Ensaio Controlado Randomizado

Prof. Dr. Octavio Marques Pontes Neto

Ensaio Controlado Randomizado (ECR)

Conteúdo

- História
- Vantagens de um ECR sobre
  - Estudos observacionais
  - Estudos experimentais não-randomizados
- Estrutura de um ECR
- Randomização
- Mascaramento
- Análise
- Ética / regras de interrupção
- Controversias

Friedman et al. 2010

Ensaio Controlado Randomizado (ECR)

História

- **1920s-30s:** Sir Ronald Fisher
  - *p-valor*
  - *Teste exato de Fisher*
  - *ECR em agricultura*
- ***1931:*** *Amberson et al.*
  - *Estudo controlado para tuberculose*
  - *Sanocrisina x salina*
  - *Moeda para randomização*
  - *Alocação cega para participantes*
- ***1948:*** *BMRC trial (Hill et al.)*
  - *Estreptomicina para tuberculose*
  - *Alocação randomizada*
- ***1980s****: FDA*
  - *Megatrials para aprovação de medicamentos*

Friedman et al. 2010

Fases da pesquisa clínica

Etapas para aprovação de uma intervenção

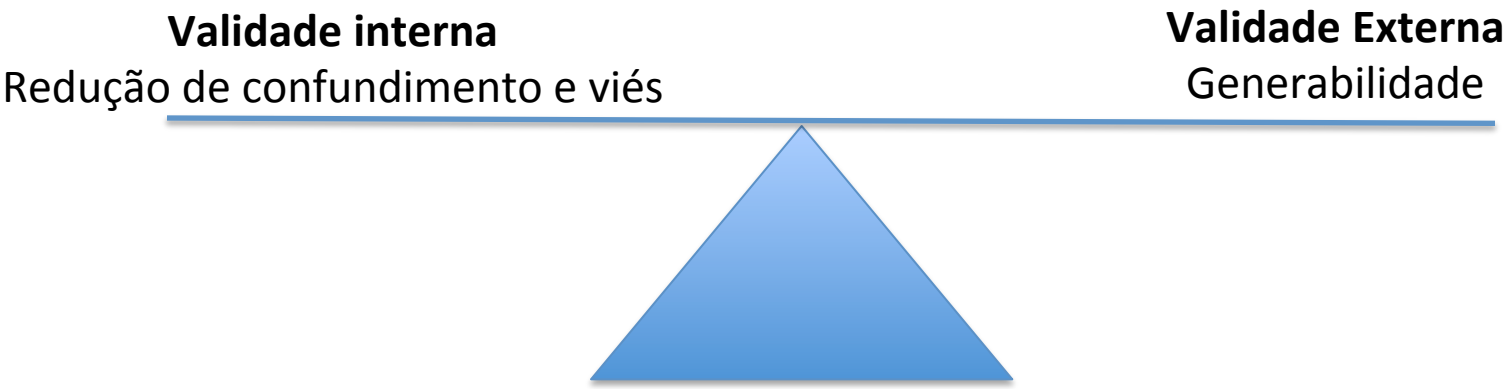
- **Fase 1: Farmacocinética**
  - Dose máxima tolerada
  - Geralmente 10-20 sujeitos
  - Voluntários sadios ou pacientes refratários
- **Fase 2: Titulação de dose**
  - Atividade biológica
  - Toxicidade e segurança
  - Geralmente ~ 100 pacientes
- **Fase 3: Eficácia**
  - Centenas a milhares de pacientes
  - População alvo
- **Fase 4: Pós comercialização**
  - Como funciona na vida real
  - ECR ou observacional

