Controversies in Prevention: What is the Evidence?

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Brief bio: Mark Ebell MD, MS

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- Member of USPSTF, 2012-2015
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- **Grazie mille alla dott.ssa Alessandra Buja per avermi invitato a Padova**

Controversies in Primary Prevention

- Aspirin for primary prevention of cardiovascular disease and cancer
- Use of statins in older patients for primary prevention
- Omega-3 fatty acids for primary prevention

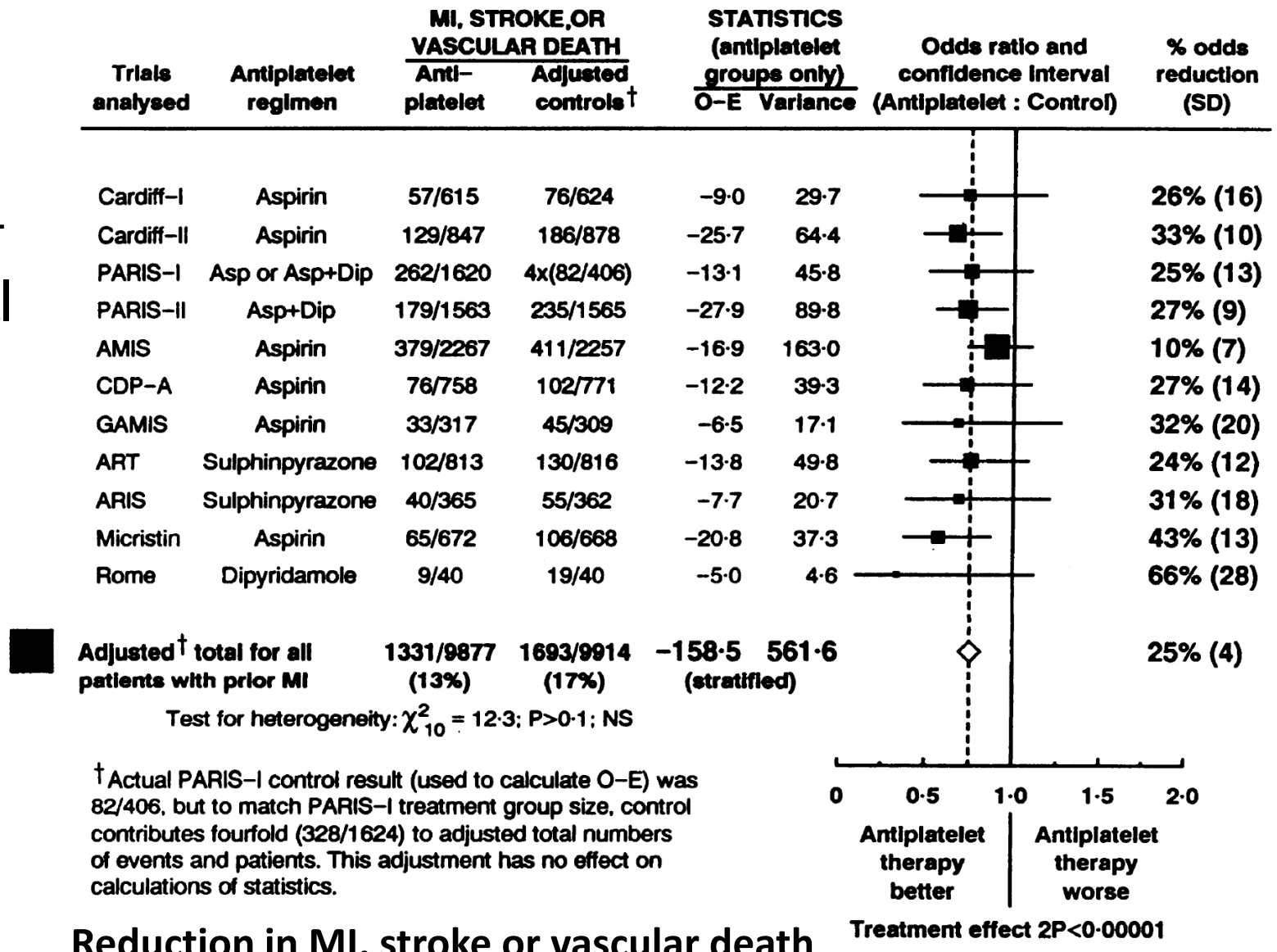
- Aspirina in prevenzione primaria delle malattie cardiovascolari e del cancro
- Uso di statine nei pazienti più anziani
- Omega-3 per la prevenzione

Aspirin for Primary Prevention

Background

- First meta-analysis in 1994
- Aspirin reduced myocardial infarction, stroke, or cardiovascular death:
  - 13% vs 17%
  - Riduzione del rischio relativo = 25%
  - Riduzione del rischio assoluto = 4%
  - Number needed to treat (NNT, numero necessario per trattare) = 25

BMJ 1994; 308:81-106.



Trials analysed	Antiplatelet regimen	MI, STROKE,OR VASCULAR DEATH: Anti-platelet	MI, STROKE,OR VASCULAR DEATH: Adjusted controls†	STATISTICS (antiplatelet groups only): O–E	STATISTICS (antiplatelet groups only): Variance	% odds reduction (SD)
Cardiff–I	Aspirin	57/615	76/624	–9·0	29·7	26% (16)
Cardiff–II	Aspirin	129/847	186/878	–25·7	64·4	33% (10)
PARIS–I	Asp or Asp+Dip	262/1620	4x(82/406)	–13·1	45·8	25% (13)
PARIS–II	Asp+Dip	179/1563	235/1565	–27·9	89·8	27% (9)
AMIS	Aspirin	379/2267	411/2257	–16·9	163·0	10% (7)
CDP–A	Aspirin	76/758	102/771	–12·2	39·3	27% (14)
GAMIS	Aspirin	33/317	45/309	–6·5	17·1	32% (20)
ART	Sulphinpyrazone	102/813	130/816	–13·8	49·8	24% (12)
ARIS	Sulphinpyrazone	40/365	55/362	–7·7	20·7	31% (18)
Micristin	Aspirin	65/672	106/668	–20·8	37·3	43% (13)
Rome	Dipyridamole	9/40	19/40	–5·0	4·6	66% (28)
Adjusted† total for all patients with prior MI		**1331/9877 (13%)**	**1693/9914 (17%)**	**–158·5 (stratified)**	**561·6**	**25% (4)**

Test for heterogeneity: χ^2_{10} = 12·3; P>0·1; NS

†Actual PARIS–I control result (used to calculate O–E) was 82/406, but to match PARIS–I treatment group size, control contributes fourfold (328/1624) to adjusted total numbers of events and patients. This adjustment has no effect on calculations of statistics.

Reduction in MI, stroke or vascular death

Riduzione dell'infarto del miocardio, ictus o morte cardiovascolare nel trattamento con aspirina

But for primary prevention patients, risk was reduced very little.

