# Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention: 10-year follow-up of the HOST-EXAM trial

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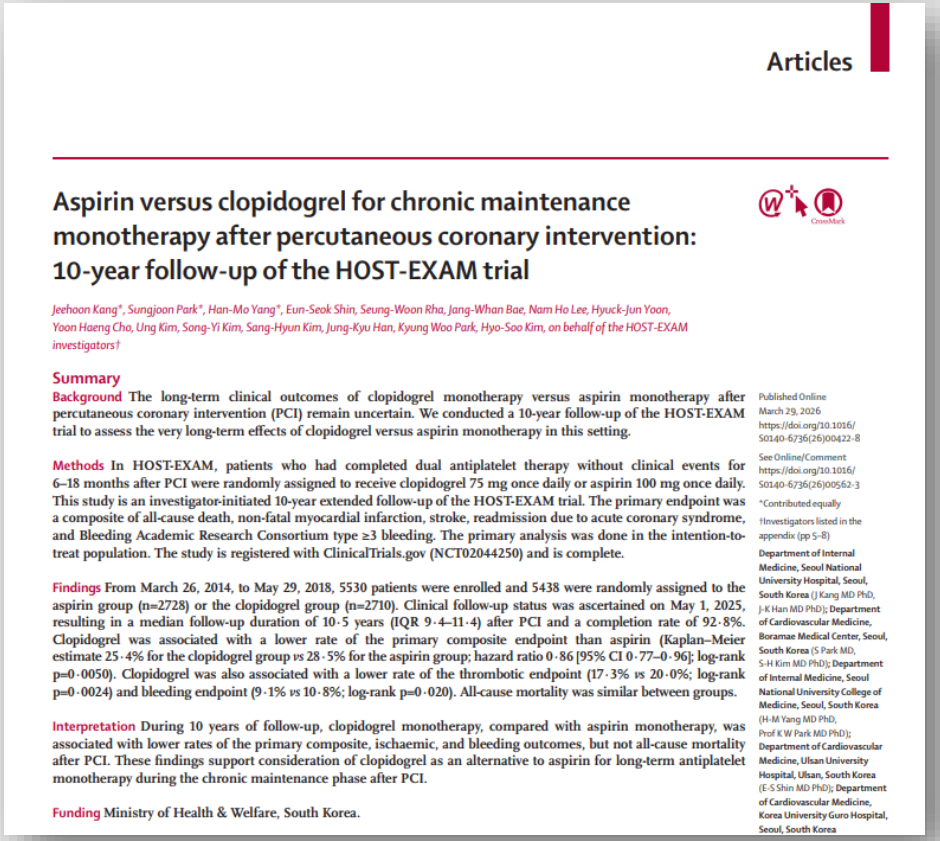
| | |
|---|---|
| **P (população)** | Pós-ICP com stent farmacológico, estáveis após 6–18 meses de DAPT |
| **I (intervenção)** | Clopidogrel 75 mg |
| **C (comparação)** | AAS 100 mg |
| **O (resultado/outcome)** | Morte, IAM, AVC, SCA, sangramento maior |
| **T (tempo/tipo)** | Seguimento mediano 10,5 anos |



Articles

Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention: 10-year follow-up of the HOST-EXAM trial

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**Summary**

**Background** The long-term clinical outcomes of clopidogrel monotherapy versus aspirin monotherapy after percutaneous coronary intervention (PCI) remain uncertain. We conducted a 10-year follow-up of the HOST-EXAM trial to assess the very long-term effects of clopidogrel versus aspirin monotherapy in this setting.

**Methods** In HOST-EXAM, patients who had completed dual antiplatelet therapy without clinical events for 6–18 months after PCI were randomly assigned to receive clopidogrel 75 mg once daily or aspirin 100 mg once daily. This study is an investigator-initiated 10-year extended follow-up of the HOST-EXAM trial. The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and Bleeding Academic Research Consortium type ≥3 bleeding. The primary analysis was done in the intention-to-treat population. The study is registered with ClinicalTrials.gov (NCT02044250) and is complete.