Friedman et al. 2010

ECR: pontos chaves

- **Padrão-ouro para teste eficácia de uma intervenção**

- **Resposta a pergunta: diferença de desfecho é devido a intervenção testada**



ECR: pontos chaves

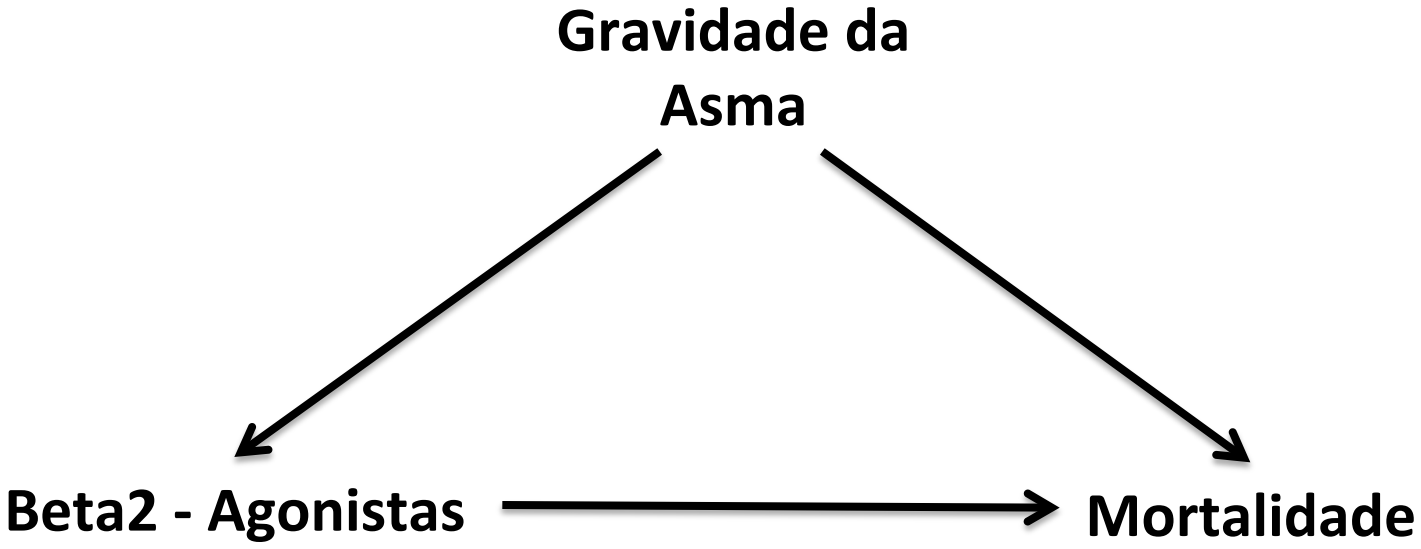
- ECR é um experimento, não a verdade.
- Em ciência: verdade requer > 1 experimento.
- FDA exige pelo menos 2 ECR para aprovação de uma droga.
- **Eficácia** não quer dizer **custo-efetividade.**

ECR vs. Estudos observacionais

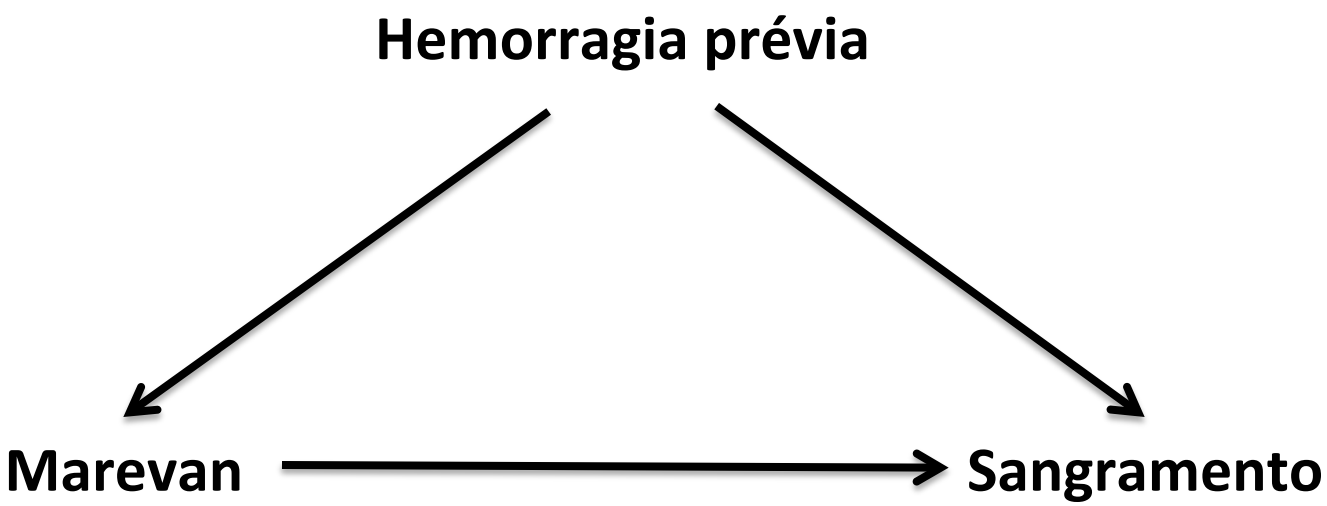
- **Estudos observacionais**
  - Fatores de risco
  - Toxicicidade
  - Conduzidos por epidemiologista
  - Desenho e análise sofisticadas para minimizar **confundimento**

- **Ensaio controlado randomizado**
  - Eficácia de medicamentos, devices, intevenções
  - Não é ético para comprovar risco ou toxicidade
  - Conduzidos por clínicos entusiastas com pouco expertise em desenho de estudos
  - **Randomização** minimiza **confundimento** por fatores conhecidos e não conhecidos

Confundimento por indicação



Confundimento por Contra-indicação



Alternativas experimentais a randomização

Controle históricos

- Efeitos seculares e confundidores desconhecidos podem invalidar
- Evidência definitiva se evidência histórica é contundente

Antes-depois

- Pareamento perfeito?
- Aplicável em condições agudas que se repetem.

Estudo randomizado cruzado

- Excelente para condições com resposta rápida sem efeito residual.
- Randomização do momento ao invés do sujeito.
- Impraticável para intervenções com efeito duradouro.

