TERAPIA TROMBOLITICA SI REGIMURILE ANTITROMBOTICE ASOCIATE IN INFARCTUL ACUT DE MIOCARD CU SUPRADENIVELARE DE SEGMENT ST

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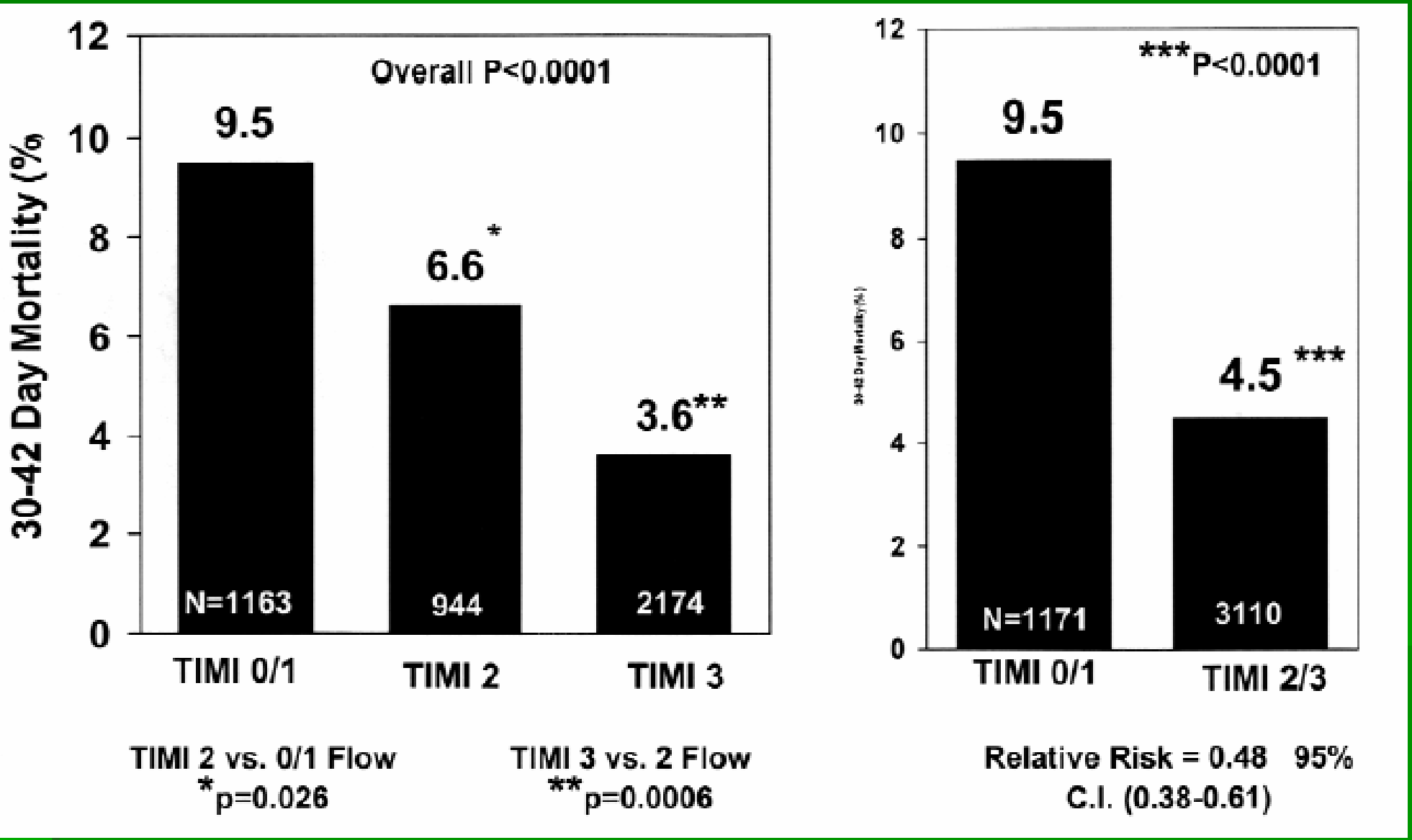
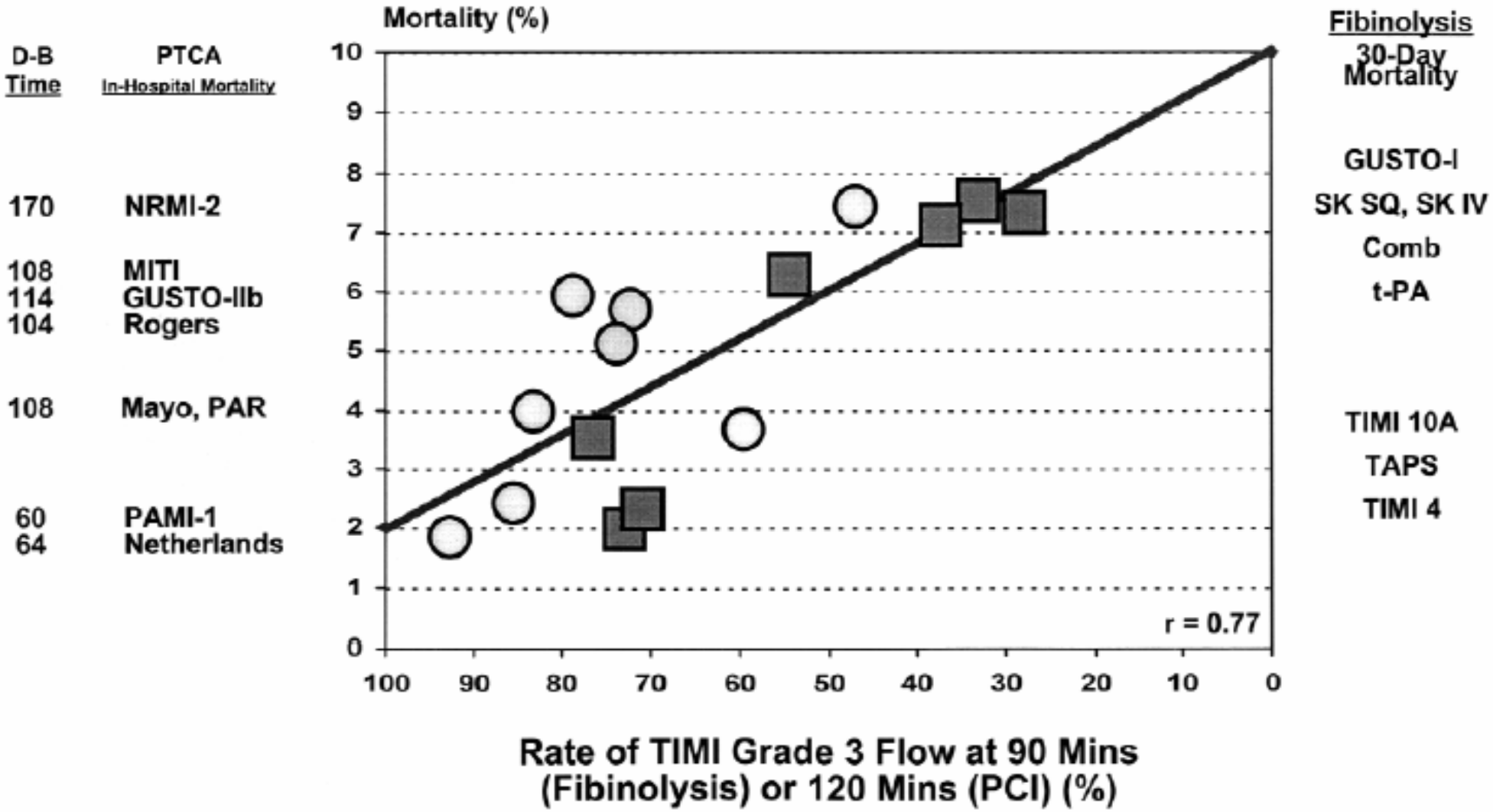
Reperfuzia in IMA

