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Aspirin for everyone: Has the time come or not yet?
GI-Bleeding: perception versus data

Disclosure of Potential Conflict of Interest:
Nothing to Disclose

Aspirin for everyone – has the time come or not yet?

Conditions to be fulfilled:

1. **The risk-benefit balance must be favourable**
2. **The measure must be cost-effective**
3. **The measure must be acceptable to ‘everyone’**

Aspirin for everyone – has the time come or not yet?

1. **The risk-benefit balance**

   - the benefits:

   a reduction in vascular disease

   a reduction in cancer

   - the risks:

   a gastrointestinal bleed

   a cerebral bleed

Aspirin for everyone – has the time come or not yet?

1. The risk-benefit balance

reduction in vascular disease

In secondary prophylaxis

the risk-benefit balance is widely accepted to be favourable

In primary prophylaxis the risk-benefit balance is debated

MI, stroke and CV death **RR 0.87** (0.80-0.93)

Bartolucci et al (2006) overview of six trials

Total CHD

Bartolucci et al (2006)

Reducti

vents **RR 0.88** (0.83-0.94)

Raju et al 2011

All cardiovascular events reduced by 15% (6%, 22%)

Sanmuganathan et al (2001) overview of four trials

but…. The number of adverse events may equal the number of vascular events prevented

Aspirin for everyone – has the time come or not yet?

1. The risk-benefit balance

reduction in cancer

Rothwell PM, Fowkes FGR, Belch JFF et al. Lancet 2011;327:31-41.

cancer deaths reduced **OR 0.79** (0.68, 0.92)

Rothwell PM

canc

Rothwell PM

all ca

Rothwell P,

color

Consistency of previous evidence:

- animal studies
- case-control studies
- cohort studies
- Mendellian randomisation studies
- randomised trials of adenoma prevention
- prediction of a 5-10 year delay

Algra AM, Rothwell PM. Lancet March 21 2012

colon cancer reduced **OR 0.62** (0.58, 0.67)

Burn J, Gerdes A-M, Macrae F et al. Lancet 2010;377(9809):2081-7.

colon cancer reduced **HR 0.63** (0.35, 1.13)