Ma per i pazienti di prevenzione primaria, il rischio è stato ridotto molto poco.

- 4.4% vs 4.8% over 5 years
- **Riduzione Rischio Assoluto 0.4%**
- **NNT = 250 over 5 years**

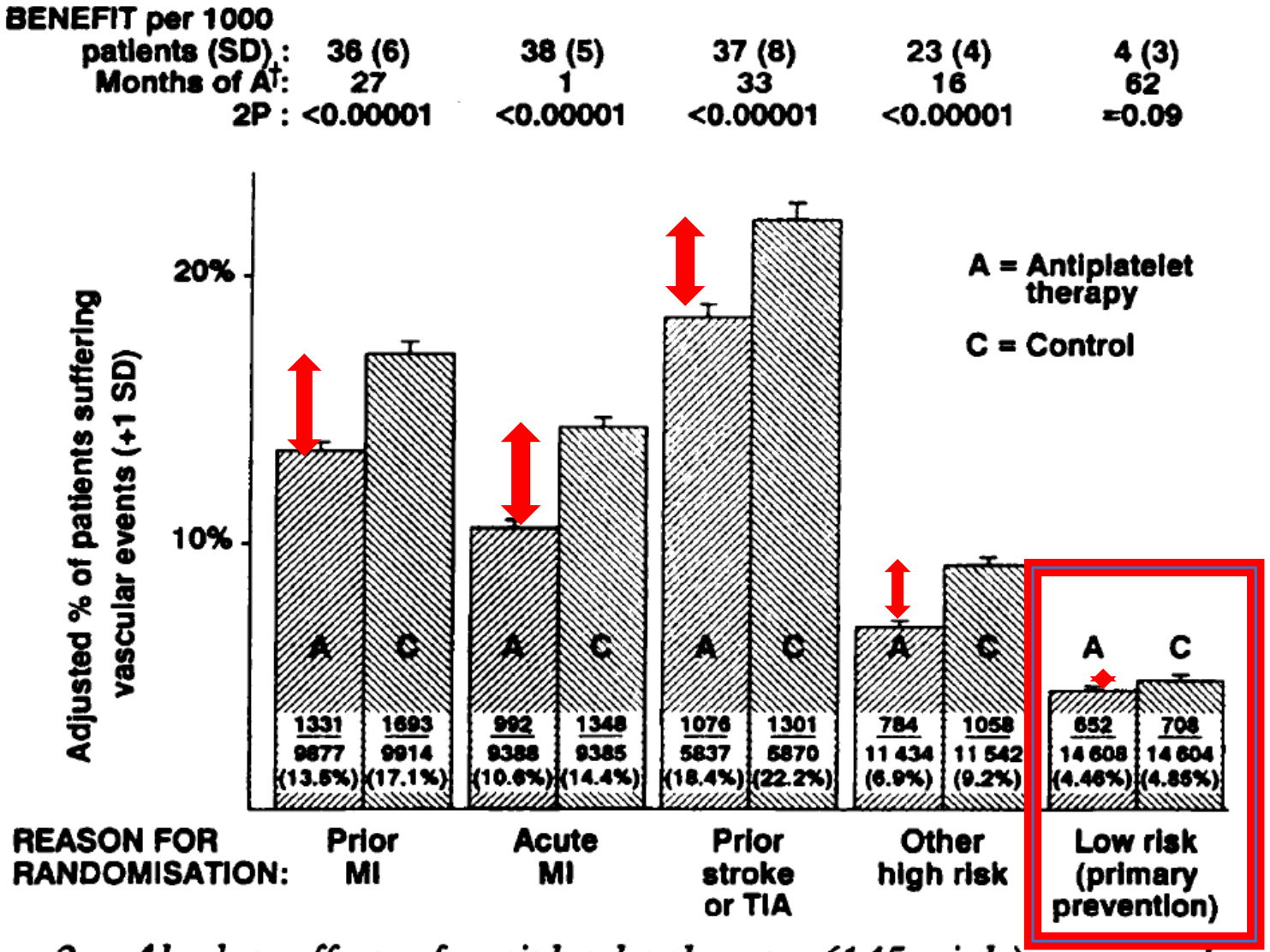


FIG 3—*Absolute effects of antiplatelet therapy (145 trials) on vascular events (myocardial infarction, stroke, or vascular death) in four main high risk categories of trial and in low risk (primary prevention)*

2015 USPSTF Recommendations

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I

Aspirin age 50 to 69 if

- ≥ 10% ten-year CVD risk of cardiovascular event
- not at increased risk for bleeding
- expected to live at least 10 years
- willing to take aspirin at least 10 years.

Rischio a dieci anni di eventi CV maggiori ≥ 10%, non ad aumentato rischio di sanguinamento, con un'aspettativa di vita di almeno 10 anni e disposto ad assumere la terapia per almeno 10 anni.

European Heart Journal (2016) **37**, 2315–2381
doi:10.1093/eurheartj/ehw106

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Downloaded from https://academic.

"Antiplatelet therapy (e.g. with aspirin) is not recommended for people with DM who do not have CVD

"Antiplatelet therapy is not recommended in individuals free from CVD, due to the increased risk of major bleeding."

Documento di consenso e raccomandazioni per la prevenzi cardiovascolare in Italia 2018

Documento coordinato da *Massimo Volpe*,
Presidente Società Italiana per la Prevenzione Cardiovascolare (SIPREC)

Based on 10 year cardiovascular event risk:

- < 10%: no aspirin
- 10-20%: consider aspirin if no increased bleeding risk
- > 20%: give aspirin if no increased bleeding risk