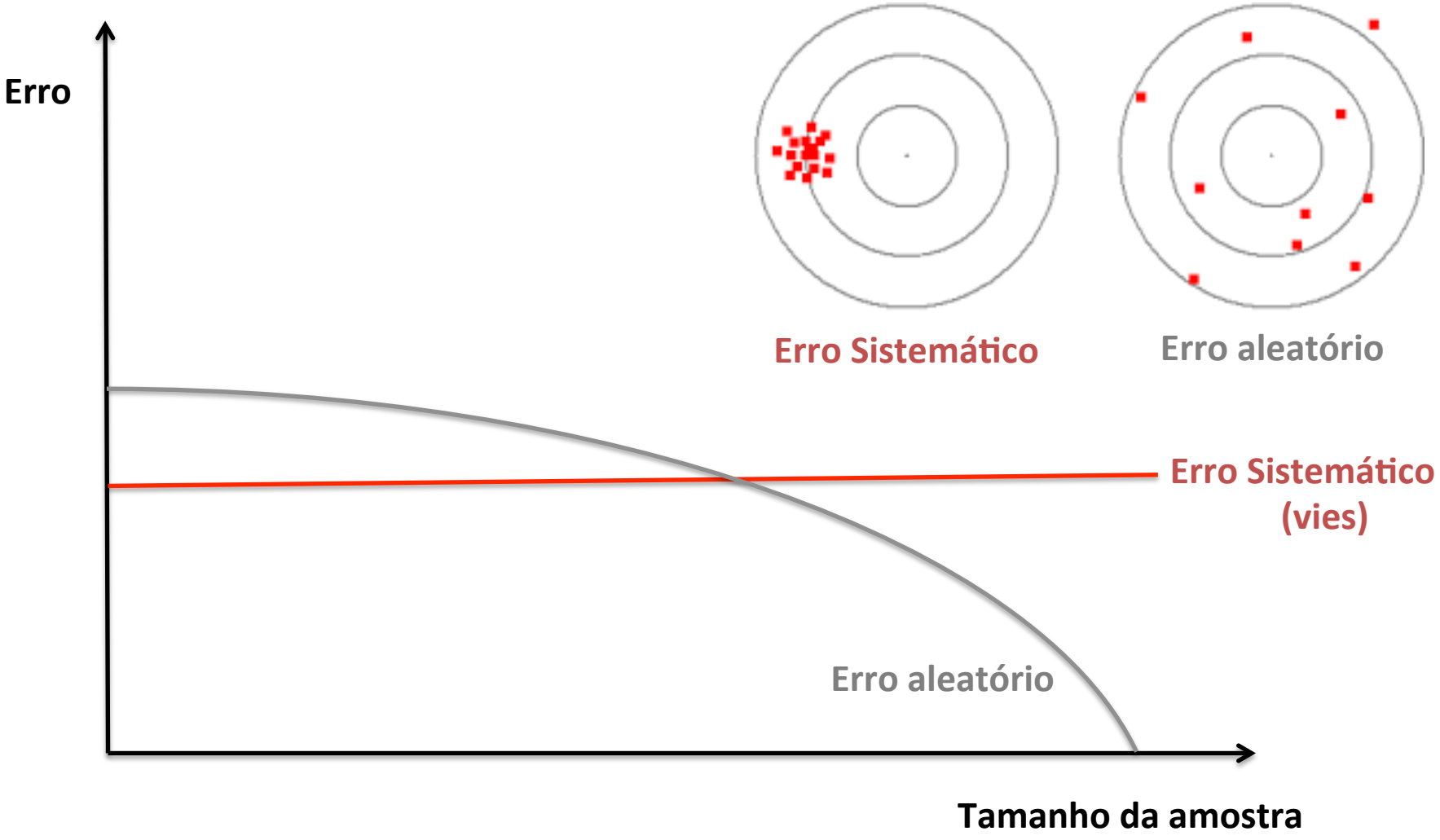
“Randomização”

- Alocação aleatória (imprevisível) da modalidade de tratamento
- Objetivo:
  - Elimina o viés de seleção
  - Balancear tanto as variáveis de confusão conhecidas como desconhecidas (eliminar o viés de confundimento)
  - Garantir risco comparável de desfecho entre os grupos no início do estudo.

- Método:
  - Cartas em um chapéu, moeda
  - Lista de números randômicos (tabela ou computador)
  - Ordem não pode ser antecipada pelo investigador: dia da semana, sobrenome, hospital, etc.

Alocação randômica ≠ Seleção randômica

Tipos de Erros em Estudos Científicos



Rothman. 2nd ed. 2012

O “milagre” da **Randomização**

ORIGINAL ARTICLE

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

Yongjun Wang, M.D., Yilong Wang, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Liping Liu, M.D., Ph.D., David Wang, D.O., F.A.H.A., F.A.A.N., Chunxue Wang, M.D., Ph.D., Chen Wang, M.D., Hao Li, Ph.D., Xia Meng, M.D., Ph.D., Liying Cui, M.D., Ph.D., Jianping Jia, M.D., Ph.D., Qiang Dong, M.D., Ph.D., Anding Xu, M.D., Ph.D., Jinsheng Zeng, M.D., Ph.D., Yansheng Li, M.D., Ph.D., Zhimin Wang, M.D., Haiqin Xia, M.D., and S. Claiborne Johnston, M.D., Ph.D., for the CHANCE Investigators*

ABSTRACT

BACKGROUND

Stroke is common during the first few weeks after a transient ischemic attack (TIA) or minor ischemic stroke. Combination therapy with clopidogrel and aspirin may provide greater protection against subsequent stroke than aspirin alone.