GI-Bleeding: perception vs data

1. The risk-benefit balance

a reduction in vascular disease

a reduction in cancer

a gastrointestinal bleed

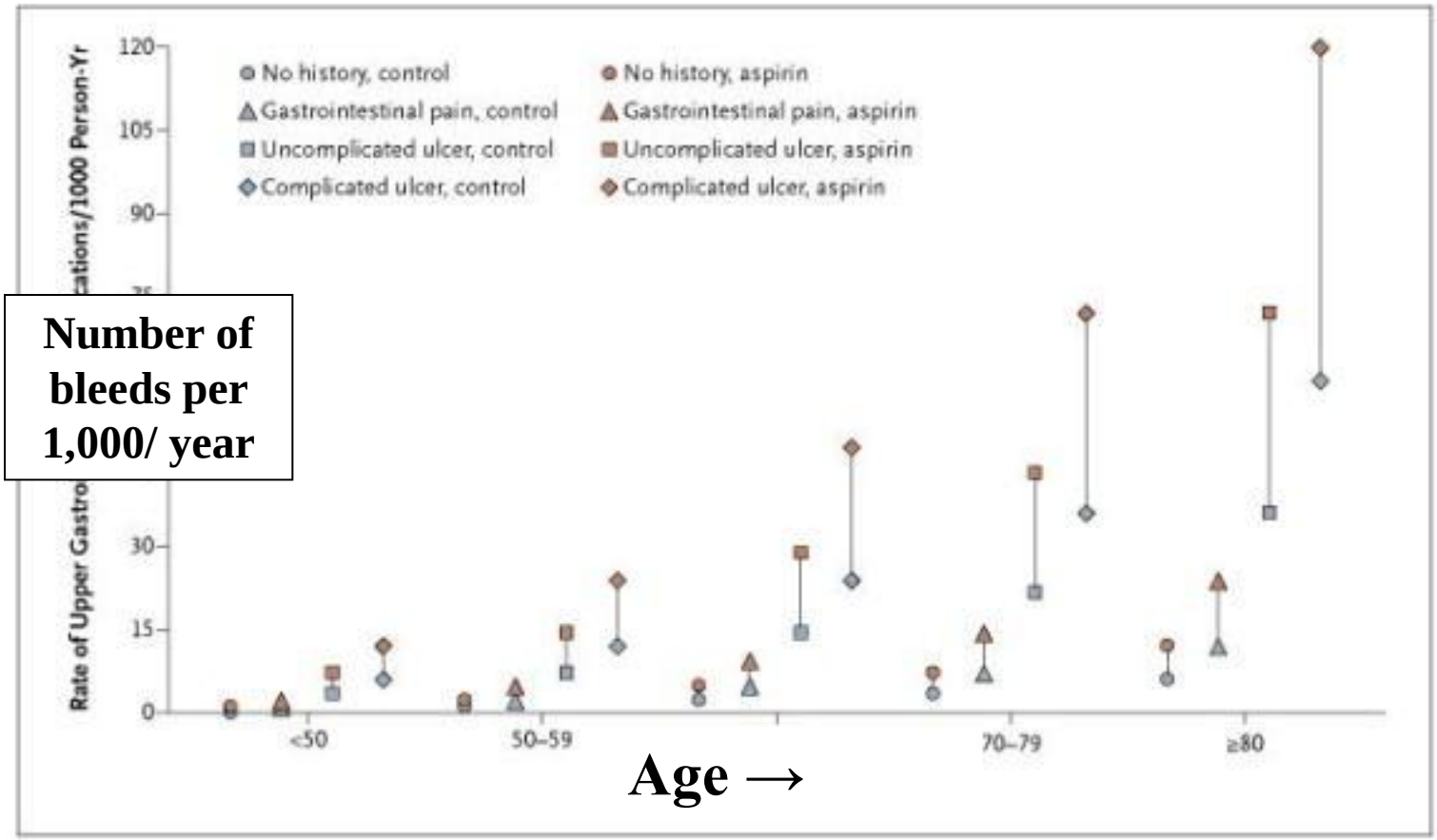
a cerebral bleed

- In 'healthy' older subjects the number of bleeds caused by aspirin may equal the number of vascular events prevented *Several papers*

- 'It is estimated 26,000 persons die per year as a consequence of adverse effects (of NSAIDs and aspirin) in the USA alone' *Three papers*

- "If aspirin were promoted we could not cope with the number of GI bleeds" *A gastroenterologist*

