¿Hay que administrar un protector gástrico a todo paciente antiagregado con AAS?

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Consideraciones previas

- Gran evidencia con AINE
- Escasa evidencia con AAS
- Influencia de la dosis
  - Prevención riesgo cardiovascular: 75-300 mg/d
- Estudios con prevención secundaria.

Preguntas

- Existe mayor riesgo de hemorragia con AAS a dosis bajas?
- Existe influencia de la dosis?
- Cuales son los factores de riesgo para desarrollar complicaciones GI?
- A quien hay que proteger?

Table 1 Bleeding Complications: Meta-analyses of Trials with Direct Comparisons of Aspirin versus Placebo

Endpoint	Number of Studies[Reference #]	Subjects Compared: Aspirin/Placebo	Relative Risk (95% CI)
Primary bleeding endpoints			
Any major bleeding	9[22,23,26,27,29,33,36,46,52,58]	26,673/26,712	1.71 (1.41-2.08)
Lower-dose aspirin	5[27,33,36,46,52]	14,578/14,642	1.84 (1.47-2.31)
Higher-dose aspirin	3[23,26,29,58]	1058/1036	0.89 (0.45-1.74)
Major GI bleeding	14[22,27-29,33,36,38,40,42,46,52,54,58,64,65]	28,686/28,719	2.07 (1.61-2.66)
Lower-dose aspirin	6[27,33,36,46,52,64]	14,778/14,842	2.22 (1.61-3.06)
Higher-dose aspirin	7[28,29,38,40,42,54,58,65]	2871/2843	2.35 (0.98-5.66)
Intracranial bleeding	11[22,23,26-29,33,36,38,46, 52,58,65]	27,671/27,712	1.65 (1.12-2.44)
Lower-dose aspirin	5[27,33,36,46,52]	14,578/14,642	1.43 (0.85-2.42)
Higher dose aspirin	5[23,26,28,29,38,58,65]		2.11 (0.71-6.28)
Additional bleed			
Any bleed	8[22,27-29,46,52,61,64,65]		(1.30-2.03)*
Lower	5[27,46,52,61,64]		.53-2.16)
High	2[28,29,65]		09-2.35)
All GI b	11[22,24,27-29,33,40,46,58, 61,		25-2.09)*
Lower-d	6[24,27,33,46,61,64]		.28-2.33)
Higher-dos	4[28,29,40,58,65]		(1.24-4.14)
All non-GI/non-intracranial bleeding	5[27,29,46,58,61]		2 (1.39-2.13)
Major non-GI/non-intracranial bleeding	7[27,29,33,46,52,55,58]		1.45 (0.95-2.20)
Any fatal bleeding	10[22,23,26,27,36,38,46,52,58, 64,67]		1.30 (0.70-2.42)
Fatal GI bleeding	12[22,23,26-28,33,38,40,46,52,58,64,65,67]	25,964/25,993	1.23 (0.45-3.41)
Fatal intracranial bleeding	12[23,26-29,38,46,52,58,62,64,65,67,74]	13,802/13,762	2.52 (1.06-5.99)
Fatal non-GI/non- intracranial bleeding	8[23,26,27,33,46,52,58,64,67]	13,314/13,335	0.80 (0.26-2.53)

*Heterogeneity: $P < .10$.

22 ensayos clínicos
75.000 pacientes

Dosis AAS: 75-325 mg/d
Bajas-bajas: 75-162 mg/d
Bajas-altas: 162-325 mg/d

Am J Epidemiol. 2004;159:23-31

TABLE 1. Relative risk and 95% confidence interval of peptic ulcer according to recency, dose, and duration of aspirin compared with nonuse, General Practice Research Database, United Kingdom, 1995–1999