- De Wood (1980) – tromboza coronariana ocluziva – evenimentul cheie in dezvoltarea IMA
- “open artery theory” – reperfuzia completa si rapida a arterei infarctate este determinantul major al prognosticului
- Reperfuzia in IMA:
  - Fibrinoliza intravenoasa
  - PTCA primara
  - Terapie multimodala (angioplastie percutana + inhibitori GIIbIIIa sau agenti antitrombinici)



Relatia dintre reperfuzia precoce si supravietuirea la 30 zile

Cannon, 1994



Relation of TIMI grade 3 flow and mortality rate in trials of fibrinolysis and primary angioplasty. For each trial listed in left and right columns, rate of TIMI grade 3 flow is plotted against mortality rate observed in that group in trial. *Circles* indicate trials of primary angioplasty; *squares* indicate fibrinolysis trials *D-B*, Door-to-balloon time. (Adapted with permission from Cannon CP, Braunwald E. J Thromb Thrombolysis 1996;3:109-17.)

Rata reperfuziei si mortalitatea in trialuri cu trombolitice si PTCA

Terapia fibrinolitica

Diferenta majora intre agentii fibrinolitici – fibrin-specificitatea:

- agenti fibrino-specifici: Alteplase (t-PA) si Tenecteplase (TNK-tPA0
- agenti nespecifici: Streptokinaza (SK) si Anistreplaza (APSAC)
- specificitate intermediara: Reteplase (rPA)

	Streptokinase	t-PA	r-PA	APSAC	TNK-tPA
Plasma half-life (h)	25	4-8	15	70-120	20-24
Dose	1.5 MU over 30-60 min	*	Two 10U injections 30 min apart	30 U over 5 min	0.5 mg/kg
Fibrin specificity	No	Yes	Yes	No	Yes
90-Min TIMI 3 flow rates	20%-30%	50%-60%	50%-60%	50%-60%†	50%-60%
Cost ($)‡	543	2750	2750	2836	2750
Heparin therapy	SQ or IV	IV	IV	SQ or IV	IV or LMWH

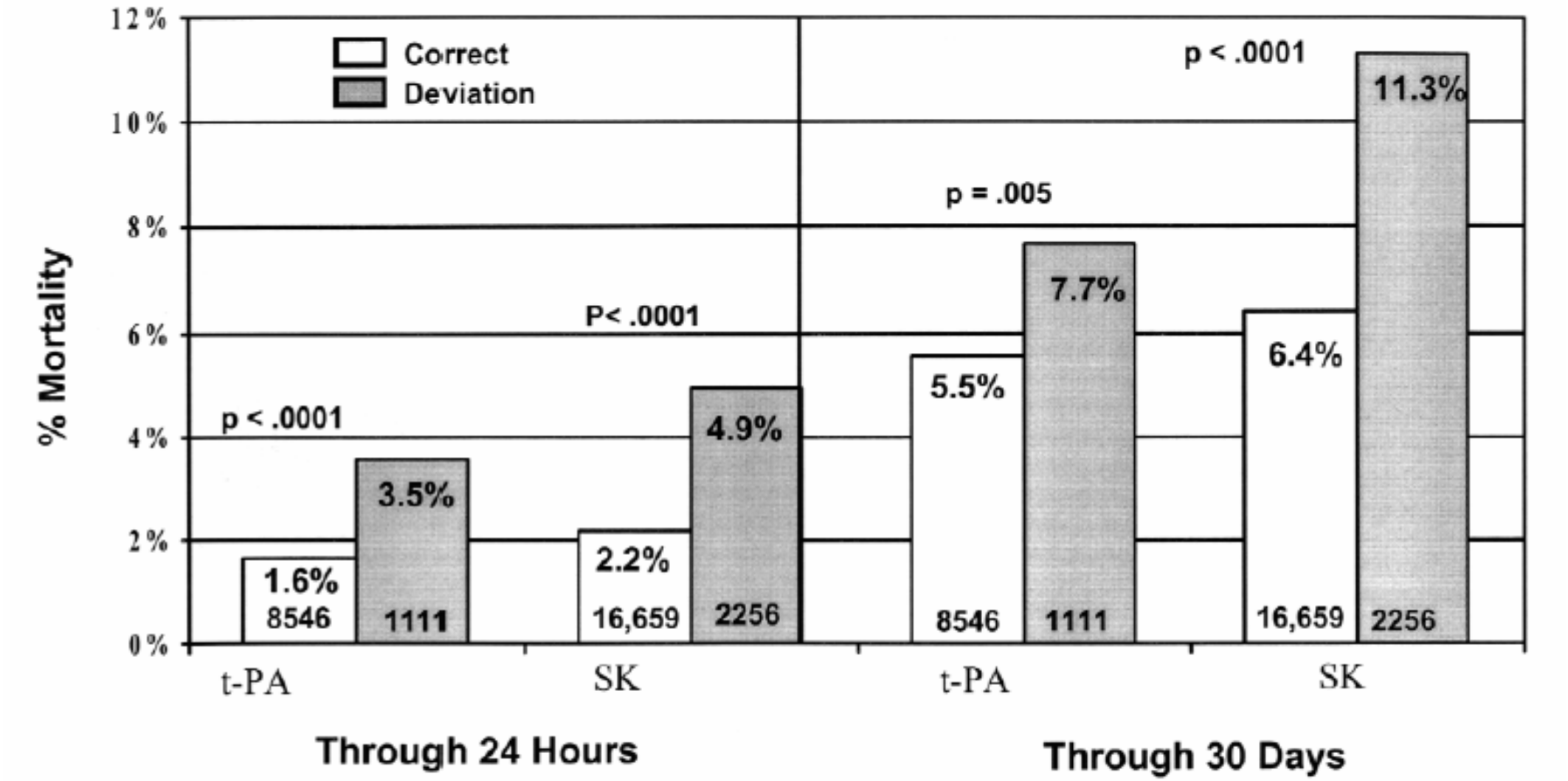
Momentul reperfuziei

- Factor critic in salvarea miocardului siderat si reducerea mortalitatii

- Infuentat de;
  - Educatia populatiei prin mijloace media
  - Strategii educationale in grupele populationale cu risc
  - Reducerea duratei de transport la spital
  - Metode de identificare rapida a pacientilor cu IMA
  - Reducerea timpului “door-to-drug”