Gastrointestinal bleeding

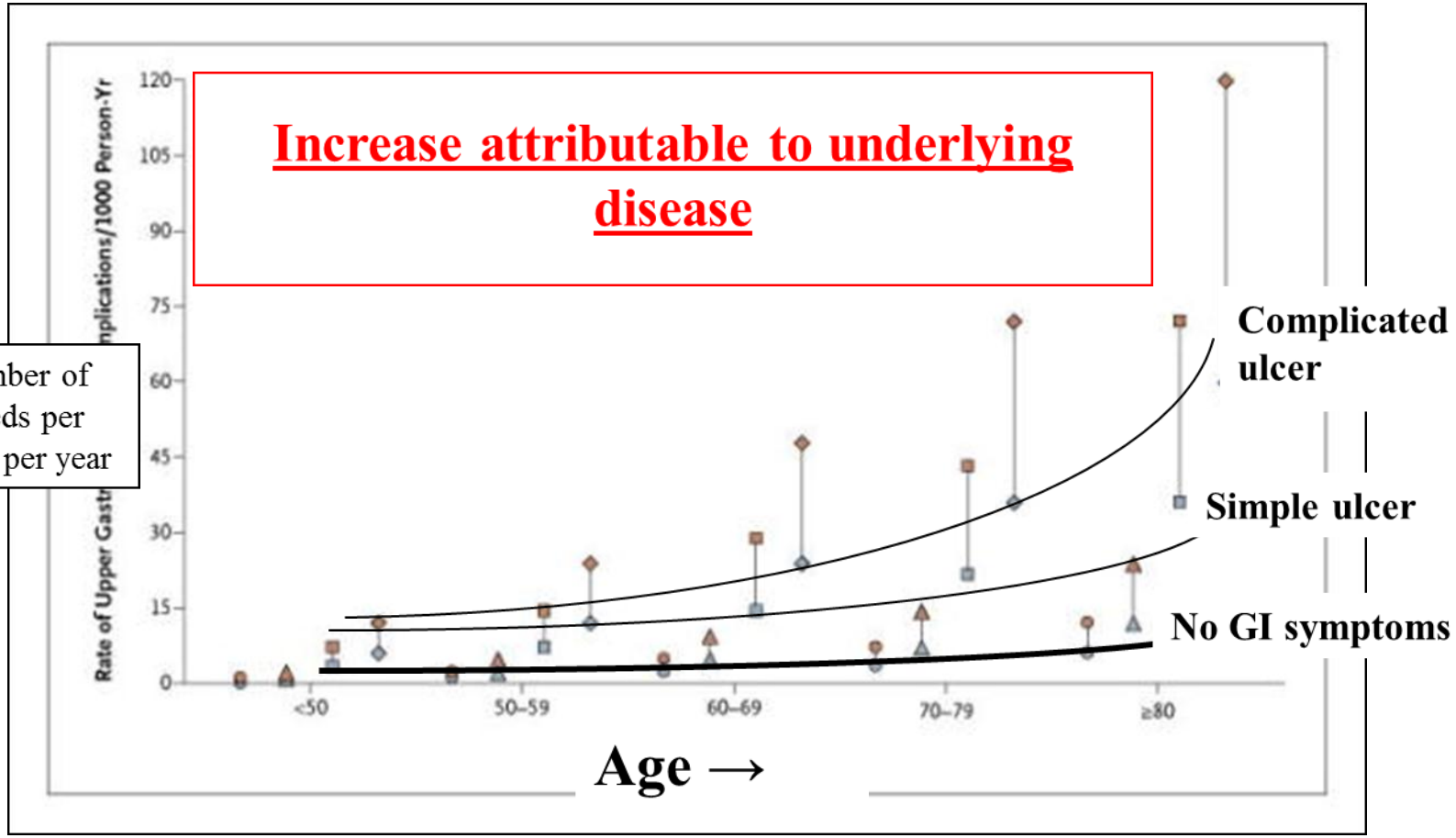


Number of bleeds per 1,000/ year

Low-Dose Aspirin for the Prevention of Atherothrombosis. Patrono et al. NEJM 2005;353:2373-83

