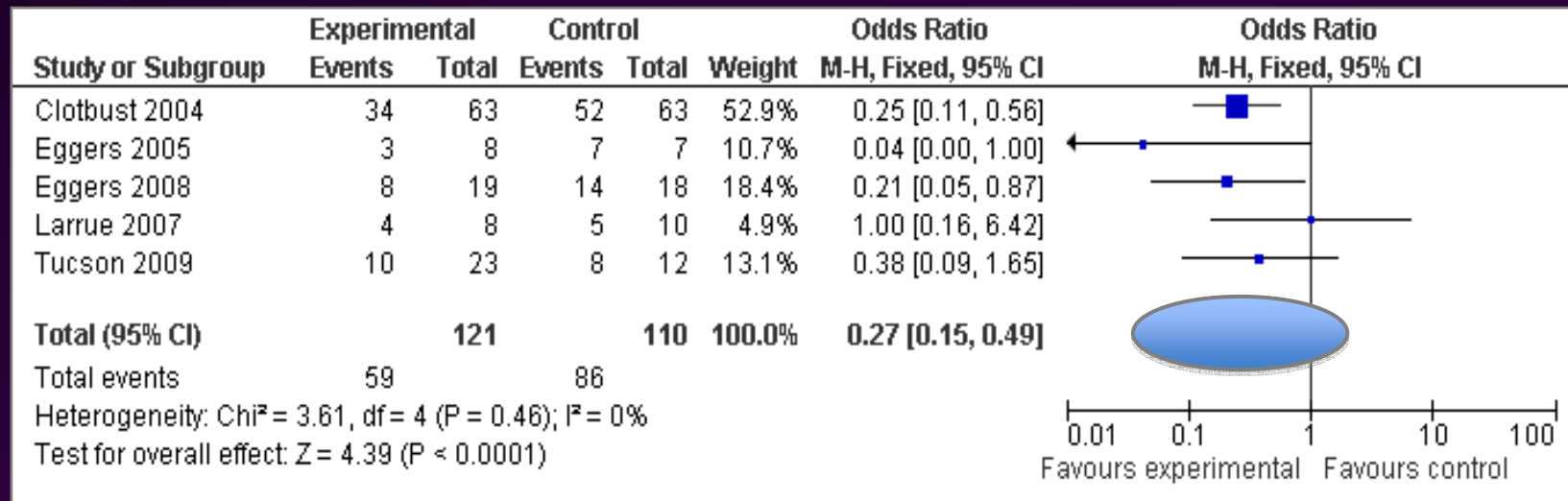
EMORRAGIA CEREBRALE SINTOMATICA E ASINTOMATICA



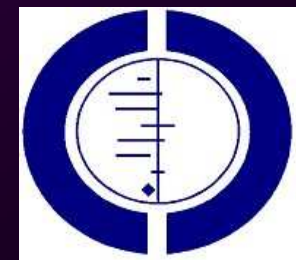
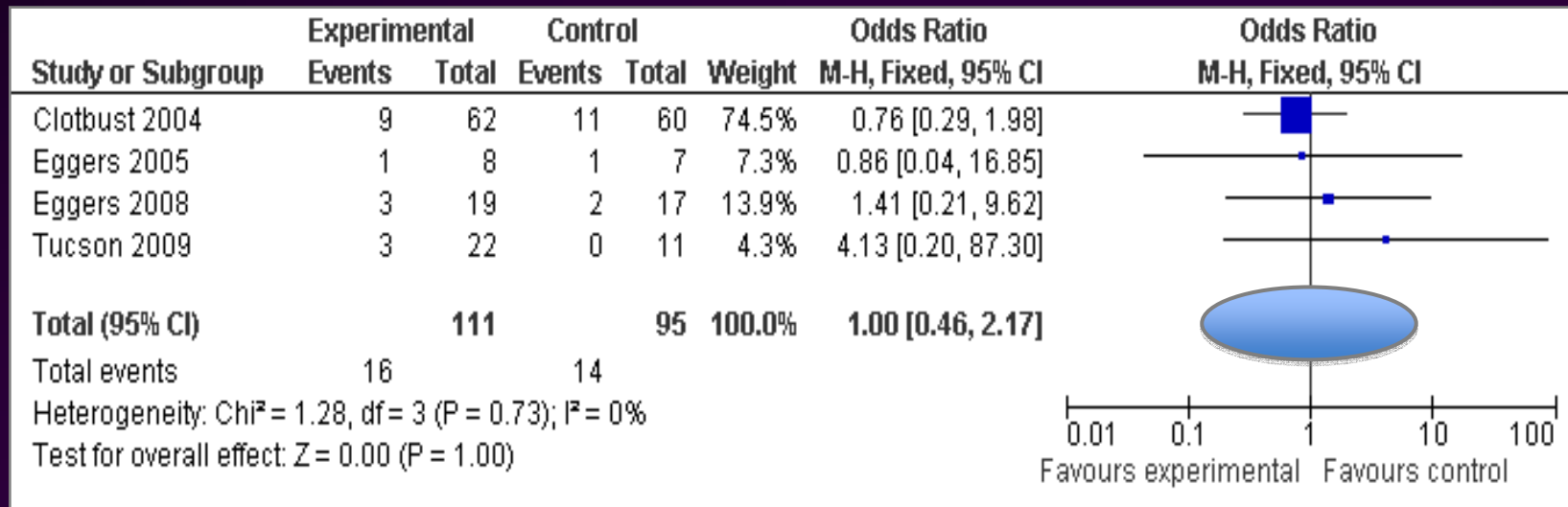
EMORRAGIA: STUDI CON MICROBOLLE