**Findings** From March 26, 2014, to May 29, 2018, 5530 patients were enrolled and 5438 were randomly assigned to the aspirin group (n=2728) or the clopidogrel group (n=2710). Clinical follow-up status was ascertained on May 1, 2025, resulting in a median follow-up duration of 10·5 years (IQR 9·4–11·4) after PCI and a completion rate of 92·8%. Clopidogrel was associated with a lower rate of the primary composite endpoint than aspirin (Kaplan–Meier estimate 25·4% for the clopidogrel group *vs* 28·5% for the aspirin group; hazard ratio 0·86 [95% CI 0·77–0·96]; log-rank p=0·0050). Clopidogrel was also associated with a lower rate of the thrombotic endpoint (17·3% *vs* 20·0%; log-rank p=0·0024) and bleeding endpoint (9·1% *vs* 10·8%; log-rank p=0·020). All-cause mortality was similar between groups.

**Interpretation** During 10 years of follow-up, clopidogrel monotherapy, compared with aspirin monotherapy, was associated with lower rates of the primary composite, ischaemic, and bleeding outcomes, but not all-cause mortality after PCI. These findings support consideration of clopidogrel as an alternative to aspirin for long-term antiplatelet monotherapy during the chronic maintenance phase after PCI.

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# Contexto

- Após a DAPT, é recomendado a monoterapia de longo prazo para prevenção secundária de eventos cardiovasculares maiores após ICP
- AAS é o agente de escolha, tradicionalmente
- Dados recentes favorecendo P2Y12 (avaliados até 5 anos)
  - *Trials* e meta análises recentes tem reportado superioridade da monoterapia com Clopidogrel sobre AAS para prevenção secundária
- HOST-EXAM com desfecho de 10 anos, prevenção secundária se estende por toda a vida

# Objetivos

- Comparar **clopidogrel** versus **aspirina** como monoterapia de manutenção após ICP em seguimento de 10 anos.

# Métodos – desenho do estudo

- Iniciado por investigador, prospectivo, randomizado, aberto, multicêntrico
- Coreia do Sul, 32 locais
- n=5438
- **Após 2 anos, antiplaquetário ficou a critério médico**
- Elegíveis: > 20 anos submetidos a ICP com DES e mantido DAPT sem eventos clínicos por 6 a 18 meses após ICP
- 1:1 Clopidogrel 75mg/dia ou AAS 100mg/dia
- Paciente e investigadores não foram cegados para tratamento proposto