GI-Bleeding: perception vs data

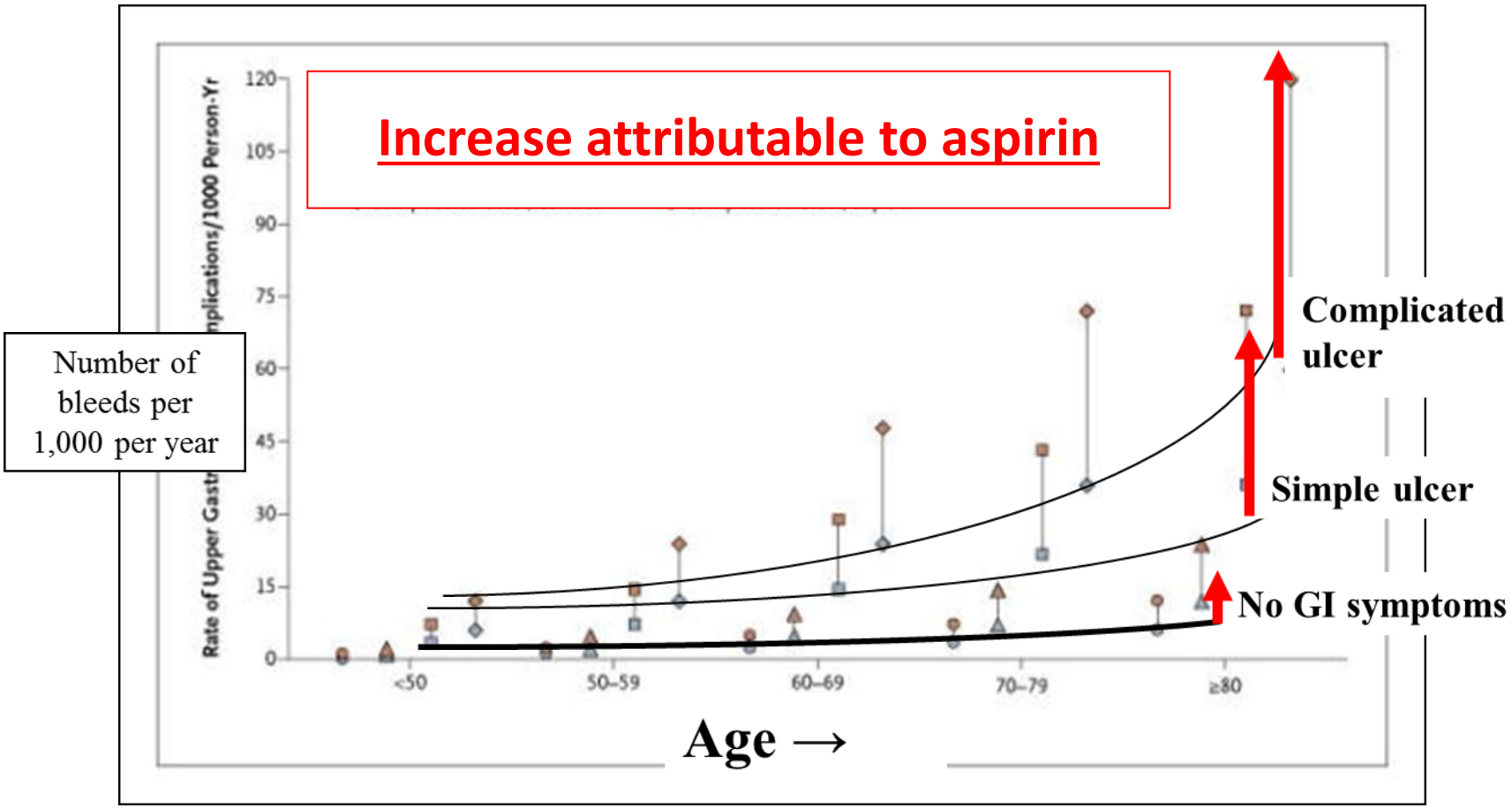
The risk-benefit balance: GI bleeds



Low-Dose Aspirin for the Prevention of Atherothrombosis. Patrono et al. NEJM 2005;353:2373-83

GI-Bleeding: perception vs data

1. The risk-benefit balance: GI bleeds – facts



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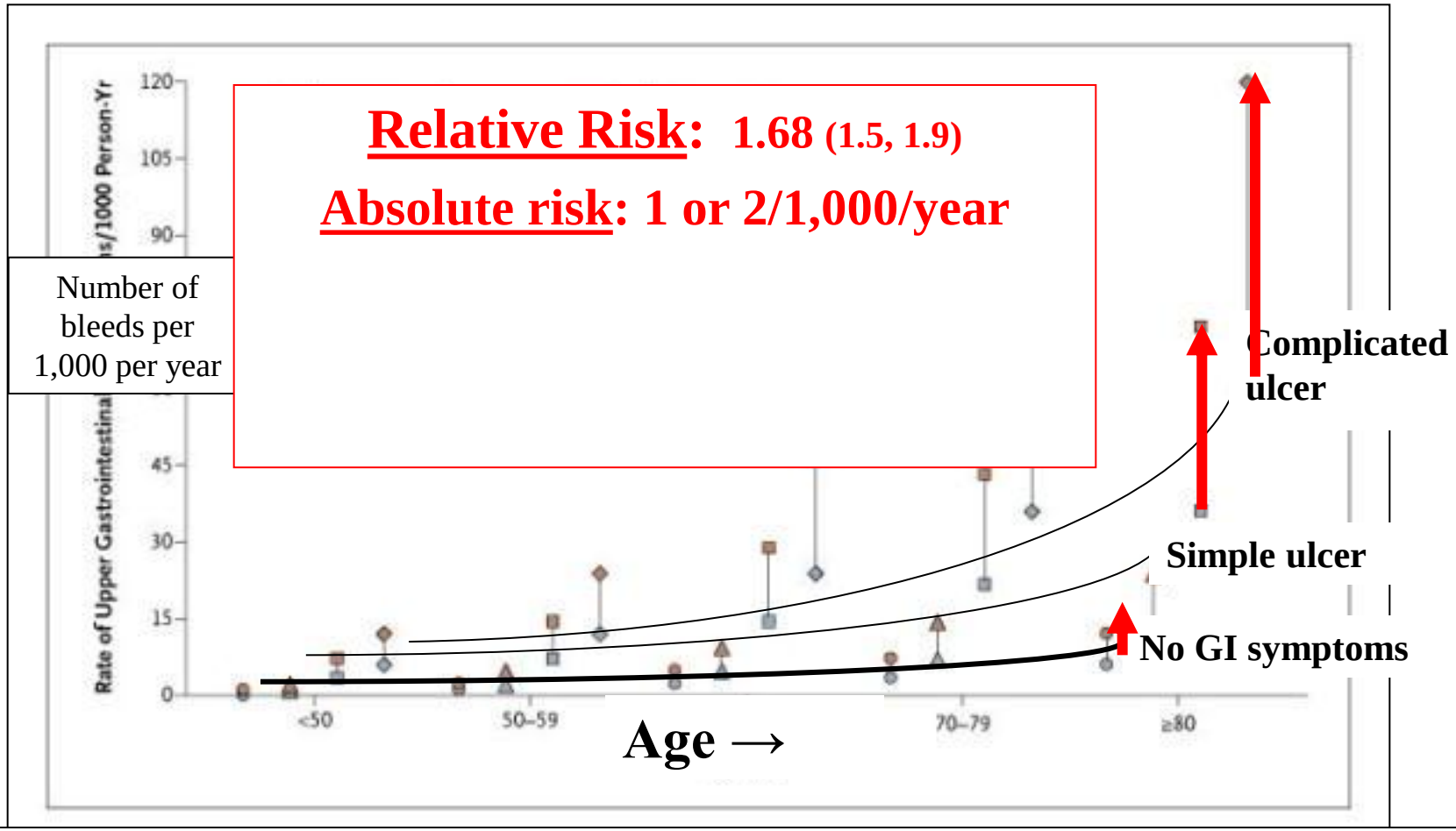