Fibrinoliza in bolus

- Beneficii:
  - Usurinta administrarii
    - (reducerea timpului necesar prepararii si administrarii fibrinoliticului – reducerea cu 19 minute a timpului “door-to-drug” in cazul r-PA comparativ cu t-PA)
  - Reducerea erorilor in administrarea trombolitic ului:
    - GUSTO-1:
      - 12% pacienti au avut administrare incorecta a SK sau t-PA
      - Mortalitate mai mare la 30 de zile a acestor pacienti comparativ cu cei tratati corect
    - TIME-II:
      - Mortalitate si rata mai mare de hemoragie intracaniana la pacientii cu erori in administrarea t-PA
      - 7,3% din pacientii tratati cu t-PA au avut doze incorecte comparativ cu 5,7% din pacientii tratati culanoteplaza ($p<0,001$)
  - Fibrinoliza prespital



Relatia dintre erorile in administrarea tromboliticului si mortalitate in trialul GUSTO-1

Agentii fibrinolitici cu administrare in bolus

- Derivate de t-PA:
  - Reteplase
  - Lanoteplase
  - Tenecteplase
- Derivate de SK (rezultate inferioare t-PA, rar utilizat):
  - APSAC

Reteplase

- Mutanta prin deletie nonglicozilata a t-PA
- Administrarea iv in doua bolusuri a cate 10 ui asigura flux TIMI 3 in masura superioara t-PA accelerat (60% fata de 45%, p=0,01)
- GUSTO III:
  - Mortalitate la 30 de zile comparabila cu regimul t-PA accelerat (7,47% fata de 7,24%)
  - Fara diferente semnificative in hemoragii intracraniene, AVC sau sangerari severe

Tenecteplase

- 3 modificari la molecula de t-PA
- Avantaje:
  - Fibrin-specificitate de 14x mai mare fata de alteplase
  - Rezistenta de 80x mai mare la degradarea prin PAI-1
  - Timp de injumatatire de 20-25 minute
  - Administrare in **DOZA UNICA**
- TIMI10A si 10B:
  - Rate de reperfuzie comparabile cu t-PA
- ASSENT-2:
  - Rate de mortalitate la 30 de zile comparabile pentru t-PA si TNK (6,18% si 6,15%)
  - Fara diferente in incidenta hemoragiilor intracerebrale
  - Semnificativ mai putine sangerari totale noncerebrale si majore ca si necesar mai mic de transfuzii la grupul TNK fata de t-PA
- TNK superioara t-PA prin usurinta de administrare atat intra cat si prespital

Lanoteplase

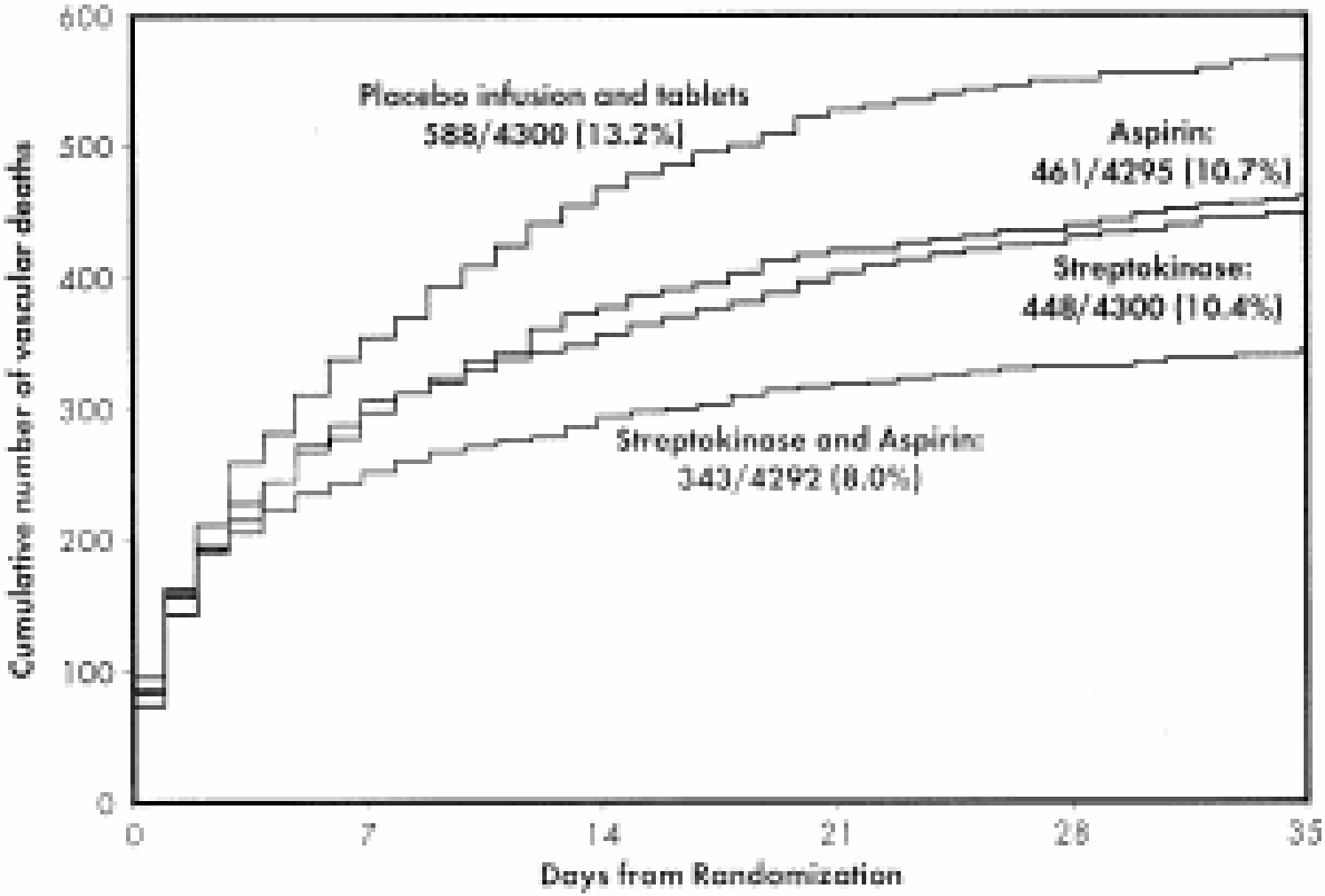
- Administrare in doza unica
- TIME-II:
  - Patenta la 90 de minute superioara fata de t-PA
  - Fara diferente in rata de mortalitate
  - Rata mai mare de hemoragii intracerebrale