# Métodos – desfechos

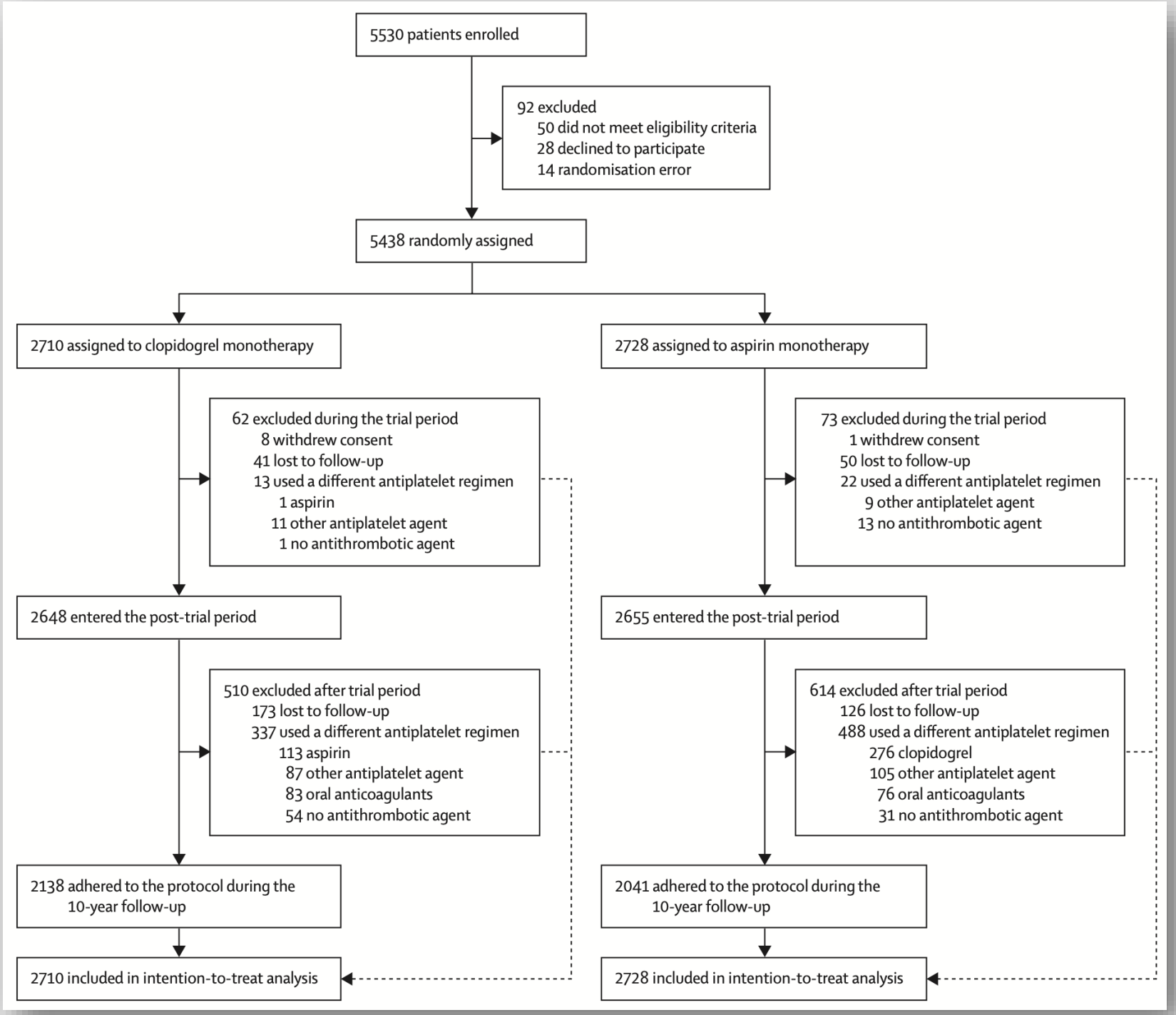
**Desfecho primário:**

- Composto de morte por todas as causas, infarto do miocárdio não fatal, acidente vascular cerebral, readmissão por síndrome coronariana aguda e eventos de sangramento maior

**Desfechos secundários:**

- Desfecho composto trombótico (definido como morte cardiovascular, infarto do miocárdio não fatal, acidente vascular cerebral isquêmico, readmissão por síndrome coronariana aguda e trombose de stent definitiva ou provável) e qualquer sangramento (definido como sangramento tipo ≥2 de acordo com o BARC).