METHODS

In a randomized, double-blind, placebo-controlled trial conducted at 114 centers in China, we randomly assigned 5170 patients within 24 hours after the onset of minor ischemic stroke or high-risk TIA to combination therapy with clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) or to placebo plus aspirin (75 mg per day for 90 days). All participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg on day 1. The primary outcome was stroke (ischemic or hemorrhagic) during 90 days of follow-up in an intention-to-treat analysis. Treatment differences were assessed with the use of a Cox proportional-hazards model, with study center as a random effect.

RESULTS

Stroke occurred in 8.2% of patients in the clopidogrel–aspirin group, as compared with 11.7% of those in the aspirin group (hazard ratio, 0.68; 95% confidence interval, 0.57 to 0.81; P<0.001). Moderate or severe hemorrhage occurred in seven patients (0.3%) in the clopidogrel–aspirin group and in eight (0.3%) in the aspirin group (P=0.73); the rate of hemorrhagic stroke was 0.3% in each group.

CONCLUSIONS

Among patients with TIA or minor stroke who can be treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage. (Funded by the Ministry of Science and Technology of the People's Republic of China; CHANCE ClinicalTrials.gov number, NCT00979589.)

N Engl J Med 2013;369:11-19.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Aspirin (N=2586)	Clopidogrel and Aspirin (N=2584)
Age — yr		
Median	62	63
Interquartile range	54–71	55–72
Female sex — no. (%)	898 (34.7)	852 (33.0)
Systolic pressure — mm Hg		
Median	150	150
Interquartile range	136–161	136–161
Diastolic pressure — mm Hg		
Median	90	90
Interquartile range	80–100	80–98
Body-mass index†		
Median	25	25
Interquartile range	23–27	23–26
Medical history — no. (%)		
Ischemic stroke	517 (20.0)	516 (20.0)
TIA	80 (3.1)	94 (3.6)
Myocardial infarction	53 (2.0)	43 (1.7)
Angina	87 (3.4)	97 (3.8)
Congestive heart failure	38 (1.5)	42 (1.6)
Known atrial fibrillation or flutter	48 (1.9)	48 (1.9)
Valvular heart disease	10 (0.4)	4 (0.2)
Hypertension	1683 (65.1)	1716 (66.4)
Diabetes mellitus	543 (21.0)	550 (21.3)
Hypercholesterolemia	283 (10.9)	290 (11.2)
Pulmonary embolism	1 (<0.1)	0
Current or previous smoking — no. (%)	1105 (42.7)	1116 (43.2)
Mean time to randomization — hr	13	13
Time to randomization — no. (%)		
<12 hr	1280 (49.5)	1293 (50.0)
≥12 hr	1306 (50.5)	1291 (50.0)
Qualifying event — no. (%)		
TIA	728 (28.2)	717 (27.7)
Minor stroke	1858 (71.8)	1867 (72.3)
ABCD² score‡		
Median	4	4
Interquartile range	4–5	4–5