Aspirina a basse dosi nella prevenzione cardiovascolare primaria

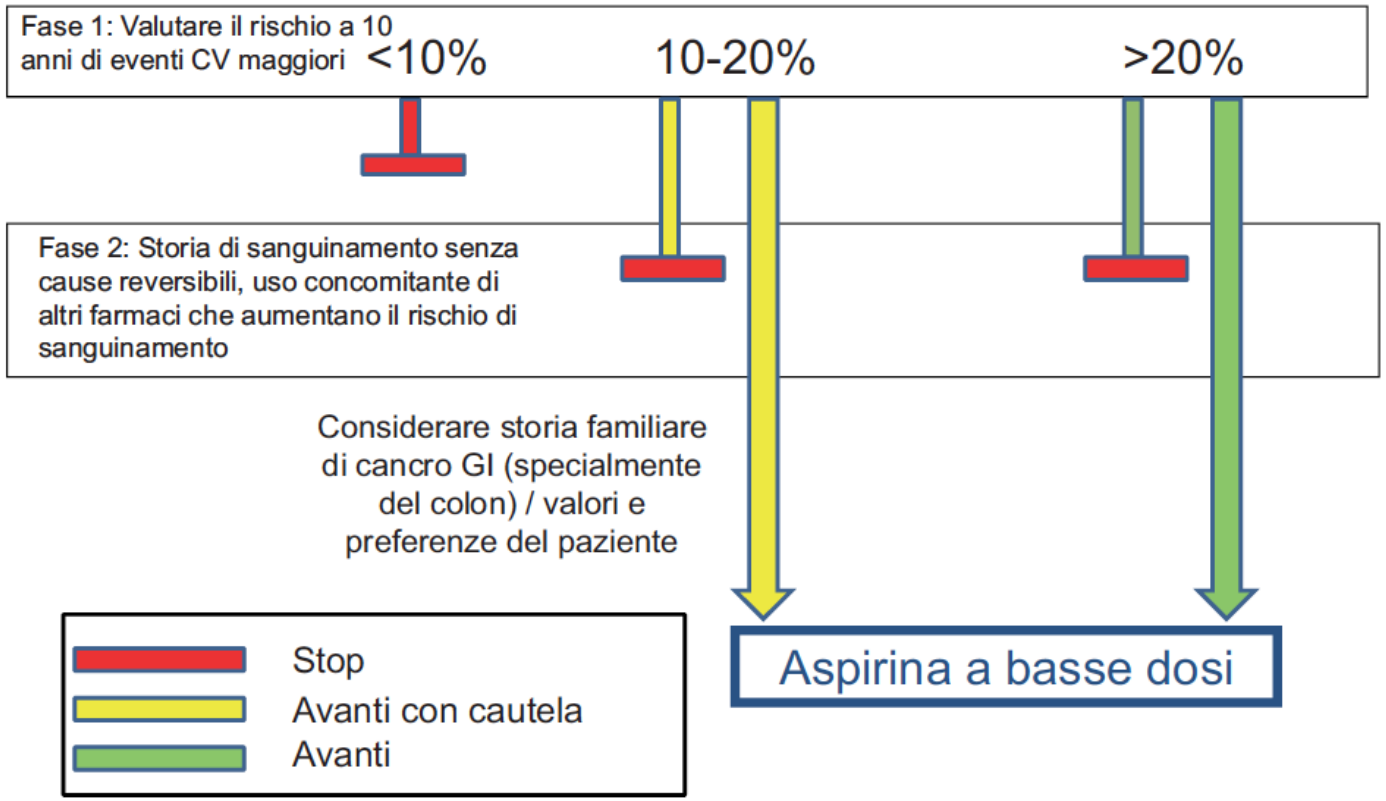


Figura 21. Algoritmo pratico proposto dal Documento di Consenso Intersocietario e dal Working Group on Thrombosis della Società Europea di Cardiologia per la prescrizione di aspirina a basse dosi in prevenzione primaria in relazione al livello di rischio.
CV, cardiovascolare; GI, gastro-intestinale.
Modificata da Halvorsen et al.[296] e riprodotta con permesso da Volpe et al.[297].

Individual Patient Data (IPD) meta-analysis (2009)

- The investigators of the big aspirin trials agreed to share data, and treated it like one very large study
- This way they could examine subgroups with more statistical power.
  - 6 primary prevention trials with 95,000 patients (1 CV event/190 person-years
  - 16 secondary prevention trials with 17,000 patients (1 CV event/13 person-years)

Antithrombotic Trialists Collaborative. Lancet 2009, 373:1849

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Metanalisi su dati individuali di singoli pazienti

- 6 studi di prevenzione primaria con 95.000 pazienti (1 evento cardiovascolare per 190 anni-persona)
- 16 studi di prevenzione secondaria con 17.000 pazienti (1 evento cardiovascolare per 13 anni-persona)

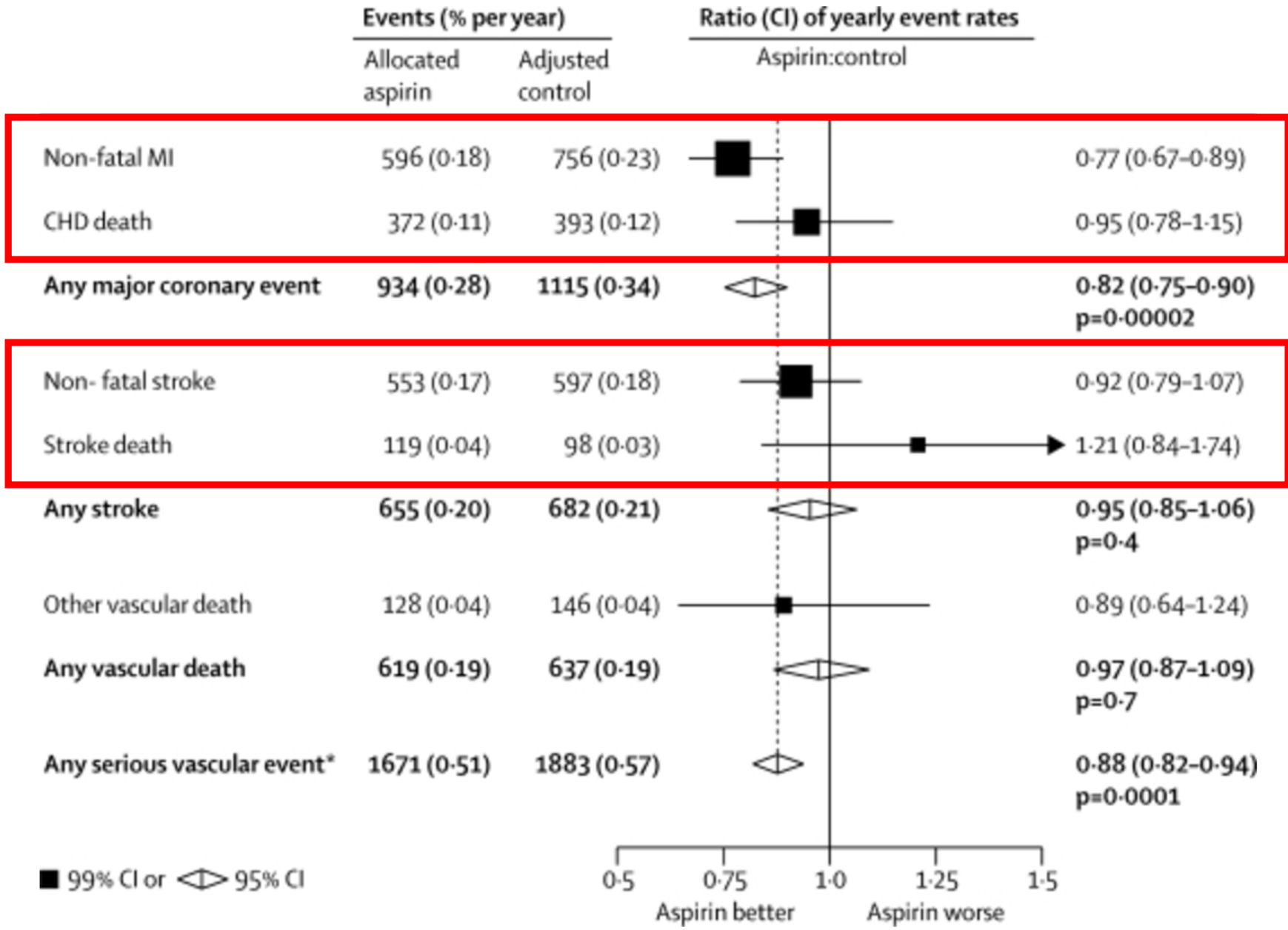
IPD Meta-analysis: Cardiovascular Benefits in Primary Prevention

Most benefit is in non-fatal events, rather than fatal events

No reduction in vascular death

La maggior parte del beneficio è in eventi non fatali, piuttosto che eventi fatali.