# Métodos

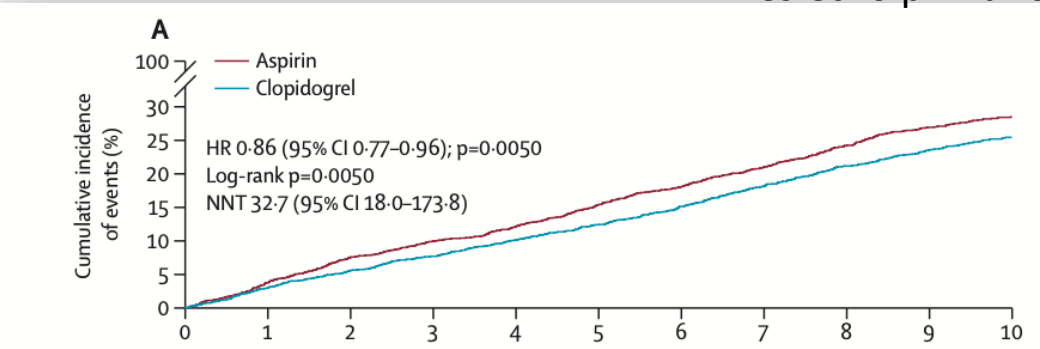

5530 patients enrolled
92 excluded
50 did not meet eligibility criteria
28 declined to participate
14 randomisation error
5438 randomly assigned
2710 assigned to clopidogrel monotherapy
2728 assigned to aspirin monotherapy
62 excluded during the trial period
8 withdrew consent
41 lost to follow-up
13 used a different antiplatelet regimen
1 aspirin
11 other antiplatelet agent
1 no antithrombotic agent
73 excluded during the trial period
1 withdrew consent
50 lost to follow-up
22 used a different antiplatelet regimen
9 other antiplatelet agent
13 no antithrombotic agent
2648 entered the post-trial period
2655 entered the post-trial period
510 excluded after trial period
173 lost to follow-up
337 used a different antiplatelet regimen
113 aspirin
87 other antiplatelet agent
83 oral anticoagulants
54 no antithrombotic agent
614 excluded after trial period
126 lost to follow-up
488 used a different antiplatelet regimen
276 clopidogrel
105 other antiplatelet agent
76 oral anticoagulants
31 no antithrombotic agent
2138 adhered to the protocol during the 10-year follow-up
2041 adhered to the protocol during the 10-year follow-up
2710 included in intention-to-treat analysis
2728 included in intention-to-treat analysis