Ensaio Clínico Randomizado

Preocupações antes da Randomização

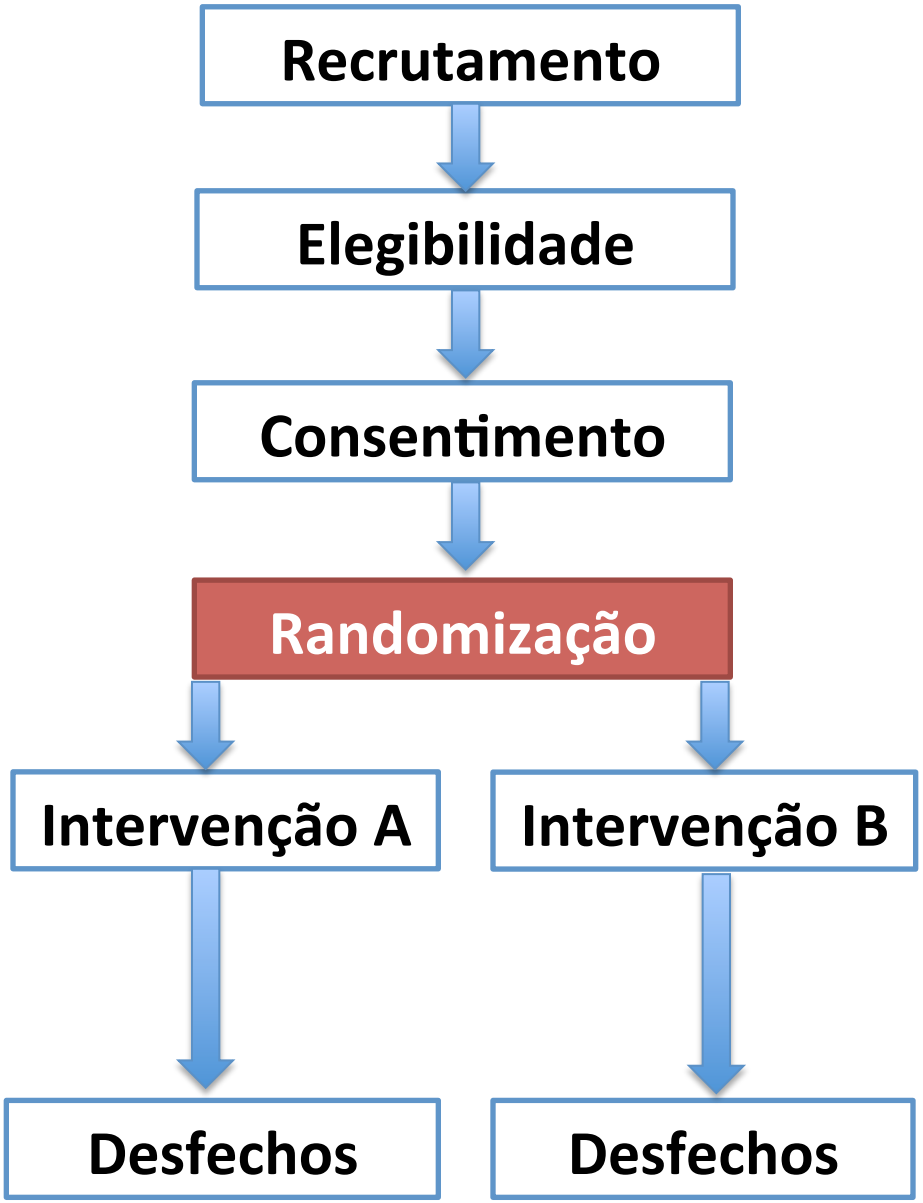
Validade Externa

- Recrutamento seletivo
- Recrutamento ineficiente

Preocupações Depois da Randomização

Validade interna

- Exclusão
- Perda de seguimento
- Adesão
- Contaminação
- Co-intervenção
- Avaliação dos desfechos
- **Viés de informação**



Problemas com a **Randomização** "Viés acidental"

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2008 VOL. 359 NO. 13

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, M.D., Markku Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D., Donata Guidetti, M.D., Vincent Larrue, M.D., Kennedy R. Lees, M.D., Zakaria Medeghri, M.D., Thomas Machnig, M.D., Dietmar Schneider, M.D., Rüdiger von Kummer, M.D., Nils Wahlgren, M.D.,

BACKGROUND

Intravenous thrombolysis with alteplase is the only approved treatment for acute ischemic stroke, but its efficacy and safety when administered more than 3 hours after the onset of symptoms have not been established. We tested the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of a stroke.

METHODS

After exclusion of patients with a brain hemorrhage or major infarction, as detected on a computed tomographic scan, we randomly assigned patients with acute ischemic stroke in a 1:1 double-blind fashion to receive treatment with intravenous alteplase (0.9 mg per kilogram of body weight) or placebo. The primary end point was disability at 90 days, dichotomized as a favorable outcome (a score of 0 or 1 on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms at all and 6 indicating death) or an unfavorable outcome (a score of 2 to 6 on the modified Rankin scale). The secondary end point was a global outcome analysis of four neurologic and disability scores combined. Safety end points included death, symptomatic intracranial hemorrhage, and other serious adverse events.

RESULTS

We enrolled a total of 821 patients in the study and randomly assigned 418 to the alteplase group and 403 to the placebo group. The median time for the administration of alteplase was 3 hours 59 minutes. More patients had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; P=0.04). In the global analysis, the outcome was also improved with alteplase as compared with placebo (odds ratio, 1.28; 95% CI, 1.00 to 1.65; P<0.05). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0% vs. 17.6%; P=0.001; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; P=0.008). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; P=0.68). There was no significant difference in the rate of other serious adverse events.

CONCLUSIONS

As compared with placebo, intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage. (ClinicalTrials.gov number, NCT00153036.)

Table 2. Demographic and Baseline Characteristics of the Patients.

Characteristic	Study Group		P Value*
	Alteplase (N=418)	Placebo (N=403)	
Age (yr)	64.9±12.2	65.6±11.0	0.36
Male sex (%)	63.2	57.3	0.10
Weight (kg)	78.5±15	78.0±16	0.62
NIHSS score†			0.03
Mean	10.7±5.6	11.6±5.9	
Median	9	10	
Systolic pressure (mm Hg)	152.6±19.2	153.3±22.1	0.63
Diastolic pressure (mm Hg)	84.4±13.5	83.9±13.6	0.58
Diabetes (%)	14.8	16.6	0.47
Previous use of aspirin or antiplatelet drugs (%)	31.1	32.5	0.65
Hypertension (%)	62.4	62.8	0.88
Atrial flutter or fibrillation (%)	12.7	13.6	0.67
History of stroke (%)	7.7	14.1	0.03
Smoking status (%)‡			0.93
Never smoked	48.6	46.2	
Ex-smoker	20.6	24.6	
Current smoker	30.6	28.8	
Time to treatment initiation			
Median	3 hr 59 min	3 hr 58 min	0.49
By 0.5-hr period§			0.44
≥3.0 to ≤3.5 hr (%)	9.6	10.4	
>3.5 to ≤4.0 hr (%)	45.7	47.9	
>4.0 to ≤4.5 hr (%)	41.6	36.7	