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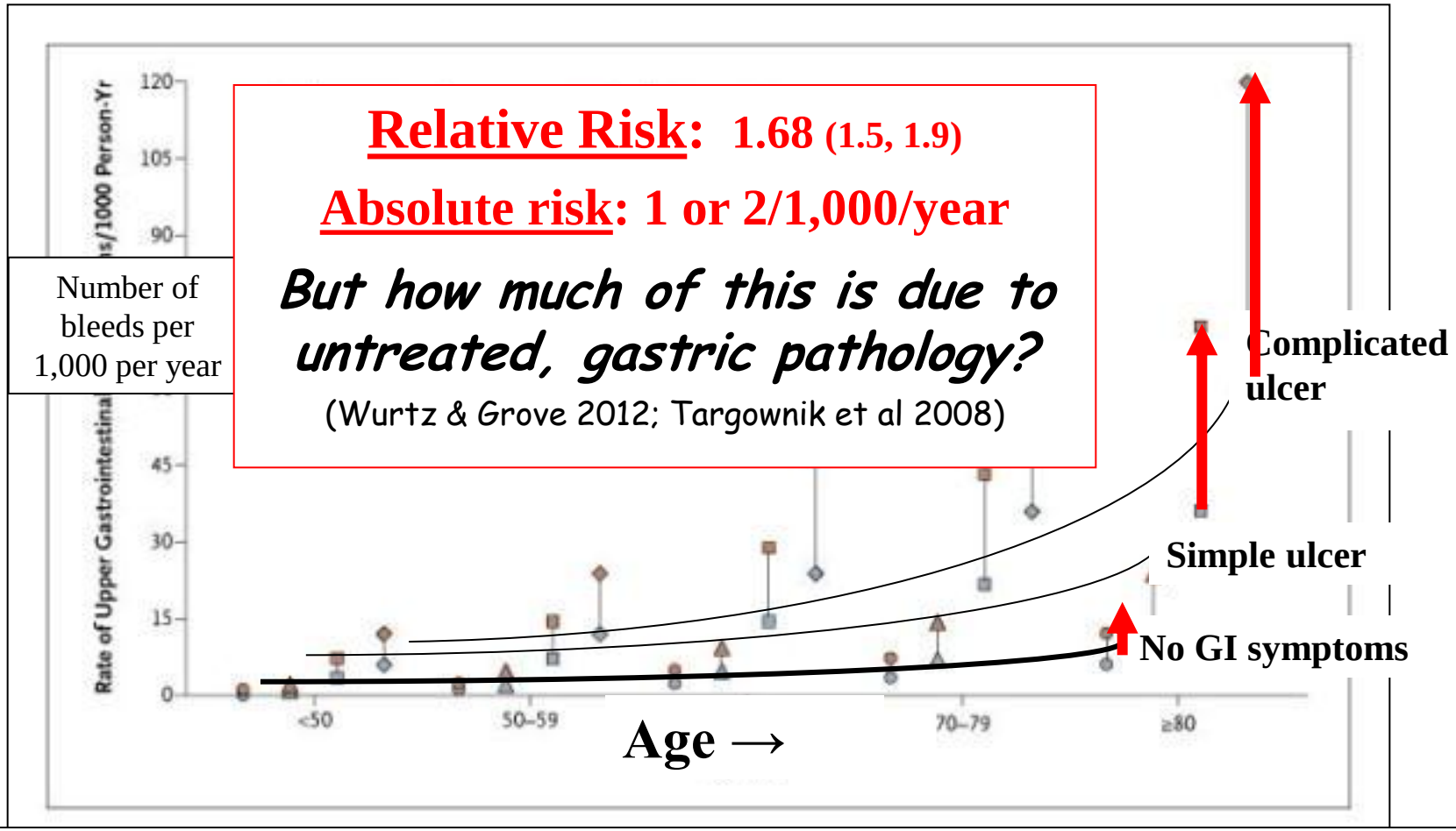