Lancet 2009, 373:1849



Serious vascular events in primary prevention trials—proportional effects of aspirin allocation

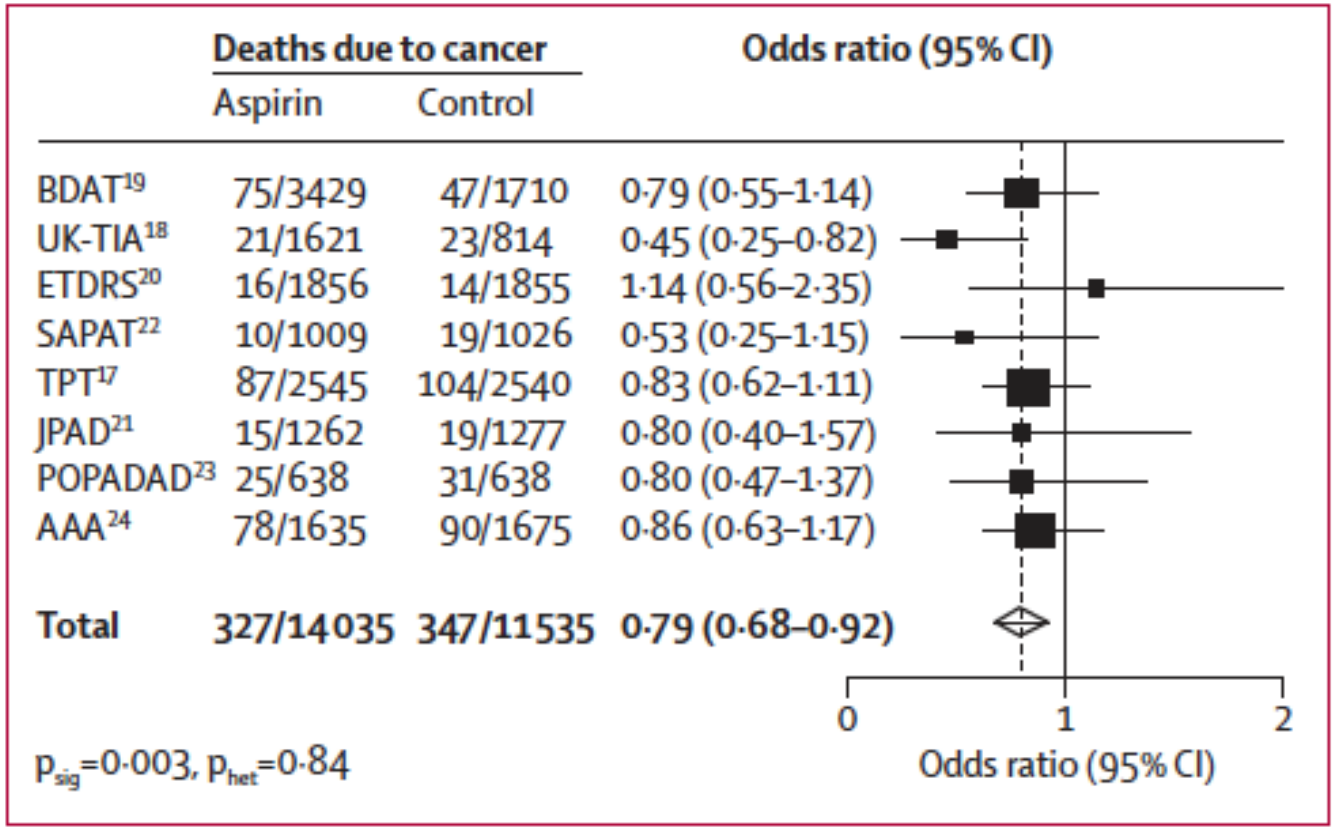


Figure 1: **Meta-analysis of the effect of aspirin on deaths due to cancer during all eligible randomised trials of aspirin versus control**

L'aspirina riduce la mortalità per cancro? IT

Riduzione statisticamente significativa delle morti dovute al cancro

- RR = 0.79 (95% CI 0.68-0.92)
- Differenza di rischio assoluto: 2.26% vs 3.01%, NNT = 133

IPD Meta-Analysis: Does Aspirin Reduce Cancer Mortality?

Statistically significant reduction in deaths due to cancer

RR = 0.79 (95% CI 0.68 to 0.92)