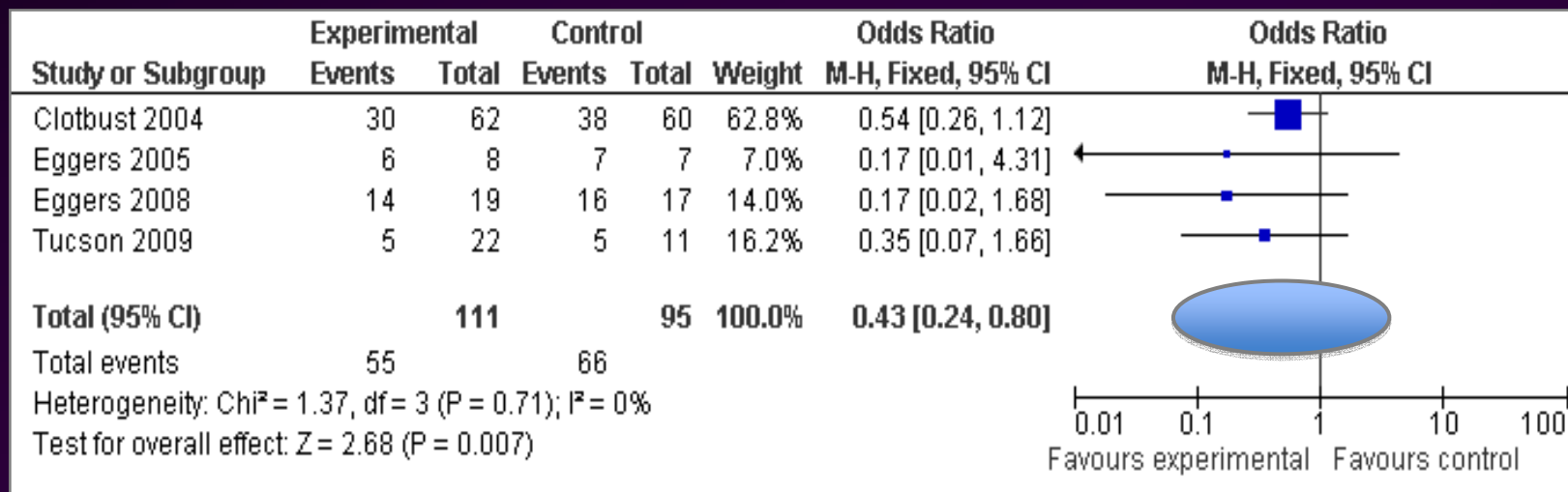
RICANALIZZAZIONE PRECOCE



MORTALITA' A TRE MESI



OUTCOME A TRE MESI



CONCLUSIONI 1

- **Gli Ultrasuoni con frequenze diagnostiche (2MHz) accelerano l'azione trombolitica dell'rt-PA.**
- **Aumentato rischio di emorragie cerebrali con:**
 - **US a basse frequenze (30 KHz)**
 - **TCCD (rispetto al TCD)**
- **L'utilizzo delle Microbolle aumenta la ricanalizzazione (più rapida e completa).**
- **L'uso delle Microbolle + TCD non aumenta il rischio di emorragia sintomatica**
- **L'infusione continua di Nanobolle comporta un aumentato rischio emorragico**

CONCLUSIONI 2

- **La sonotrombolisi aumenta il tasso di ricanalizzazione completa.**
- **La sonotrombolisi migliora l'outcome a 3 mesi**
- **La sonotrombolisi non modifica la mortalità**