N Engl J Med 2008;359:1317-29

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Table 3. Odds Ratios for Primary End Point and Secondary End Point, Including Components, in the Intention-to-Treat and Per-Protocol Populations at 90 Days.*

End Point	Intention-to-Treat Population				Per-Protocol Population			
	Alteplase Group (N=418)	Placebo Group (N=403)	Odds Ratio (95% CI)	P Value	Alteplase Group (N=375)	Placebo Group (N=355)	Odds Ratio (95% CI)	P Value
	no. (%)				*no. (%)*			
Primary end point								
mRS score of 0 or 1 — unadjusted analysis	219 (52.4)	182 (45.2)	1.34 (1.02–1.76)	0.04†	206 (54.9)	161 (45.4)	1.47 (1.10–1.97)	0.01†
mRS score of 0 or 1 — adjusted analysis‡	—	—	1.42 (1.02–1.98)	0.04§				
Secondary end point								
Global outcome¶	—	—	1.28 (1.00–1.65)	0.05	—	—	1.39 (1.07–1.80)	0.02
mRS score of 0 or 1‖	219 (52.4)	182 (45.2)	1.34 (1.02–1.76)	0.04†	206 (54.9)	161 (45.4)	1.47 (1.10–1.97)	0.01†
Barthel Index score ≥95**	265 (63.4)	236 (58.6)	1.23 (0.93–1.62)	0.16†	248 (66.1)	211 (59.4)	1.33 (0.99–1.80)	0.06†
NIHSS score of 0 or 1††	210 (50.2)	174 (43.2)	1.33 (1.01–1.75)	0.04†	197 (52.5)	155 (43.7)	1.43 (1.07–1.91)	0.02†
GOS score of 1‡‡	213 (51.0)	183 (45.4)	1.25 (0.95–1.64)	0.11†	200 (53.3)	165 (46.5)	1.32 (0.98–1.76)	0.06†

* GOS denotes Glasgow Outcome Scale, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, and NINDS National Institute of Neurological Disorders and Stroke.
† P value was obtained by the Pearson chi-square test of proportions.
‡ This analysis was adjusted for NIHSS score at presentation and the time to start of treatment.
§ P value was obtained by stepwise logistic regression.

N Engl J Med 2008;359:1317-29

“Randomização”

- Tipos de randomização
  - Alocação randômica fixa (igual ou desigual)
    - Alocação randômica simples
    - Alocação randômica em bloco
      - Equilíbrio da alocação ao longo do estudo
    - Alocação randômica estratificada
      - Equilíbrio da alocação ao longo do estudo para fatores prognósticos críticos
      - Requer coleta de informações sobre os fatores prognósticos para randomização
  - Alocação randômica adaptativa
    - Adaptativa a alocação basal
    - Adaptativa a resposta (*play the winner*)

“Randomização”

Recomendações gerais

- Para grandes estudos multicêntricos:
  - randomização em bloco estratificada por centro.
- Para estudos multicêntricos menores:
  - randomização em bloco estratificada por centro e fatores prognósticos críticos
- Para estudos menores de centro único:
  - Randomização em bloco estratificada por fatores prognósticos críticos

“Randomização”

Ameaças a randomização

- Aderência e conformidade
- Exclusão após a alocação
  - Pode ser inevitável
  - Particularmente suscetível a viés de seleção
  - ***Intention-to-treat vs. per-protocol***
  - Resultados discordantes = Resultados indeterminados

Intention-to-treat vs. per-protocol

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

BACKGROUND

Whether closure of a patent foramen ovale is effective in the prevention of recurrent ischemic stroke in patients who have had a cryptogenic stroke is unknown. We conducted a trial to evaluate whether closure is superior to medical therapy alone in preventing recurrent ischemic stroke or early death in patients 18 to 60 years of age.

METHODS

In this prospective, multicenter, randomized, event-driven trial, we randomly assigned patients, in a 1:1 ratio, to medical therapy alone or closure of the patent foramen ovale. The primary results of the trial were analyzed when the target of 25 primary end-point events had been observed and adjudicated.

RESULTS

We enrolled 980 patients (mean age, 45.9 years) at 69 sites. The medical-therapy group received one or more antiplatelet medications (74.8%) or warfarin (25.2%). Treatment exposure between the two groups was unequal (1375 patient-years in the closure group vs. 1184 patient-years in the medical-therapy group, P=0.009) owing to a higher dropout rate in the medical-therapy group. In the intention-to-treat cohort, 9 patients in the closure group and 16 in the medical-therapy group had a recurrence of stroke (hazard ratio with closure, 0.49; 95% confidence interval [CI], 0.22 to 1.11; P=0.08). The between-group difference in the rate of recurrent stroke was significant in the prespecified per-protocol cohort (6 events in the closure group vs. 14 events in the medical-therapy group; hazard ratio, 0.37; 95% CI, 0.14 to 0.96; P=0.03) and in the as-treated cohort (5 events vs. 16 events; hazard ratio, 0.27; 95% CI, 0.10 to 0.75; P=0.007). Serious adverse events occurred in 23.0% of the patients in the closure group and in 21.6% in the medical-therapy group (P=0.65). Procedure-related or device-related serious adverse events occurred in 21 of 499 patients in the closure group (4.2%), but the rate of atrial fibrillation or device thrombus was not increased.