TABLE 1. Main End Point Data From Trials of Different Thrombolytic Agents in Patients With Acute ST-Segment Elevation Myocardial Infarction

Trial	No.	Treatments	Primary End Point	Results		*P* Value
GISSI-1[2]	11,806	SK 1.5 MU/h versus placebo	21-day in-hospital mortality	SK	10.7%	$P = .0002$
				Placebo	13.0%	18% reduction; relative risk 0.81
ISIS-2[3]	17,187	2 × 2 factorial design	5-week cardiovascular mortality	SK	9.2%	Odds reduction:
				Placebo	12.0%	25% SD 4; 2 $P < .00001$
		Aspirin 162.5 mg versus placebo		Aspirin	9.4%	Odds reduction:
				Placebo	11.8%	23% SD 4; 2 $P < .00001$
GUSTO[6]	41,021	SK 1.5 MU/h plus SC UFH, SK 1.5 MU/h plus I V UFH, accelerated tPA plus IV UFH, both thrombolytic	30-day mortality	SK + SC UFH	7.2%	$P = .001$
				SK + IV UFH	7.4%	14% reduction (95% CI: 5.9-21.3)
		drugs plus IV UFH		tPA + IV UFH 6.3% both + IV UFH 7.0%		
GUSTO III[10]	15,059	Reteplase, two bolus doses of 10 MU each	30-day mortality	Reteplase:	7.47%,	Adjusted $P = .54$ (OR, 1.03; 95% CI: 0.91-1.18); the 95% CI for absolute difference in death was −1.1-0.66%
				Alteplase:	7.24%	
		Accelerated infusion of alteplase, up to 100 mg/90 min				
TIMI 10B[17]	866	Tenecteplase, 30, 40, or 50 mg	TIMI grade 3 flow at 90 min	Tenecteplase 30:	54.3%,	$P = .035$ (30 mg versus tPA)
		Alteplase, front-loaded		Tenecteplase 40: Alteplase:	62.8%, 62.7%	P = NS (40 mg versus tPA)
ASSENT-2[4]	16,949	Tenecteplase (weight adjusted)	30-day mortality	Tenecteplase:	6.18%,	Equivalent
		Alteplase (rapid infusion)		Alteplase:	6.15%	

Terapia antitrombotica asociata fibrinolizei

- Terapia antiagreganta
- Antitrombinice directe
- Antitrombinice indirecte
- Heparinele cu greutate moleculara mica
- Inhibitorii de glicoproteina IIb IIIa



Results of ISIS-2. Efficacy of aspirin, streptokinase, and streptokinase and aspirin compared with placebo on cumulative vascular mortality through 35 days. Adapted from Reference 3.