# Resultados - Endpoint primário

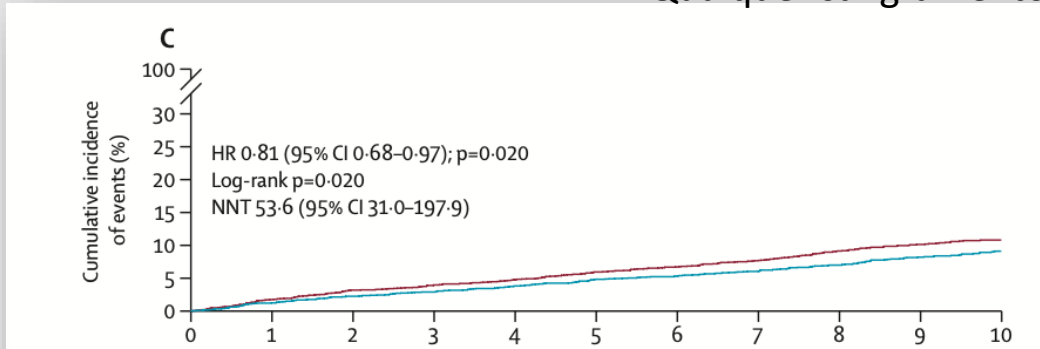
- 25,4% vs 28,5%
- HR 0,86
- p=0,005

# Resultados

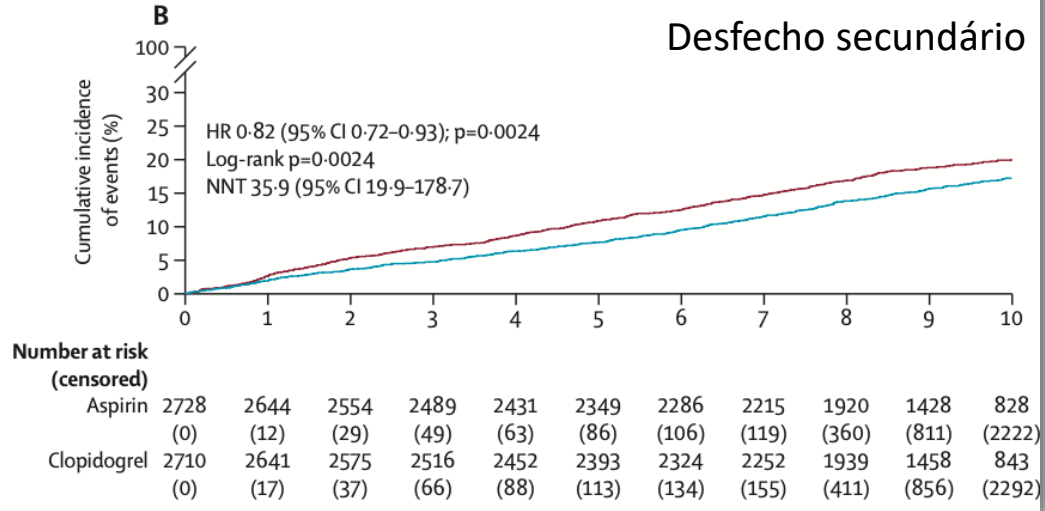
Desfecho primário



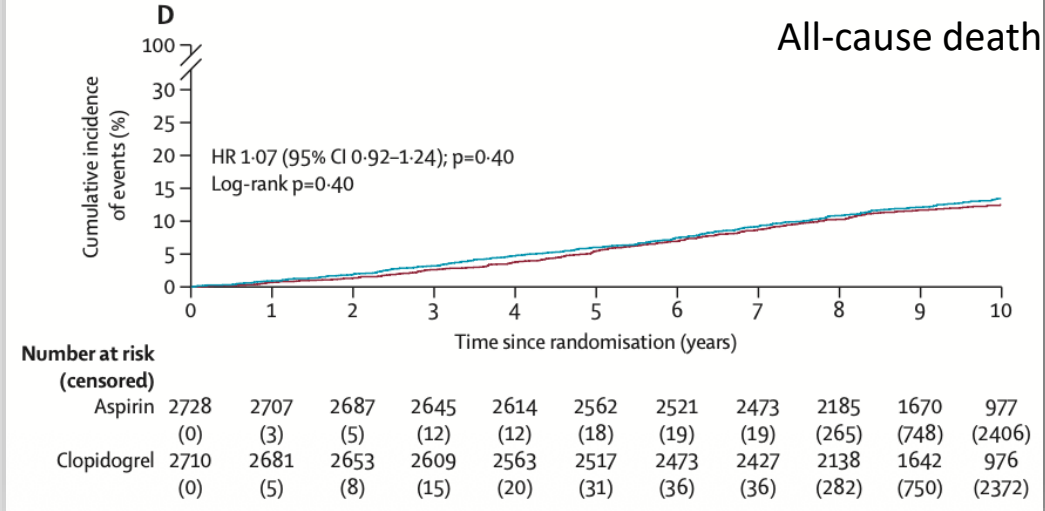

Qualquer sangramento




Desfecho secundário




All-cause death



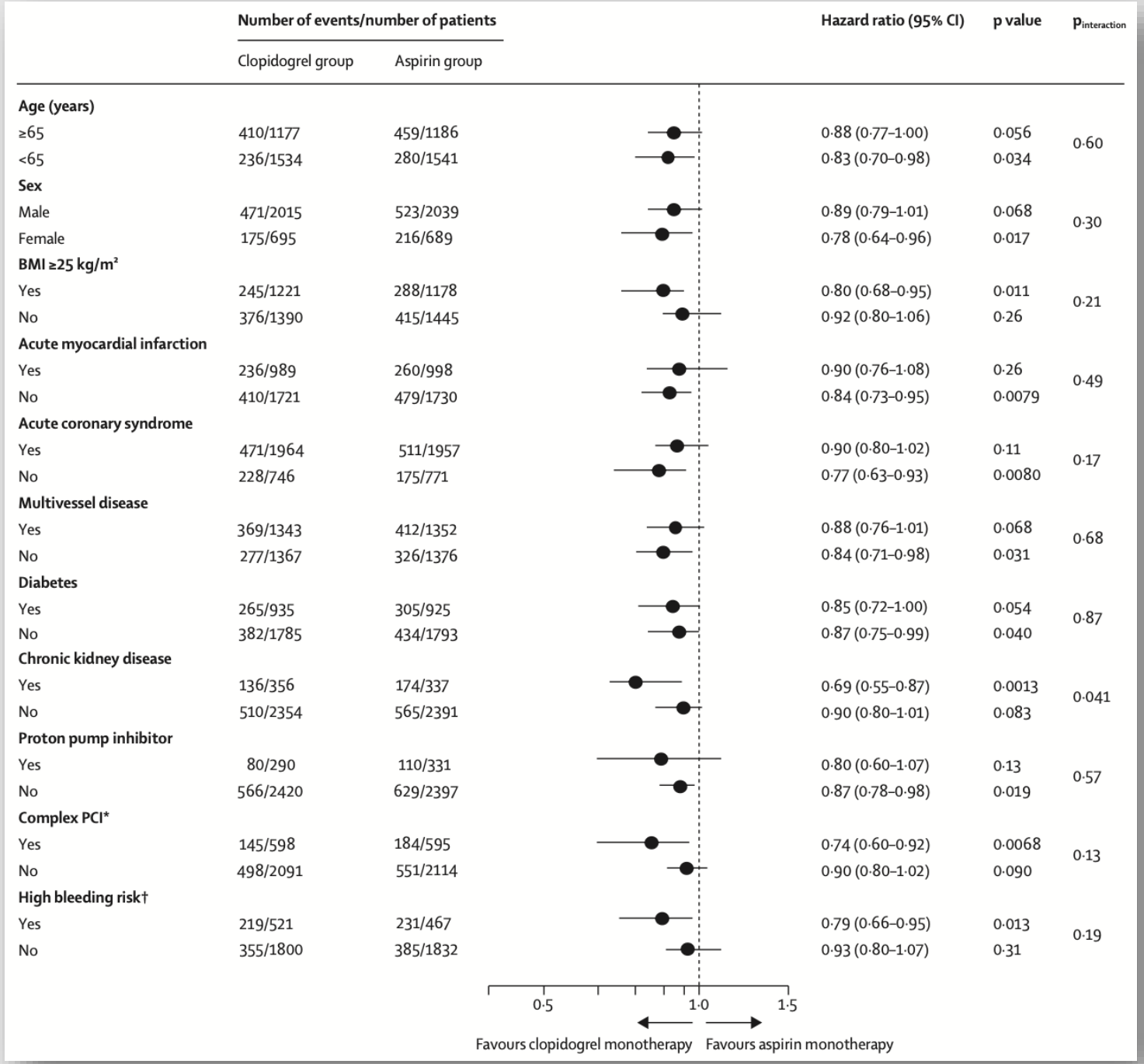
| | Clopidogrel (n=2710) | Aspirin (n=2728) | Hazard ratio (95% CI) | p value | Absolute risk reduction (95% CI) | Number needed to treat (95% CI) |
|---|---|---|---|---|---|---|
| Primary composite endpoint* | 646 (25·4%) | 739 (28·5%) | 0·86 (0·77–0·96) | 0·0050 | 3·1 (0·6 to 5·6) | 32·7 (18·0–173·8) |
| Thrombotic composite endpoint† | 418 (17·3%) | 506 (20·0%) | 0·82 (0·72–0·93) | 0·0024 | 2·8 (0·6 to 5·0) | 35·9 (19·9–178·7) |