	Cases (no.)	Controls (no.)	Adjusted RR*,†	95% CI*
Aspirin recency				
Nonu		8,608	Referent	
C		917	2.9	2.3, 3.6
		720	2.9	2.3, 3.6
		197	2.8	1.9, 4.0
Re		147	2.0	1.3, 3.3
Past (>		328	1.0	0.7, 1.5
Aspirin dose‡				
Nonuse	935	8,608	Referent	
75 mg	112	529	2.9	2.2, 3.7
150 mg	44	234	2.6	1.8, 3.9
300 mg	34	144	3.0	1.9, 4.6
>300 mg	4	10	3.8	1.0, 14.4
Aspirin duration‡				
Nonuse	935	8,608	Referent	
1–30 days	11	56	2.4	1.2, 4.8
31–180 days	37	145	3.3	2.2, 5.1
181–365 days	22	123	2.8	1.7, 4.7
>365 days	124	593	2.8	2.2, 3.5

Estudio retrospectivo cohortes
base de datos AP
Reino Unido

Consideraciones previas

- Con dosis elevadas (> 300 mg al día) el riesgo parece superior que con dosis bajas (< 300 mg al día).
- Con menos de 300 mg/día no parece existir influencia de la dosis.
- Tto. con AAS a dosis bajas incrementa de 2 a 3 veces el riesgo de complicaciones gastrointestinales.

Preguntas

- Existe mayor riesgo de hemorragia con AAS a dosis bajas?
- Existe influencia de la dosis?
- Cuales son los factores de riesgo para desarrollar complicaciones GI?
- A quien hay que proteger?

Factores de Riesgo de hemorragia GI

AINE **AAS**

- Enferm. concomitantes graves
- Combinación con otros AINE
- Ulcus previo
- Mayores 60 años
- Alcohol
- Enfermed. cardiovasculares
- HP positivo
- Combinación corticoides o ACO
- Historia previa de HDA

TABLE 2. FREQUENCY OF USE OF MEDICATIONS AND ADJUSTED ODDS RATIOS FOR UPPER GASTROINTESTINAL BLEEDING ASSOCIATED WITH EACH TYPE OF MEDICATION, ACCORDING TO LOGISTIC-REGRESSION ANALYSIS.*

Estudio casos-controles

Ingresados de forma consecutiva por hemorragia secundaria a ulcera

TYPE	PATIENTS (N=1122)	CONTROLS (N=[illegible])	[illegible]	[illegible] VALUE
	no. (%)			
Any nonsteroidal antiinflammatory drug other than low-dose aspirin†	520 (46.3)	229 (10.3)	[illegible]	<0.001
Low-dose aspirin alone	120 (10.7)	206 (9.2)	2.4 (1.8–3.3)	<0.001
Nitrovasodilator	60 (5.3)	137 (6.1)	0.6 (0.4–0.9)	0.03
Antisecretory medication	135 (12.0)	206 (9.2)	0.6 (0.4–0.8)	0.001

*Low-dose aspirin was defined as aspirin at a dose ≤300 mg per day. Variables included in the model were a history of upper gastrointestinal bleeding (P<0.001), a history of ulcer (P<0.001), cardiovascular disease (P=0.01), cerebrovascular disease (P<0.001), rheumatic disease (P=0.002), sex (P=0.73), age (P=0.001), and the hospital (P=0.60). Similar results were obtained when nitrovasodilator-drug use was introduced as a continuous variable according to dose (odds ratio, 0.6; 95 percent confidence interval, 0.4 to 0.9). CI denotes confidence interval.

†Twenty-eight patients and 14 controls took both nonsteroidal antiinflammatory drugs and low-dose aspirin and are included in this category.

NEJM 2000;343:834-9.

TABLE 4. ADJUSTED ODDS RATIO FOR UPPER GASTROINTESTINAL BLEEDING ASSOCIATED WITH CLINICAL VARIABLES AND MEDICATION USE AMONG STUDY SUBJECTS TAKING ASPIRIN, ACCORDING TO LOGISTIC-REGRESSION ANALYSIS.*