Absolute risk difference:
2.26% vs 3.01% = -0.75%

NNT = 100%/0.75% = 133 over ~ 10 years

Rothwell, et al. Lancet 2011; 377: 31–41

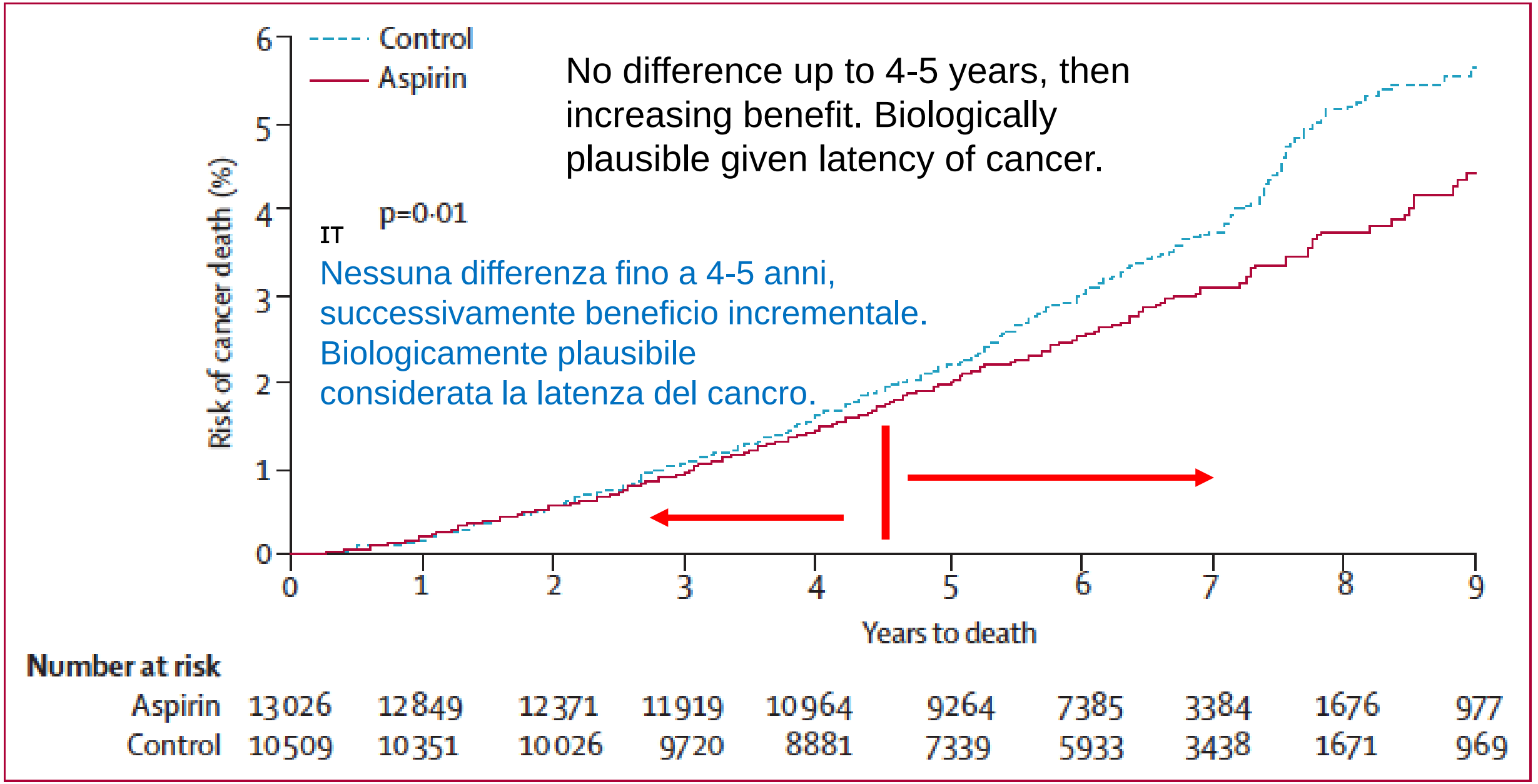


Figure 2: Effect of allocation to aspirin versus control on risk of death due to cancer during the trial treatment periods in a pooled analysis of the 23 535 patients in seven trials[17-21,23,24]

Results by duration of aspirin treatment

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Risultati per durata del trattamento con aspirina

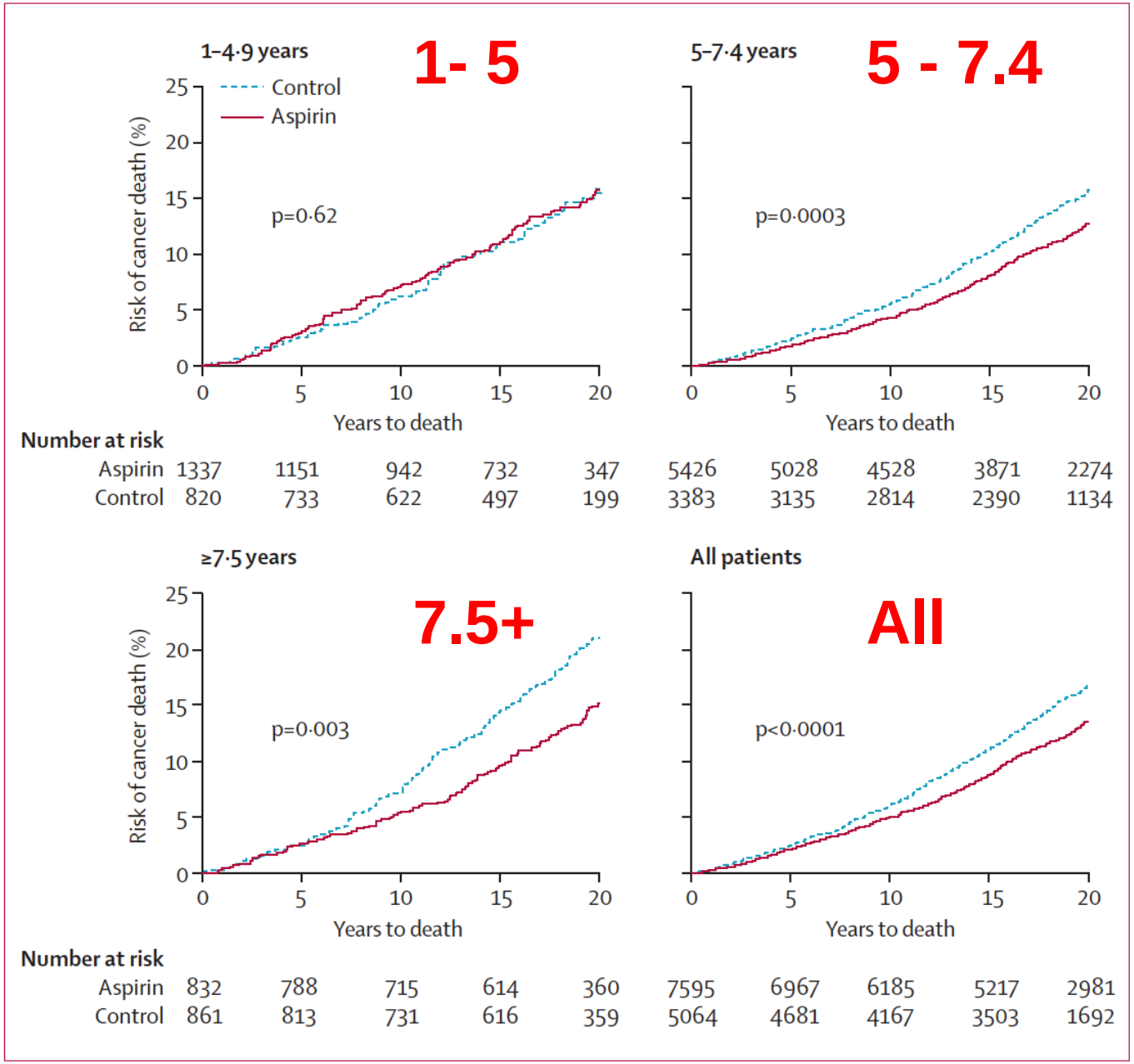

Figure 3: **Effect of allocation to aspirin versus control on 20-year risk of death due to any solid cancer stratified by scheduled duration of trial treatment in three trials with long-term follow-up[17–19]**
Continuous variable interaction, p=0·01.