| Any bleeding (BARC type ≥2)‡ | 217 (9·1%) | 270 (10·8%) | 0·81 (0·68–0·97) | 0·020 | 1·7 (0·0 to 3·4) | .. |
| All-cause death‖ | 338 (13·4%) | 322 (12·5%) | 1·07 (0·92–1·24) | 0·40 | −0·9 (−2·8 to 0·9) | .. |
| Cardiovascular death | 167 (7·1%) | 171 (6·9%) | 0·99 (0·80–1·23) | 0·95 | −0·1 (−1·6 to 1·4) | .. |
| Non-cardiovascular death | 171 (6·9%) | 151 (6·0%) | 1·15 (0·93–1·43) | 0·21 | −0·9 (−2·3 to 0·5) | .. |
| Non-fatal myocardial infarction | 85 (3·6%) | 105 (4·2%) | 0·82 (0·62–1·09) | 0·17 | 0·6 (−0·5 to 1·7) | .. |
| Stroke | 110 (4·6%) | 154 (6·4%) | 0·72 (0·56–0·92) | 0·0081 | 1·8 (0·4 to 3·1) | 57·2 (32·7–228·5) |
| Ischaemic stroke | 85 (3·6%) | 104 (4·3%) | 0·81 (0·61–1·08) | 0·16 | 0·8 (−0·4 to 1·9) | .. |
| Haemorrhagic stroke | 25 (1·0%) | 50 (2·1%) | 0·50 (0·31–0·81) | 0·0050 | 1·1 (0·4 to 1·8) | 92·5 (55·5–279·1) |
| Readmission due to acute coronary syndrome | 208 (8·7%) | 277 (11·0%) | 0·75 (0·63–0·90) | 0·0017 | 2·3 (0·6 to 4·0) | 42·9 (24·8–158·5) |
| Percutaneous coronary intervention | 157 (6·8%) | 207 (8·5%) | 0·76 (0·62–0·93) | 0·0084 | 1·7 (0·1 to 3·2) | 59·1 (30·9–690·3) |
| Coronary artery bypass surgery | 5 (0·2%) | 8 (0·3%) | 0·62 (0·20–1·90) | 0·41 | 0·1 (−0·2 to 0·4) | .. |
| Medical treatment | 46 (1·8%) | 62 (2·4%) | 0·74 (0·51–1·09) | 0·13 | 0·6 (−0·2 to 1·4) | .. |
| Major bleeding (BARC type ≥3) | 133 (5·6%) | 190 (7·7%) | 0·71 (0·57–0·88) | 0·0019 | 2·1 (0·7 to 3·5) | 47·5 (28·3–148·4) |