ISIS-2: Beneficiul terapiei antiplachetare cu aspirina asociata la fibrinoliza cu SK

Antitrombinicele directe

- **GUSTO IIb – HIRUDINA:**
  - Compararea hirudinei cu heparina nefractionata (HNF)ca terapie asociata la fibrinolitic (SK sau t-PA)
  - 12.142 pacienti cu SCA stratificati in functie de prezenta/absenta supradenivelarii ST
  - Mortalitate si risc de reinfarctare reduse la 30 de zile
  - Fara diferente la 30 de zile (8.9% pentru hirudina, 9,8% pentru HNF)
- **TIMI9B - HIRUDINA:**
  - Hirudina nu este superioara HNF la 3002 pacienti cu IMA trombolizat in privinta deceselor, reinfarctarii, IC evere sau socului cardiogen la 30 de zile (11,9% pentru HNF si 12,9% la hirudina, p=ns)
- **HERO-2 – BIVALIRUDINA:**
  - BIVALIRUDINA vs. HNF in asociere cu SK la 17.073 pacienti cu IMA cu supradenivelare de segment ST
  - Fara diferente in mortalitatea la 30 de zile (desi mortalitatea a fost cu 30% mai mare fata de alte trialuri contemporane)
  - Reinfarctare semnificativ mai mica in grupul tratat cu bivalirudina
  - Semnificativ mai multe hemoragii usoare si moderate ca si hemoragii intracerebrale in grupul tratat cu bivalirudina

Trialurile cu antitrombinice directe

Trial	No.	Treatments	Primary End Point	Results		*P* Value
GUSTO IIb[20]	12,142	UFH bolus 0.1 mg/kg IV then infusion 0.1 mg/kg per hour	30-day mortality or nonfatal MI (or recurrent MI)	UFH	9.8%	*P* = .06
		Hirudin bolus 5000 U IV then infusion 1000 U/h		Hirudin	8.9%	(OR risk of end point in hirudin group, 0.89; 95% CI: 0.79-1.00)
TIMI 9B[21]	3002	Hirudin bolus 0.1 mg/kg, then infusion 0.1 mg/kg per hour	30-day death, recurrent MI, severe heart failure, or cardiogenic shock	UFH	11.9%	*P* = NS
		UFH bolus 5000 U, then infusion 1000 U/h Additionally: IV alteplase/90 min or SK, 1.5 MU/h		Hirudin	12.9%	(OR hirudin: UFH 1.09; 95% CI: 0.88-1.36)
HERO-2[22]	17,073	SK plus bivalirudin SK plus UFH	30-day mortality	30-day mortality: UFH: Bivalirudin: Recurrent MI: UFH: Bivalirudin:	 10.9%, 10.5% 2.3%, 1.6%	 *P* = 46 (OR 0.96; 95% CI: 0.86-1.07) *P* = .001 (OR 0.70; 95% CI: 0.56-0.87)

Abbreviations: UFH, unfractionated heparin; IV, intravenous; OR, odds ratio; MI, myocardial infarction; CI, confidence interval; NS, not significant; SK, streptokinase; MU, million units.

Antitrombinicele indirecte - HNF

- HNF:
  - Creste capacitatea AT3 circulante de blocare a unor factori ai coagularii (XIIa, XIa, IXa, Xa, IIa) dintre care esentiale sunt:
    - Activitatea anti-Xa
    - Activitatea anti-IIa
  - Protocol in asociere cu t-PA:
    - Bolus HNF 60UI/kg la initierea fibrinolizei
    - Doza de intretinere 12UI/kg/h ajustata dupa APTT (1,5-2x VN) timp de 48 de ore (sau mai mult daca exista risc de tromboembolism)
  - Dezavantaje:
    - Necesitatea monitorizarii datorita efectului anticoagulant impredictibil
    - trombocitopenie

Heparinele cu greutate moleculara joasa

- Masa moleculara inferioara HNF (1/3)
- Activitate predominanta anti-Xa
- Efect anticoagulant predictibil, proportional cu doza
- Biodisponibilitate crescuta
- Timp de injumatatire lung
- Nu necesita determinarea APTT (necesita insa urmarirea nivelului anti-Xa la pacientii obezi, subponderali si la cei cu insuficienta renala)
- Trombocitopenia rara (verificarea trombocitelor o data pe saptamana)
- Sangerari mai rare fata de HNF
- **Diferitele preparate:**
  - **Rapoarte antiXa/antilla diferite**
  - **Nu ofera un beneficiu echivalent**

Enoxaparina

- Superioritate fata de HNF in SCA fara supradenivelare de ST
- Superioritate fata de HNF in IMA netrombolizat in reducerea deceselor, reinfarctarilor si necesarului de revascularizari de urgenta (ESSENCE, TIMI 11B)