N Engl J Med 2013;368:1092-100.

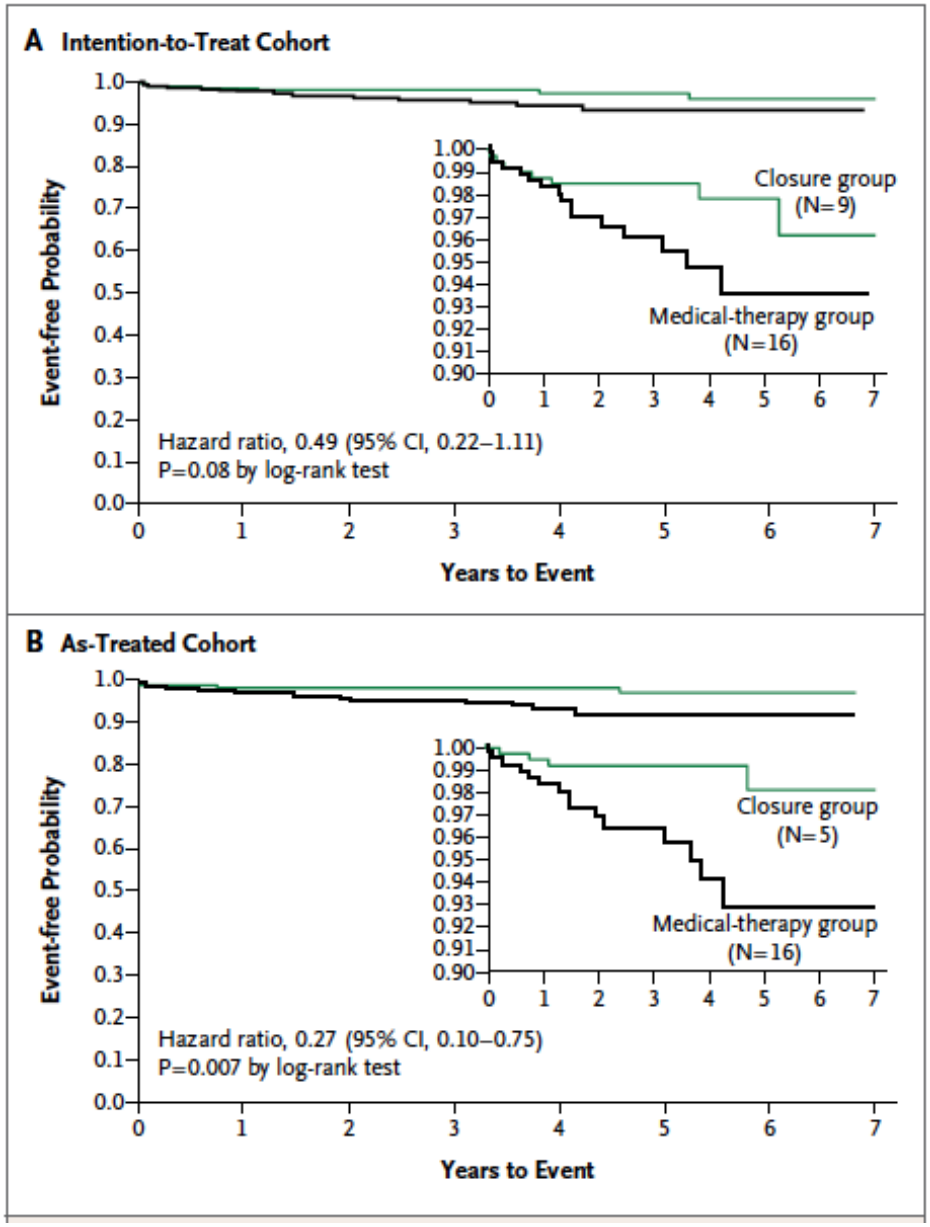
Intention-to-treat vs. per-protocol

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Closure Group (N=499)	Medical Group (N=481)	All Patients (N=980)
Age — yr	45.7±9.7	46.2±10.0	45.9±9.9
Male sex — no. (%)	268 (53.7)	268 (55.7)	536 (54.7)
Medical history — no./total no. (%)			
Diabetes mellitus	33/499 (6.6)	40/481 (8.3)	73/980 (7.4)
Systemic hypertension	158/499 (31.7)	150/481 (31.2)	308/980 (31.4)
Smoking status			
Current smoker	75/499 (15.0)	55/481 (11.4)	130/980 (13.3)
Former smoker	134/499 (26.9)	143/481 (29.7)	277/980 (28.3)
Hypercholesterolemia	194/499 (38.9)	193/481 (40.1)	387/980 (39.5)
Coronary artery disease	19/499 (3.8)	9/481 (1.9)	28/980 (2.9)
Previous myocardial infarction	5/499 (1.0)	2/481 (0.4)	7/980 (0.7)
Peripheral vascular disease	5/499 (1.0)	1/481 (0.2)	6/980 (0.6)
Previous transient ischemic attack	58/499 (11.6)	61/481 (12.7)	119/980 (12.1)
Previous stroke	53/498 (10.6)	51/481 (10.6)	104/979 (10.6)
Family history of stroke	135/495 (27.3)	108/480 (22.5)	243/975 (24.9)
Migraine	195/499 (39.1)	185/481 (38.5)	380/980 (38.8)
Deep-vein thrombosis	20/499 (4.0)	15/481 (3.1)	35/980 (3.6)
Congestive heart failure	3/499 (0.6)	0/481 (0)	3/980 (0.3)
Chronic obstructive pulmonary disease	4/499 (0.8)	7/481 (1.5)	11/980 (1.1)
Birth control or hormone-replacement therapy	41/499 (8.2)	52/481 (10.8)	93/980 (9.5)
Patent foramen ovale — no. (%)			
Maximum right-to-left shunt grade at rest or during Valsalva release†			
Grade 1	108 (21.6)	114 (23.7)	222 (22.7)
Grade 2	138 (27.7)	121 (25.2)	259 (26.4)
Grade 3	247 (49.5)	231 (48.0)	478 (48.8)
Atrial septal aneurysm	180 (36.1)	169 (35.1)	349 (35.6)

Engl J Med 2013;368:1092-100.

Intention-to-treat vs. per-protocol



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Intention-to-treat vs. per-protocol

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Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

John D. Carroll, M.D., Jeffrey L. Saver, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Scott Berry, Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

CONCLUSIONS

In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ischemic stroke. However, closure was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)

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  - ***Intention-to-treat vs. per-protocol***
  - Resultados discordantes = Resultados indeterminados
- Perda do mascaramento
- Análise dos desfechos
  - Viés de informação: não-diferencial e diferencial

Análise

- **Geralmente simples comparada a estudos observacionais**
- **Pré-especificada e divulgada**
- **Significado estatístico vs. significado clínico**
- **Riscos**
  - **Controle de covariáveis não balanceadas**
  - **Perda de seguimento: censura informativa?**