What we thought in 2014, based largely on IPD meta-analysis of mostly older studies

- For primary prevention, aspirin reduces non-fatal CV events but not fatal events
- Aspirin used for more than 5 years reduces cancer mortality
- This led to USPSTF guideline
- Then came Japanese trial (2014), and in 2018 ASPREE, ASCEND, and ARRIVE trials

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- In prevenzione primaria, l'aspirina riduce gli eventi CV non fatali ma non gli eventi fatali
- L'aspirina utilizzata per più di 5 anni riduce la mortalità per cancro
- Ora 4 nuovi studi (Giapponese, ASPREE, ASCEND, and ARRIVE) nel 2014 e nel 2018

3 meta-analyses (blue) and 4 recent trials (black): Patient characteristics

Studio	#	Età media	% uso tabacco	% in terapia con statine	% con diabete	Follow-up
ATC, 1994 (meta-analysis of 11 trials)	19,791					5.0 mean
Berger, 2006 (meta-analysis of 6 studies)	95,456	57.4	14.7%	NR	4.0%	3.6 – 10 years
ATC, 2009 (IPD meta-analysis of 6 studies)	95,456	57.4	14.7%	NR	4.0%	3.7 – 10 years
Ikeda, 2014	14,464	71	13.1%	NR	34%	5.0 median
ASPREE, 2018	19,114	74	4.0%	34%	11%	4.7 median
ASCEND, 2018 *	15,480	63	8.3%	75%	94%	7.4 mean
ARRIVE, 2018	12,546	64	29%	43%	0%	5.0 mean

3 meta-analyses (blue) and 4 recent trials (black): Potential benefits (bold or * = statistically significant)

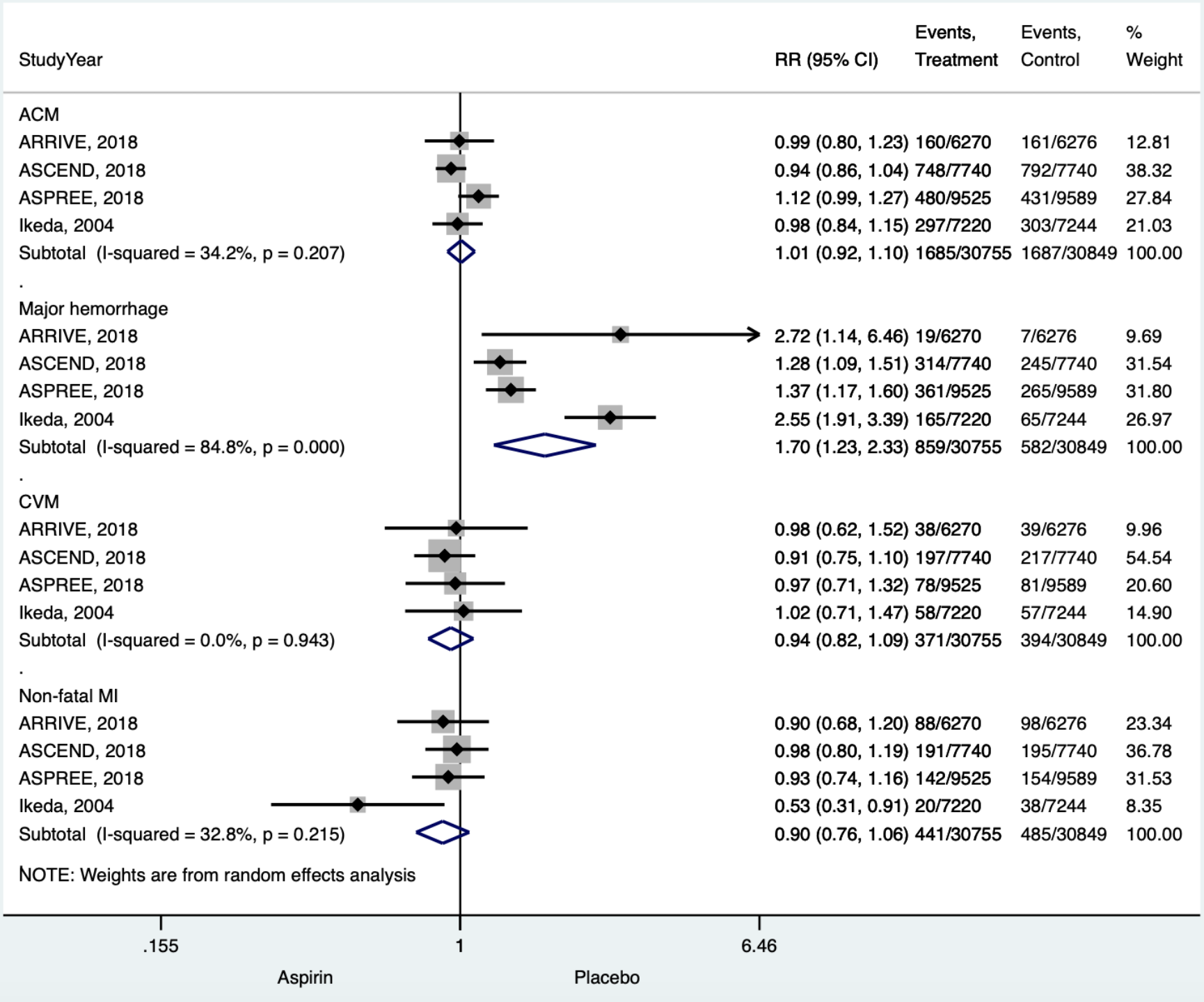
*** = p < 0.05**

Study	All-cause mortality	Cardiovascular mortality	Non-fatal myocardial infarct	Cancer mortality
ATC, 1994 (meta-analysis of 11 trials)	3.9% vs 4.1%	1.92% vs 1.99%	**1.5% vs 2.0% ***	NR
Berger, 2006 (meta-analysis of 6 studies)	3.41% vs 3.43%	1.24% vs 1.15%	**1.39% vs 1.75% ***	NR
ATC, 2009 (IPD meta-analysis of 6 studies)	0.5% vs 0.53% (per year)	0.19% vs 0.19% (per year)	**0.18% vs 0.23% (per year) ***	**OR 0.79 (better)**
Ikeda, 2014	4.3% vs 4.1%	0.86% vs 0.78%	**0.30% vs 0.58% ***	NR
ASPREE, 2018	**5.9% vs 5.2% (worse) ***	1.0% vs 1.2%	1.5% vs 1.6%	**3.1% vs 2.3% (worse) ***
ASCEND, 2018 *	9.7% vs 10.2%	2.5% vs 2.8%	2.5% vs 2.5%	4.0% vs 4.1%
ARRIVE, 2018	2.6% vs 2.6%	0.6% vs 0.6%	1.4% vs 1.6%	NR
Comment:	**No difference or harm**	**No difference**	**Benefit only in pre-statin era**	**Benefit in pre-screening era**