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GI-Bleeding: perception vs data

GASTROINTESTINAL BLEED:

Absolute risk in short term trials:

2 or 3 per 1,000 subjects per year

(overviews by Sanmuganathan et al 2001; Guise et al 2002; McQuaid and Laine 2006;).

But the risk appears to reduce over time……

An overview of 17 studies reported that the risk of a GI bleed is highest during the first month of aspirin use…..

RR 4.4 (*3.2, 6.1*) …..*and reduces thereafter*. (Garcia Rodriquez 2001)

An overview of 51 trials:

0 to 2.9 years on aspirin	**1.95** *(1.47, 2.59)*
3 to 4.9 years	**1.37** *(0.87, 2.14)*
5 or more years	**0.63** *(0.34, 1.16)*

(Rothwell, Price Fowkes et al 2012)

Aspirin and bleeding

GASTROINTESTINAL BLEED:

Absolute risk in short term trials:

2 or 3 per 1,000 subj

(overviews by Sanmug

The natural response to a bleed is to withdraw the aspirin

use…..

thereafter. Garcia Rodriquez

Reduction in GI bleeds over time:

0 to 2.9 years on aspirin	**1.95** *(1.47, 2.59)*
3 to 4.9 years	**1.37** *(0.87, 2.14)*
5 or more years	**0.63** *(0.34, 1.16)*

(Rothwell, Price Fowkes et al 2012)

Rebound on stopping aspirin

GASTROINTESTINAL BLEED:

Absolute risk in short term trials:

2 or 3 per 1,000 subj

(overviews by Sanmug

The natural response to a bleed is to withdraw the aspirin

Withdrawal of aspirin is followed by a rebound in vascular events:

Risk estimates: **6.9** (Derogar e al); **2.05** (Collett et al); **2.13** (Ferri et al); **1.72** (Newby et al); **3.4** (Maulaz et al); **2.40** (after CABG)

In an overview of six RCTs (50,000 subjects), the risk of a major coronary event 8-10 days after the withdrawal of aspirin, **OR 3.14** (1.75-5.61)

iBiondo-Zocail 2006

(1.47, 2.59)

1.37 *(0.87, 2.14)*

0.63 *(0.34, 1.16)*

years

(Rothwell, Price Fowkes et al 2012)

Continuing aspirin after a bleed

GASTROINTESTINAL BLEED:

Absolute risk in short term trials:

2 or 3 per 1,000 subj

(overviews by Sanmug

Sung et al (2005) took this further...

156 patients who had bled were started on a PPI.
A random half then put back onto aspirin.

Mortality was 1.3% on aspirin; 10.3% without aspirin:
HR 0.2 (0.05, 0.90)

ears on aspirin	**1.95** *(1.47, 2.59)*
3 to 4.9 years	**1.37** *(0.87, 2.14)*
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(Rothwell, Price Fowkes et al 2012)

Seriousness of bleeding attributable to aspirin

GASTROINTESTINAL BLEED:

Absolute risk in short term trials:

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The most serious GI bleeds are those that are fatal.....

Seriousness of bleeding attributable to aspirin

GASTROINTESTINAL BLEED:

Absolute risk in short term trials:
2 or 3 per 1,000 subjects per year

The most serious GI bleeds are those that are fatal…..