Data are n (%), unless otherwise specified. Number needed to treat is shown only when the 95% CI for the absolute risk reduction excludes 0. BARC=Bleeding Academic Research Consortium. *Primary composite endpoint is defined as a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding (BARC type ≥3). †Thrombotic composite endpoint is defined as cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to acute coronary syndrome, and definite or probable stent thrombosis. ‡Any bleeding defined as any BARC type ≥2 bleeding events. ‖The specific causes of mortality events are described in the appendix (pp 23–24).

***Table:*** **Clinical outcomes during the 10-year follow-up in the intention-to-treat population**

# Resultados

- Análise de subgrupos
- Desfecho primário composto
- Intention to treat



| | Number of events/number of patients | | Hazard ratio (95% CI) | p value | $p_{interaction}$ |
|---|---|---|---|---|---|
| | Clopidogrel group | Aspirin group | | | |
| **Age (years)** | | | | | |
| ≥65 | 410/1177 | 459/1186 | 0·88 (0·77–1·00) | 0·056 | 0·60 |
| <65 | 236/1534 | 280/1541 | 0·83 (0·70–0·98) | 0·034 | |
| **Sex** | | | | | |
| Male | 471/2015 | 523/2039 | 0·89 (0·79–1·01) | 0·068 | 0·30 |
| Female | 175/695 | 216/689 | 0·78 (0·64–0·96) | 0·017 | |
| **BMI ≥25 kg/m²** | | | | | |
| Yes | 245/1221 | 288/1178 | 0·80 (0·68–0·95) | 0·011 | 0·21 |
| No | 376/1390 | 415/1445 | 0·92 (0·80–1·06) | 0·26 | |
| **Acute myocardial infarction** | | | | | |
| Yes | 236/989 | 260/998 | 0·90 (0·76–1·08) | 0·26 | 0·49 |
| No | 410/1721 | 479/1730 | 0·84 (0·73–0·95) | 0·0079 | |
| **Acute coronary syndrome** | | | | | |
| Yes | 471/1964 | 511/1957 | 0·90 (0·80–1·02) | 0·11 | 0·17 |
| No | 228/746 | 175/771 | 0·77 (0·63–0·93) | 0·0080 | |
| **Multivessel disease** | | | | | |
| Yes | 369/1343 | 412/1352 | 0·88 (0·76–1·01) | 0·068 | 0·68 |
| No | 277/1367 | 326/1376 | 0·84 (0·71–0·98) | 0·031 | |
| **Diabetes** | | | | | |
| Yes | 265/935 | 305/925 | 0·85 (0·72–1·00) | 0·054 | 0·87 |
| No | 382/1785 | 434/1793 | 0·87 (0·75–0·99) | 0·040 | |
| **Chronic kidney disease** | | | | | |
| Yes | 136/356 | 174/337 | 0·69 (0·55–0·87) | 0·0013 | 0·041 |
| No | 510/2354 | 565/2391 | 0·90 (0·80–1·01) | 0·083 | |
| **Proton pump inhibitor** | | | | | |
| Yes | 80/290 | 110/331 | 0·80 (0·60–1·07) | 0·13 | 0·57 |
| No | 566/2420 | 629/2397 | 0·87 (0·78–0·98) | 0·019 | |
| **Complex PCI*** | | | | | |
| Yes | 145/598 | 184/595 | 0·74 (0·60–0·92) | 0·0068 | 0·13 |
| No | 498/2091 | 551/2114 | 0·90 (0·80–1·02) | 0·090 | |
| **High bleeding risk†** | | | | | |
| Yes | 219/521 | 231/467 | 0·79 (0·66–0·95) | 0·013 | 0·19 |
| No | 355/1800 | 385/1832 | 0·93 (0·80–1·07) | 0·31 | |

0·5 1·0 1·5

Favours clopidogrel monotherapy Favours aspirin monotherapy

# Análise per protocol

- Analise per protocol foi feita incluindo os pacientes que completaram o follow up e aderiram ao medicamento
- 4179 pacientes: 2138 (78,9%) Clopidogrel e 2041 (74,8%) AAS foram incluídos
- Aderência ao medicamento foi maior no grupo Clopidogrel ($p < 0,0004$)
- Razões: desconforto gastrointestinal e sangramentos menores foram mais comuns no grupo AAS
- Endpoint Primário Composto: 24% vs 29,8% - HR 0,76; $p < 0,0001$
- Endpoint Secundário Composto: 15,5% vs 21% - HR 0,69; $p < 0,0001$
- Endpoint de Sangramento: 8,6% vs 11,3% - HR 0,73; $p = 0,002$
- NNT 17 (menor que Intention to treat)

# Discussão

- 1º estudo a avaliar os desfechos clínicos de 10 anos da monoterapia antiplaquetária após ICP com stents farmacológicos
- Benefício cumulativo
  - Menos sangramento
  - Menos isquemia
  - Melhor tolerabilidade
- Adesão melhor no clopidogrel
- Clopidogrel continuou sendo superior à aspirina em termos dos desfechos primários compostos, trombóticos e hemorrágicos por até 10 anos
- **Diretrizes ESC 2024 – clopidogrel classe I, nível A, para manutenção a longo prazo na prevenção secundária pós-ICP**

# Limitações

- Open-label
- Asiáticos apenas
- Após 2 anos tratamento não randomizado
- Mudança de medicação durante follow-up
  - 18,7% do grupo AAS e 12,9% do grupo do clopidogrel alteraram seu regime antiplaquetário durante o acompanhamento
- Discussão sobre manejo perioperatório
- Alelos de perda de função do CYP2C19

# Conclusão – Take-home messages

- Clopidogrel foi superior à aspirina como monoterapia após PCI em 10 anos.
- Houve redução simultânea de eventos trombóticos e hemorrágicos.
- O papel da aspirina como terapia padrão indefinida pós-PCI deve ser reavaliado.