FACTOR	ASPIRIN AT ANY DOSE		ADJUSTED ODDS RATIO (95% CI)	P VALUE	LOW-DOSE ASPIRIN		ADJUSTED ODDS RATIO (95% CI)	P VALUE
	PATIENTS (N=396)	CONTROLS (N=266)			PATIENTS (N=148)	CONTROLS (N=220)		
	no. (%)				no. (%)			
History of gastrointestinal bleeding	41 (10.4)	8 (3.0)	5.1 (2.0–13.1)	<0.001	20 (13.5)	5 (2.3)	6.5 (2.0–21.2)	0.001
History of ulcer	82 (20.7)	34 (12.8)	1.7 (1–2.9)	0.06	39 (26.4)	26 (11.8)	2.1 (1.0–4.1)	0.03
Nonsteroidal antiinflammatory drug other than aspirin	73 (18.4)	18 (6.8)	3.8 (2.1–6.9)	<0.001	28 (18.9)	14 (6.4)	3.8 (1.8–7.8)	<0.001
Nitrovasodilator	36 (9.1)	68 (25.6)	0.5 (0.2–0.8)	0.01	32 (21.6)	67 (30.5)	0.5 (0.2–0.9)	0.03
Antisecretory medication	30 (7.6)	42 (15.8)	0.3 (0.2–0.6)	0.001	19 (12.8)	39 (17.7)	0.4 (0.2–0.9)	0.04

*Low-dose aspirin was defined as aspirin at a dose ≤300 mg per day. Variables included in both models were cardiovascular disease, cerebrovascular disease, sex, age, and the hospital; rheumatic disease was included in the model for aspirin at any dose. CI denotes confidence interval.

NEJM 2000;343:834-9.

HP como factor de riesgo

Table 2. Frequency of *Helicobacter pylori* infection and CagA- and VacA-positive serology in cases and controls. Crude odds ratios (OR) with 95% confidence intervals (95% CI) are also expressed

Variable	Cases ($n = 98$). n (%)	Controls ($n = 147$). n (%)	P value	Crude OR (95% CI)
H. pylori infection*	88/98 (89.79)	102/147 (69.4)	0.0001	3.88 (1.84–8.15)
Positive serology†	83/96 (86.5)	93/145 (64.1)	0.0001	3.56 (1.81–7.01)
Positive ^{13}C-urea breath test	63/78 (80.7)	61/97 (62.9)	0.01	2.47 (1.23–4.97)
Positive CagA	51/96 (53.1)	66/145 (45.5)	0.247	1.35 (0.80–2.27)
Positive VacA	36/96 (37.5)	49/145 (33.8)	0.555	1.17 (0.68–2.01)

Aliment Pharmacol Ther 2002; 16: 779–786.

Preguntas

- Existe mayor riesgo de hemorragia con AAS a dosis bajas?
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- A quien hay que proteger?

A quien hay que proteger?

- Prevención primaria
  - No hay estudios randomizados donde a un brazo le añadan IBP y al otro no en pacientes con AAS a dosis bajas de forma crónica buscando prevención de ulcera o complicación .

REDUCCION DEL DAÑO AGUDO PRECOZ EN MUCOSA GASTRICA

Table 1. Evidence of Effective Therapy in the Prevention of Gastrointestinal (GI) Toxicity Associated with Low-Dose Aspirin (75–300 mg/day)

Drug	Dose	Acute Mucosal Damage	Chronic GU/DU	Upper GI Complications	References
Omeprazole	20 mg/day	+++ (3)	?	++ (3)	6, 22, 23
Lansoprazole	15 mg/day	++ (3)	?	?	7
Ranitidine	150–300 mg/day	± (3)	?	?	7, 10, 21
Misoprostol	?	?	?	?	—
Helicobacter pylori	Eradication	+ (1)	?	± (2) ++ (3)	8, 24, 25 22

DU = duodenal ulcer; GU = gastric ulcer.

Effectivity: (±) controversy, (+) slightly effective, (++) effective, (+++) very effective.

Evidence: (1) observational studies, (2) case–control studies, (3) intervention studies.

TABLE 4. ADJUSTED ODDS RATIO FOR UPPER GASTROINTESTINAL BLEEDING ASSOCIATED WITH CLINICAL VARIABLES AND MEDICATION USE AMONG STUDY SUBJECTS TAKING ASPIRIN, ACCORDING TO LOGISTIC-REGRESSION ANALYSIS.*

FACTOR	ASPIRIN AT ANY DOSE		ADJUSTED ODDS RATIO (95% CI)	P VALUE	LOW-DOSE ASPIRIN		ADJUSTED ODDS RATIO (95% CI)	P VALUE
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	no. (%)				no. (%)			
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*Low-dose aspirin was defined as aspirin at a dose ≤300 mg per day. Variables included in both models were cardiovascular disease, cerebrovascular disease, sex, age, and the hospital; rheumatic disease was included in the model for aspirin at any dose. CI denotes confidence interval.