3 meta-analyses (blue) and 4 recent trials (black): Potential harms (bold or * = statistically significant)

*** = p < 0.05**

Study	Any major bleeding (qualsiasi sanguinamento maggiore)	Hemorrhagic stroke (Ictus emorragico)	Intracranial hemorrhage
ATC, 1994 (meta-analysis of 11 trials)	NR		
Berger, 2006 (meta-analysis of 6 studies)	**0.76% vs 0.47% *** major bleeding	0.26% vs 0.18% (NS women, p < 0.05 men)	NR
ATC, 2009 (IPD meta-analysis of 6 studies)	**0.10% vs 0.07% per year *** major GI and other extracranial bleeds	HR 1.32 (95% CI 0.9 – 1.9)	NR
Ikeda, 2014	**0.86% vs 0.51% *** serious extracranial bleed	NR	0.1% vs 0.12%
ASPREE, 2018	**3.8% vs 2.8% *** major hemorrhage	1.0 vs 0.8 per 1000 py	**2.5 vs 1.7 per 1000 py ***
ASCEND, 2018 *	4**.1% vs 3.2%** * any major bleeding	0.3% vs 0.3%	0.7% vs 0.6%
ARRIVE, 2018	**0.30% vs 0.11%** * moderate or severe GI bleeding	0.13% vs 0.18%	NR
Comment:	**Consistent harm**	**No difference**	**Unclear**



Meta-analysis of most recent 4 studies

No significant difference for any outcome other than more major hemorrhage.

Using control event rate of 2%, with RR 1.7, NNH for major hemorrhage is 74 over ~5 years

Using control rate of 1.5% for non-fatal MI, with RR 0.9, NNT for non-fatal MI is 636 over ~5 years

Ebell MH and Moriarty F, manuscript in preparation

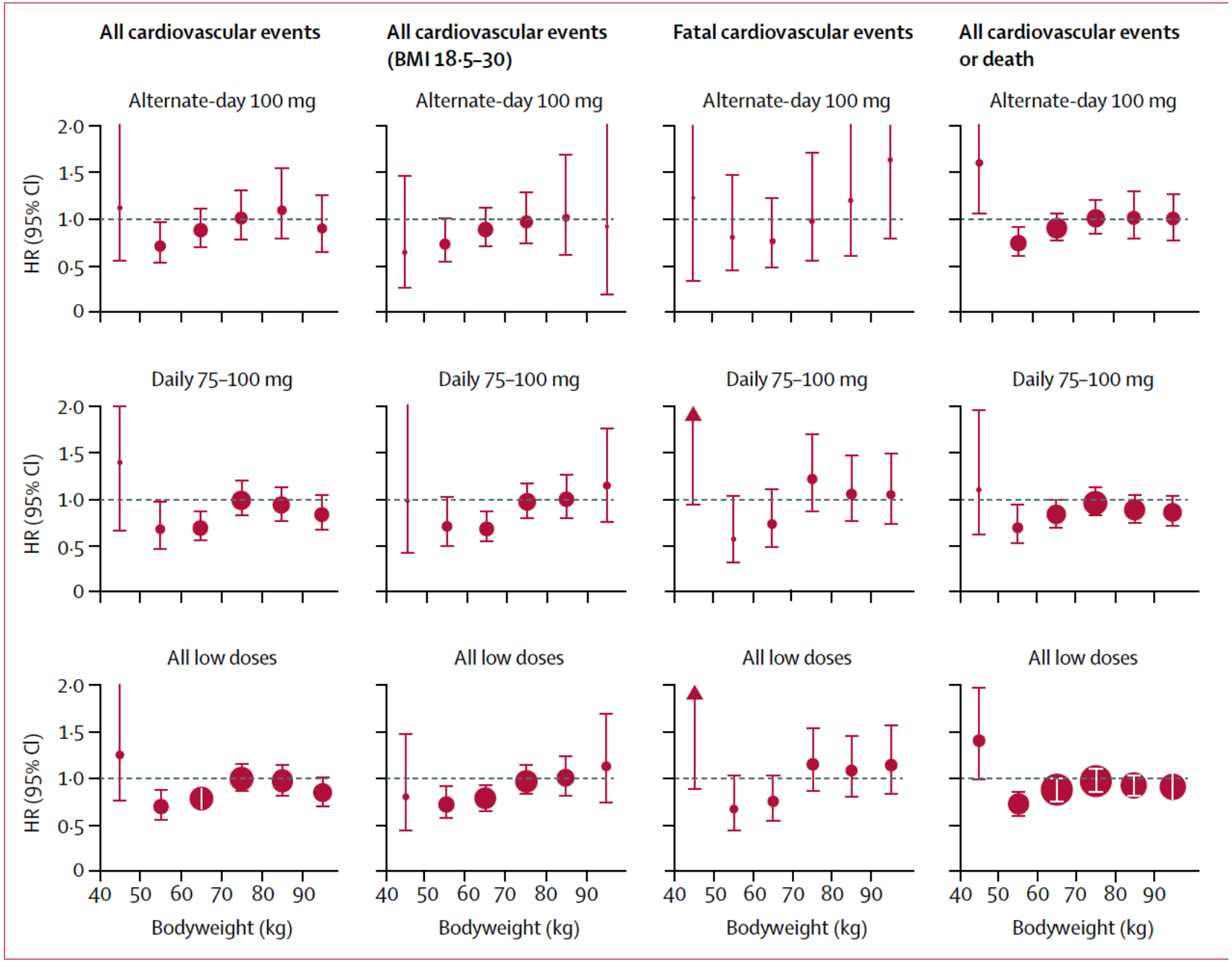


Figure 1: Effect of low-dose aspirin versus control on risks of cardiovascular events, death, and major bleeding according to body

Lower weight is associated with greater benefit, especially less than 70 kg

Un minor peso è associato a maggiori benefici,
in particolare < 70 kg

Lancet 2018; 392: 387–99

Summary

- In the prestatin era, aspirin reduced the likelihood of non-fatal myocardial infarction
- In the modern era, there is no clear benefit (Statins? DM? Less smoking? More obesity?)
- The harms of aspirin have been consistent
- The reduction in cancer mortality only seen in older studies (less cancer screening?)