'…there were actually fewer fatal bleeds in participants allocated to aspirin than in the controls' (ATT overview 2009)

aspirin nine vs twenty placebo **OR: 0.48** *(0.17, 1.34)*

'….case-fatality from major extracranial bleeds was lower on aspirin than on control (Rothwell et al 2012)

aspirin eight vs fifteen placebo **OR 0·32** *(0·12, 0·83)*

'fatal bleeds were not associated significantly with low-dose ASA…. this was also the case with fatal GI bleeds Lanas, Wu et al 2011)

aspirin sixteen vs seventeen placebo **OR 0·94** *(0·47, 1.87)*

Seriousness of bleeding attributable to aspirin

DEATHS FROM GI BLEED:

'…there were actually fewer fatal bleeds in participants allocated [illegible] than in the controls' (ATT overview 2009)

nine vs twenty

A later examination of [illegible]
Fatal bleed[illegible]

BUT….

The absence of any significant increase in fatal bleeds attributable to aspirin within clinical trials, could be due to the selection of subjects at low risk of bleeding for inclusion in clinical trials. Lanas PerezAsia

[illegible] 12, 0·83)

[illegible] significantly with low-dose ASA…. this [illegible] fatal GI bleeds Lanas, Wu et al 2011)

sixteen vs seventeen **OR 0·94** *(0·47, 1.87)*

In the US Physicians Study deaths from bleeding in 11,007 and 11,034 subjects there was **one vs no** death from bleeding Tranmer et al 2000

GI deaths from bleeding attributable to aspirin

The absence of any significant increase in fatal bleeds attributable to aspirin within clinical trials, could be due to the selection of subjects at low risk of bleeding for inclusion in clinical trials. Lanas PerezAsia (2005)

Fatal GI bleeds in selected subjects in RCTs:

In the ATT overview (2009) **5.2% of bleeds were fatal**

In Rothwell et al (2012) **4.0% of bleeds were fatal**

Fatal bleeds in unselected subjects in the community:

In two community based cohorts mortality rate from GI complications (mostly upper GI bleeding) was **5.7%** and **5.6%** (Lanas et al 2005)

In three thousand UK hospital admissions because of adverse drug reactions to aspirin, 162 subjects had been taking low-dose aspirin…. of these **4.3%** had died. (Piromahamed et al 2004)

In the UK 'Yellow Card' scheme, 1,572 bleeds attributed to low-dose aspirin have been reported. **3.8%** of these were fatal. MHRA

G.I. Bleeds – summary

INCIDENCE: 2 or 3 per 1,000 subjects per year

(overviews by Sanmuganathan et al 2001; Guise et al 2002; McQuaid and Laine 2006;).

A CRISIS! but….

- *the risk of a bleed seems to diminish with time*

(Garcia Rodriguez et al 2001; Rothwell et al 2012)

- *fatal bleeds are not increased by aspirin*

(ATT 2009; Morgan 2009; Sostres & Lanas 2011; Cham 2012; Pirmohamed 2004)

- *gastroprotective drugs are highly effective but are seriously underused*

(Wurtz & Grove 2012 Lanas et al, 2000; Targownik 2008; Chan et al 2012)

Aspirin and bleeding

CEREBRAL BLEEDS *Haemorrhagic stroke:*

INCIDENCE: **1 or 2 per 10,000** subjects per year

(overviews by He et al Sanmuganathan et al 2001; McQuaid and Laine 2006;) Lanas et al

The role played by uncontrolled hypertension in cerebral bleeding attributable to aspirin is unknown

Aspirin and bleeding

CEREBRAL BLEEDS *Haemorrhagic stroke:*

INCIDENCE: **1 or 2 per 10,000** subjects per year
(overviews by He et al Sanmuganathan et al 2001; McQuaid and Laine 2006;) Lanas et al

Hypertension is a major factor in haemorrhagic stroke.

In the major ATT overview there was a doubling of cerebral haemorrhage for a rise of 20 mmHg in blood pressure.

RR 2.18, *(1.65, 2.87)* (ATT Overview 2009)

In the Hypertensive Optimal Treatment (HOT) **trial there was no excess in cerebral bleeds** (Hansson et al 1998)

20,000 patients with hypertension, all adequately treated

	Aspirin (9,399 subjects)	**Placebo** (9,391 subjects)
Cerebral bleeds:		
- fatal	**2**	**3**
- non fatal	**12**	**12**
All fatal bleeds	**7**	**8**

Aspirin and bleeding

STOMACH BLEEDs:

INCIDENCE: 2 or 3 per 1,0

(overviews

2006;).

leeds

not increased by aspirin

bleed seems to diminish with time

(overviews by Lanas et al, Morgan, Elwood et al)

If there is any past history, or any suspicion of present stomach disease, then a gastro-protective drug should be advised

CEREBRAL BLEEDs *Haemorrhagi*

iNCIDENCE: 1 or 2 per 10

(overviews by H

ine 2006;) Lanas et al

ly only in patients with uncontrolled hypertension

Blood pressure should be checked before long-term aspirin is recommended

Aspirin and bleeding

STOMACH BLEEDs:

INCIDENCE: 2 or 3 per 1,0

(overviews

;).