- **Cuidado com a tentação da análise *pos hoc***

"Equipoise"

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

HULTON/GETTY

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Monitorização dos dados e regras de interrupção

- Consentimento informado: indivíduo vs. coletivo
- Ética vs. informação
  - Analise interina: segurança e eficácia
  - Proteção dos sujeitos de pesquisa
  - Multiplicidade de checagens requer reajuste do p-value!
- Potencial impacto da interrupção precoce
  - Estimativa de efeito com viés randômico
  - Dados imprecisos
    - Intervalos de confiança largos
    - Limitação para análise de subgrupos
  - Pode perder efeito tardios da intervenção
  - Inibição da repetição do estudo

Interrupção precoce do estudo

- Consentimento informado: indivíduo vs. coletivo
- Ética vs. informação
  - Analise interina: segurança e eficácia
  - Proteção dos sujeitos de pesquisa
  - Multiplicidade de checagens requer reajuste do p-value!
- Potencial impacto da interrupção precoce
  - Estimativa de efeito com viés randômico
  - Dados imprecisos
    - Intervalos de confiança largos
    - Limitação para análise de subgrupos
  - Pode perder efeito tardios da intervenção
  - Pode perder o poder de analisar segurança da intervenção
  - Inibição da repetição do estudo

Comunicação dos resultados

ClinicalTrials.gov

REGISTRO BRASILEIRO DE
Ensaios Clínicos

SPIRIT
Standard Protocol Items: Recommendations for Interventional Trials

Conclusões

- Experimento: exposição controlada pelo investigador
- Confundimento por indicação
- Randomização controle para confundimento de base
- Mascaramento e conformidade: controle do vies de informação
- Importante minimizar as perdas pós-randomização
- Importante minimizar não-aderência
- Análise pre-especificada e por intenção de tratar
- Análise interina independente e regras de interrupção claras
- Limitações: generabilidade, analise de subgrupo e desfechos combinados

Conclusões

- ECR são caros e difíceis porém podem produzir resultados de alto impacto clínico
- Conselhos:
  - Foco/parsimônia: responda bem 1 pergunta
  - Taxas de eventos são geralmente menores do que esperamos
  - Recrutamento geralmente é mais lento do que desejado
  - Planejar recursos = ser pessimista
  - Pior resultado de um ECR = não ser concluído

Homework

1. Liste a hipotese primária do seu estudo.
2. Liste o desfecho primário do seu estudo.
3. Liste as principais variáveis de teste e confundimento do seu estudo.
4. Monte a tabela 1 do seu estudo.
5. Monte a tabela de análise univariada do seu estudo.
6. Quais seriam as variáveis que você acredita que deverá incluir no seu modelo multivariado?
7. Qual o melhor modelo de controle de confundimento na análise do seu trabalho?

AGENDAR HORARIO PARA DISCUSSÃO: opontesneto@fmrp.usp.br

Segunda-feira: 14:00 as 17:00

Terça-feira: 14:00 as 17:00