A quien hay que proteger?

- Prevención secundaria
  - Erradicación HP vs IBP
  - Terapia combinada
  - Sustitución de AAS por otros antiagregantes

Kaplan-Meier Estimates of the Li… Upper Gastrointestinal Bleeding at Six Month… oxen Group

400 pacientes
HDA e infectados por HP
En tto con AAS (80 mg/d) o AINE

TABLE 4. KAPL… OF THE LIKELIHOOD OF RECURRENT UPPER G… OINTESTINAL BLEEDING AT SIX MONTHS IN THE ASPIRIN G… UP AND THE NAPROXEN GROUP.*

GROUP	PROB…	ABSOLUTE DIFFERENCE IN THE PROBABILITY OF RECURRENT BLEEDING (95% CI)†
	OMEPRA… THERAPY … APY	
	percent	
Aspirin	0.9 (−0.8 to 2.6) … 0.7 to 4.5)	1.0 (−1.9 to 3.9)
Naproxen	4.4 (−0… …)	14.4 (4.4 to 24.4)

*CI denotes co…

†The two treatme… …t if the upper limit of the 95 percent confidenc… …ce … the probability of recur- … at si… onths did not exceed 5 perc… t.

Cicatrizan ulcera
20 mg omeprazol
8 semanas

Reintroducen AAS (80mg/d)
o AINE (naprox.)

20 mg omeprazol

Erradicación HP

…J Med 2001;344:967-973

…NE

123 pacientes
Ulcus complicado (HDA, obstrucción, perforación)
En tto con AAS (100 mg/d)
HP positivo

Cicatrizan ulcera
Erradican HP

AAS 100mg/d
+
Lansoprazol 30mg/d

AAS 100mg/d
+
placebo

VARIABLE	…RAZOLE GROUP (N=62)	PLACEBO GROUP (N=61)
Patients with recurrences of complicat		
Total — no. (%)	1 (1.6)	9 (14.8)
Site of relapse — no.		
Gastric ulcer	1	8
Duodenal ulcer	0	1
Time to relapse — no.		
<6 mo	0	2
≥6 mo	1	7
Recurrence of *H. pylori* i	0	4
Deaths — no.	1	0
Patients with clinical r		
Total — no.	0	8
Age — yr	—	66.5±8.5
Female sex — no. (%)	—	4 (50.0)
Transfusion required — units	—	1.13±1.46
Range		0–4
Location of ulcer — no.		
Gastric	—	8
D…		0
…		…15
…		…09

…g/dl
…n — no. (%)
…g on admission — n…
…no. (%)
…no. (%)
…ns ±SD.

†Two … not included, because their rebleeding was ide… a decrease in hemoglobin levels.