Enoxaparina in IMA

- HART II:
  - Patenta la 90 minute comparabila cu HNF in asociere la tromboliza cu t-PA
  - Reocluzii la 7 zile mai putine
  - Efecte adverse comparabile la cele 2 grupuri
- AMI-SK:
  - 496 pacenti cu IMA trombolizat cu SK
  - Enoxaparina superioara placebo in ceea ce priveste patenta vasului si evenimentele ischemice recurente
- ASSENT-3:
  - 6095 pacienti cu IMA impartiti in 3 grupuri:
    - TNK doza completa + enoxaparina (TNK/enox)
    - TNK demi-doza + HNF + abciximab (TNK/abciximab)
    - TNK doza completa + HNF (TNK/UFH)
  - End-point primar: indice compozit la 30 zile – decese, reinfarctare sau ischemie refractara intraspital

ASSENT-3

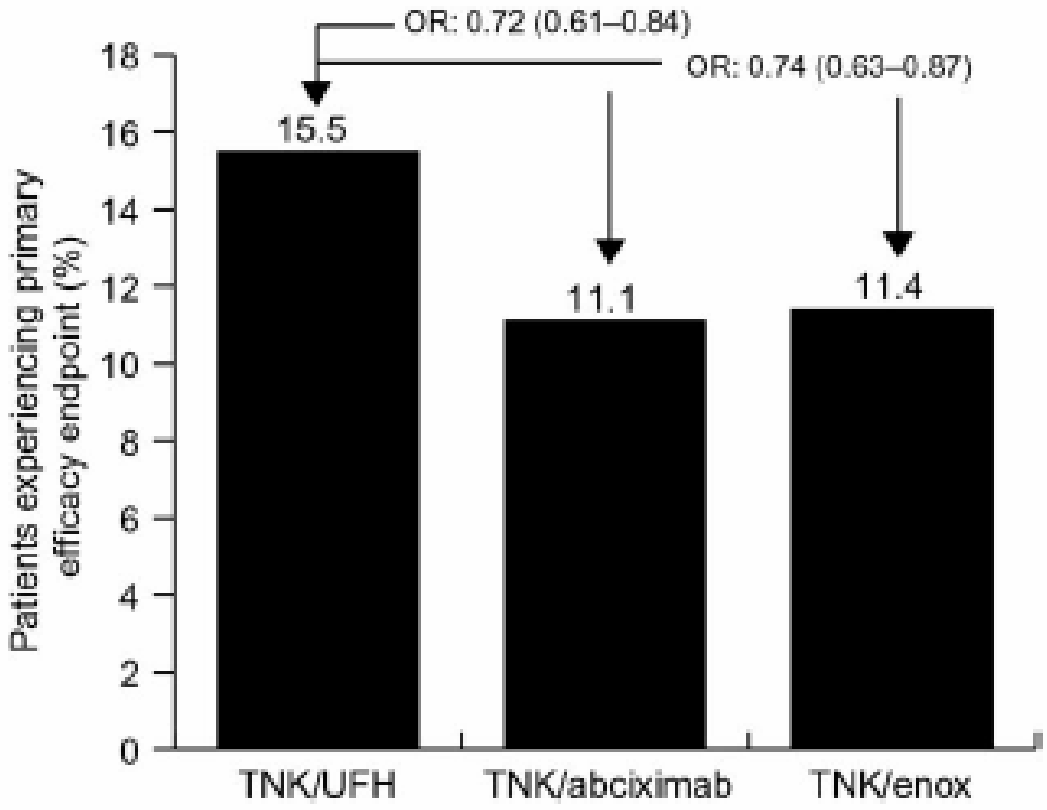


FIGURE 1. Efficacy results from the ASSENT-3 study. Primary efficacy end point (30-day mortality, in-hospital reinfarction, in-hospital refractory ischemia) by treatment group (n = 6095). Abbreviations: OR, odds ratio; TNK/UFH, full-dose tenecteplase plus unfractionated heparin; TNK/abciximab, half-dose tenecteplase plus unfractionated heparin and abciximab; TNK/enox, full-dose tenecteplase plus enoxaparin.

ASSENT-3

TABLE 4. Safety Results From the ASSENT-3 Study

Event	TNK/Enoxaparin	TNK/Abciximab (%)	TNK/UFH	*P* Value
Major hemorrhage	3.0*	4.3†	2.2	.0005
Transfusions	3.4*	4.2†	2.3	.0032
Thrombocytopenia	1.2*	3.2†	1.3	<.0001
ICH	0.9	0.9	0.9	.98

*Not significant when compared with UFH.
†Significant when compared with UFH.
Abbreviations: TNK/enoxaparin, full-dose tenecteplase plus enoxaparin; TNK/abciximab, half-dose tenecteplase plus UFH and abciximab; TNK/UFH, full-dose tenecteplase plus UFH; ICH, intracranial hemorrhage; UFH, unfractionated heparin.