If there is any past history, or any suspicion of present stomach disease, then a gastro-protective drug should be given

Good clinical practice

Blood pressure should be checked before long-term aspirin is recommended

C

001; McQuaid and Laine 2006;) Lanas et al

BUT Probably only in patients with uncontrolled hypertension

Aspirin for everyone – has the time come or not yet?

Conditions to be fulfilled

1. A favourable risk benefit balance
2. **Cost effective**
3. Acceptable to ‘everyone’

Cost-effectiveness of aspirin prophylaxis

"a 10% reduction in cancer could tip the balance of benefits and risks favourably in average-risk populations"
Thun, Jacobs, Patrono 2012

'aspirin appears beneficial for a large proportion of middle-aged men at low-moderate CHD risk, and that if its effects on cancer are real, this proportion would be even larger'.
Pignone et al 2013

'…the addition of aspirin [to colorectal screening] ***would give substantial reductions in colorectal cancer deaths, together with cost savings per life-year gained'.*** Hassan et al 2012

Aspirin for everyone – has the time come or not yet?

Conditions to be fulfilled

1. A favourable risk benefit balance
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3. **Acceptable to ‘everyone’**

Aspirin for everyone – has the time come or not yet

WHO IS '<u>EVERYONE</u>'?

All over 50?

Elwood et al 2005; Vandvik et al 2012

All over 45?

Rothwell et al

The verdict of the public - a Citizen's jury

1. **The preservation of health is a subject's own responsibility.**
2. **Information on healthy behaviours should be made readily available**
3. **The public should be informed about preventive medicines**

even before there is agreement amongst doctors!

Elwood PC, Longley M. My health – whose responsibility: *a jury decides.* J Epidem Comm Hlth 2010;64:

The risk-benefit balance of low-dose aspirin

There is a difference between
the treatment of disease
and the protection of health

It is my decision

…Whether or not I smoke,
…what diet I take,
…how much I drink,
…what my body weight is,
…whether or not I take exercise……
…whether or not I take a preventive medicine

The verdict of a Citizen's jury

1. The preservation of health is a subject's own responsibility.
2. Information on healthy behaviours should be made readily available
3. **The public should be informed about preventive medicines** ***even before there is agreement amongst doctors!***

Already, people have taken their own decision....

- 37% of adults aged over 50 in Wales are taking aspirin 'regularly'

(Elwood et al 2007; 2011)

- 36% in the USA take aspirin daily

(Ajani et al 2006)

Elwood PC, Longley M. My health – whose responsibility: *a jury decides.* J Epidem Comm Hlth 2010;64:

Aspirin for everyone
– has the time come or not yet?

The risk-benefit balance of low-dose prophylactic aspirin appears now to be favourable, and cost effective

ATT 2002,2009; Sanmuganathan et al 2001; Bartolucci et al 2006;
Flossman & Rothwell 2007; Rothwell et al 2010,2011,2012; Burn et al 2010
Thun, Jacobs, Patrono 2012; Pignone et al; 2013; Hassan et al 2012

Sufficient information should now be given to subjects/patients to enable them to make informed decisions about the protection of their own health

SUMMARY:

Sufficient information should be given to subjects/patients to enable them to make an informed decisions about the protection of their own health

- Information about aspirin should always be given within the context of healthy living (non-smoking, exercise, low body weight etc….)
- underlying gastric pathology should be identified and treated and if there is uncertainty, a gastroprotective drug should be advised
- in comparison with the serious disease events aspirin can prevent, a gastrointestinal bleed is a crisis, but not a disaster
- a cerebral bleed is a tragedy. Blood pressure should be measured and treated if raised, before aspirin is taken
- only 100mg or less aspirin should be taken *?with a glass of milk**
- if aspirin is to be stopped, *?withdraw it gradually**

**This has not be tested in an RCT, but is good common sense!*