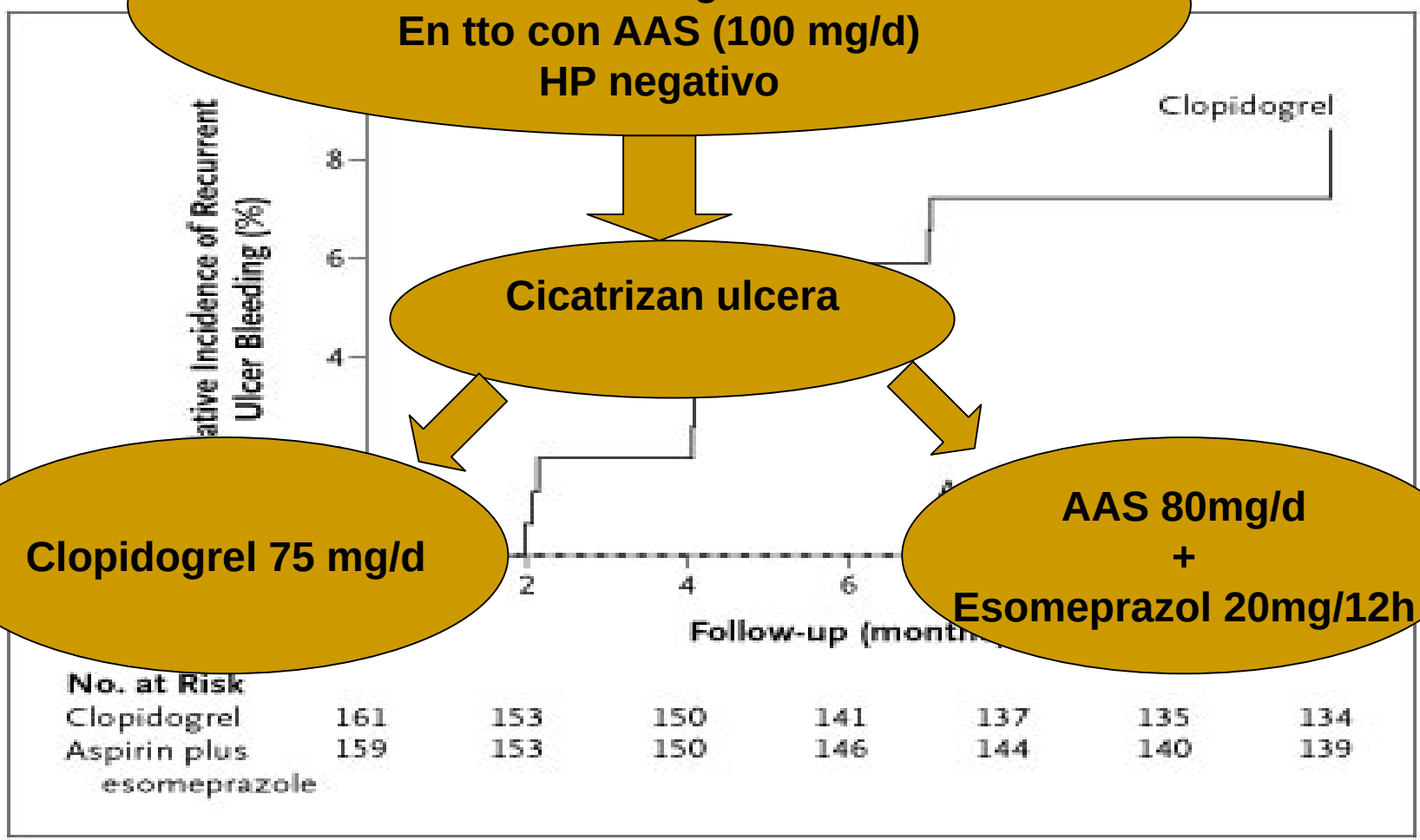
‡Shock was defined as a systolic blood pressure of less than 100 mm Hg with a pulse of 100 beats per minute or more.

Lai K et al. N Engl J Med 2002;346:2033-2038

The NEW ENGLAND JOURNAL of MEDICINE

Cumulative Incidence of Recurrent Ulcer Bleeding in the Group Receiving Clopidogrel and the

320 pacientes
Ulcus sangrante
En tto con AAS (100 mg/d)
HP negativo



Cicatrizan ulcera

Clopidogrel 75 mg/d

AAS 80mg/d
+
Esomeprazol 20mg/12h

Chan F et al. N Engl J Med 2005;352:238-244

Otras posibilidades

- AntiH2
  - Reducción menor del riesgo que IBP
- Cubiertas entéricas
  - No han demostrado disminución riesgo *(disminución de lesiones agudas de la mucosa gástrica pero no reducción de riesgo de lesiones mucosas duodenales o HDA)*

Estrategias

- Aproximación inicial:
  - ✓ Prevención primaria: en función de factores de riesgo
  - ✓ Si hay indicación de protección lo más razonable según los estudios realizados es la utilización de IBP.
  - ✓ Detección y erradicación asociada del HP sería deseable, aunque existe menos consenso.
    - ✓ En prev. primaria no parece indicado rutinariamente
    - ✓ En prev. secundaria la erradicación de HP forma parte del tratamiento.
    - ✓ La erradicación del HP no parece eximir de tto. con IBP


GRACIAS
www.matoh.com