Rezultate:

-Eficienta crescuta a asocierii TNK/enox si TNK/abciximab

-Incidenta crescuta a sangerarilor (semnificativ) in grupul TNK/abciximab

-Incidenta crescuta a sangerarilor in grupul TNK/enox dar nesemnificativ

-Rata similara de hemoragii intracerebrale

ENTIRE-TIMI 23

- 483 pacienti cu IMA
- Evaluarea enoxaparinei ca alternativa la HNF la pacienti tratati cu TNK full dose sau cu asocierea TNK demi doza + abciximab
- 50% din pacienti au avut flux TIMI 3 la 60 minute indiferent de regimul fibrinolitic si de asocierea HNF sau enoxaparinei
- Enoxaparina a fost superioara in prevenirea ischemiei recurente (mortalitate globala la 30 zile si reinfarctare) fata de HNF (4,4% fata de 15,9%, p=0,005) la doza full de TNK.

Trial	No.	Treatments	Primary End Point	Results		P Value
FRAMI[24]	776	SK plus dalteparin	Left ventricular thrombus formation and arterial embolism	Dalteparin:	14.2%,	$P = .03$; risk reduction of thrombus formation (OR 0.69; 95% CI: 0.49-0.92)
		SK plus placebo		Placebo:	21.9%	
BIOMACS II[25]	101	SK plus dalteparin	TIMI grade 3 flow 20-28 h after the start of thrombolysis	Dalteparin:	68%	$P = .10$
		SK plus placebo		Placebo:	51%	
Cohen et al[31]*	252	Enoxaparin	Death/MI/urgent revascularization	At 43 days:		$P = .04$; risk reduction 31.7%
		UFH		Enoxaparin:	26%,	OR 0.58; 95% CI: 0.34-0.98
				UFH:	37%	
Glick et al[32]	103	SK plus enoxaparin	Unstable angina (after	Enoxaparin:	14%	$P < .001$
		SK plus placebo	AMI), recurrent MI, death, 6-month follow up	Placebo:	43%	
AMI-SK[33]	496	SK plus enoxaparin	Patency: TIMI grade 3 flow at day 9 (range: 5-10 days)	TIMI 2 or 3:		$P = .001$
		SK plus placebo		Enoxaparin:	72%	
				UFH:	58%	
				Death/recurrent MI/recurrent angina:		$P = .03$ (36% lower)
				Enoxaparin:	13%	
				UFH:	21%	
HART II[6]	400	Alteplase plus enoxaparin	Patency: TIMI grade 2 or 3 flow at 90 min	Enoxaparin:	80.1%,	Equivalent
		Alteplase plus UFH		UFH:	75.1%	
			(Reocclusion at 5-7 days from TIMI grade 2 or 3 flow	(5.9% and 3.1% of the enoxaparin group, and		$P = .12$ enoxaparin
			to TIMI grade 0 or 1 flow, and TIMI grade 3 flow to TIMI grade 0 or 1 flow, respectively also determined)	9.8% and 9.1% in the UFH group)		$P = .26$ UFH
ASSENT-3[7]	6095	Full-dose teneteplase and enoxaparin, half-dose tenecteplase and abciximab, full-dose tenecteplase and UFH	30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia	Enoxaparin:	11.4%,	Enoxaparin versus UFH: risk reduction 0.74; 95% CI: 0.63-0.87; $P = .0002$
				Abciximab:	11.1%	Abciximab versus UFH: risk reduction 0.72; 95% CI: 0.61-0.84; $P < .0001$
				UFH:	15.4%	
ENTIRE-TIMI 23[35]	483	Full-dose tenecteplase with either UFH or enoxaparin,	Patency: TIMI grade 3 flow at 60 min	Full-dose tenecteplase:		Equivalent
				UFH:	52%	
				Enoxaparin:	48-51%	
		half-dose tenecteplase plus abciximab with either UFH or enoxaparin		Half-dose tenecteplase:		
				UFH:	48%	
				Enoxaparin:	47-58%	
			(30-day death/recurrent MI also determined)	Full dose tenecteplase:		$P = .005$
				UFH:	15.9%	
				Enox:	4.4%	
				Half-dose tenecteplase:		$P = .67$
				UFH:	6.5%	
				Enoxaparin:	5.5%	
PENTALYSE[36]	333	Alteplase plus UFH†	Patency: TIMI grade 3 flow at 90 min	Pentasaccharide:	64%,	$P = .6$
		Alteplase plus pentasaccharide†		UFH:	68%	
				TIMI 3 to TIMI 0 or 1:		$P = .065$
			(Day 5 to 7 reocclusion data also determined):	Pentasaccharide:	0.9%	
				UFH:	7.0%	
				TIMI 2 or 3 to TIMI 0 or 1:		$P = .091$
				Pentasaccharide:	2.3%	
				UFH:	8.0%