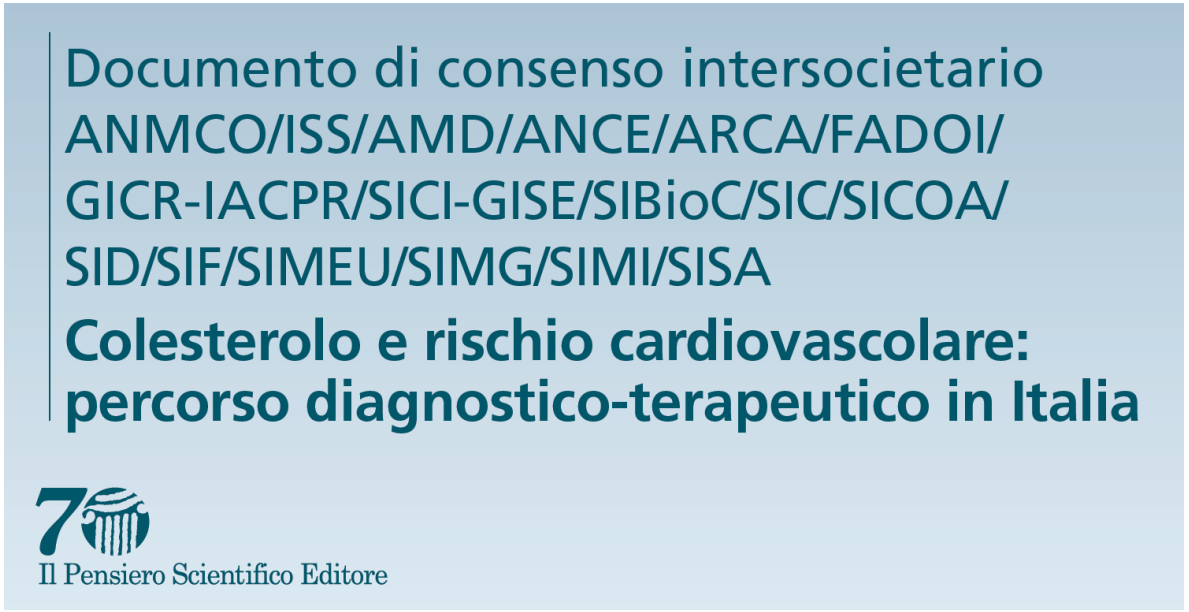
- Nell'era pre-statine l'aspirina riduceva la probabilità di infarto miocardico non fatale
- Nell'era delle statine, non ci sono benefici
- I danni dell'aspirina sono stati costanti
- La riduzione della mortalità per cancro non è chiara

Statins for Primary Prevention in the Elderly

2018 ACC/AHA Guidelines:
Treatment of hyperlipidemia in persons over 75 years

Recommendations for Older Adults Referenced studies that support recommendations are summarized in Online Data Supplements 18 and 19.		
COR	**LOE**	**Recommendations**
IIb	**B-R**	**1. In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable (S4.4.4.1-1–S4.4.4.1-8)**
IIb	**B-R**	**2. In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy (S4.4.4.1-9).**
IIb	**B-R**	**3. In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy (S4.4.4.1-10, S4.4.4.1-11).**

”It may be reasonable…” also means “It may NOT be reasonable…”!



For elderly refers to ESC: “The literature on the therapeutic decision in the elderly is limited and the guidelines of the Scientific Societies are not straightforward…It is necessary to consider that age represents, on the one hand, an important determinant of cardiovascular risk estimation but on the other hand, introduces the evaluation of a possible situation of fragility. The fact that the patient is already following a well-tolerated statin therapy may be a factor favouring the continuation of therapy; in any case, the international guidelines consider the use of less aggressive treatments to be justified.”

Review of the best evidence

Recent RCTs of statins for primary prevention in the elderly

- JUPITER – 70+ years subset (2010)
- PROSPER – 70-82 years subset, 57% primary prevention (2002)
- ALLHAT-LLT – 65-74 and 75+ years subsets (2017)

Individual patient meta-analysis (Cholesterol Treatment Trialists' Collaboration, 2019)

JUPITER Older Adults (Ann intern Med 2010; 152: 488)

- 5695 adults 70 years and older with LDL < 130 mg/dl, CRP >= 2.0 mg/L
- Rosuvastatin 20 mg vs placebo, 2.8 year follow-up

	Rosuvastatin (n=2878)	Placebo (n=2817)	P	NNT/ year
All cause death	1.63/100 py	2.04/100 py	0.09	(244)
MI, stroke, death	2.11/100 py	3.04/100 py	0.001	107
CV death	0.34/100 py	0.41/100 py	0.53	NS
MI	0.27/100 py	0.50/100 py	0.05	435
Stroke	0.35/100 py	0.64/100 py	0.02	345

PROSPER (Lancet 2002; 360: 1623)

- 5804 adults 70 to 82 years with risk factors for CVD; 43% with known CVD, baseline cholesterol 4.0 – 9.0 mmol/L
- Pravastatin 40 mg vs placebo, 3.2 year follow-up
- CV death no different

	Pravastatin (n=2913)	Placebo (n=2891)	P	NNT/ year
All cause death	298 (10.3%)	306 (10.5%)	NS	
Nonfatal MI, non-fatal stroke, or CV death	292 (10.1%)	356 (12.2%)	0.006	154
CV death	135 (4.7%)	157 (5.4%)	0.17	(458)
Non-fatal MI	222 (7.7%)	254 (8.7%)	0.10	(320)
Non-fatal Stroke	116 (4.0%)	119 (4.1%)	0.85	

ALLHAT-LLT 65 – 74 yrs (JAMA IM 2017; 177: 955)

- 2141 adults 65-74 years (mean age 69)
- All had hypertension plus 1 more CV risk factor, mean cholesterol 5.8 mmol/L. Patients with known CVD excluded
- Pravastatin 40 mg vs placebo, 4.7 year follow-up
- No significant differences

	Pravastatin (n=1092)	Usual care (n=1049)	P
All cause death	15.5/600 py	14.2/600 py	0.55
CV death	7.2/600 py	6.8/600 py	0.91
Any MI	8.4/600 py	10.2/600 py	0.29
Any stroke	5.2/600 py	4.7/600 py	0.89

ALLHAT-LLT > 75 yrs (JAMA IM 2017; 177: 955)

- 726 adults > 75 years (mean age 79), all hypertension + 1 CV risk factor, mean cholesterol 5.8 mmol/L. Patients with CVD excluded
- Pravastatin 40 mg vs placebo, 4.7 year follow-up
- Data shown as events/600 py and also events/100 py (estimated)
- No difference between groups

	Pravastatin (n=375)	Usual care (n=351)	Pravastatin (n=375)	Usual care (n=351)	P
All cause death	31/600 py	22.7/600 py	5.2/100 py Higher	3.8/100 py	0.09
CV death	11.2/600 py	10.1/600 py	1.9/100 py	1.7/100 py	0.20
Any MI	9.9/600 py	14.9/600 py	1.7/100 py	2.5/100 py	0.14
Any stroke	9.0/600 py	9.6/600 py	1.5/100 py	1.6/100 py	0.76

Individual Patient Data Meta-analysis

- 27 randomized trials with 174,149 patients
- Divided into 6 age groups:
  - <= 55, 56-60, 61-65, 66-70, 71-75, and > 75 years
- 14,483 patients in > 75 year group

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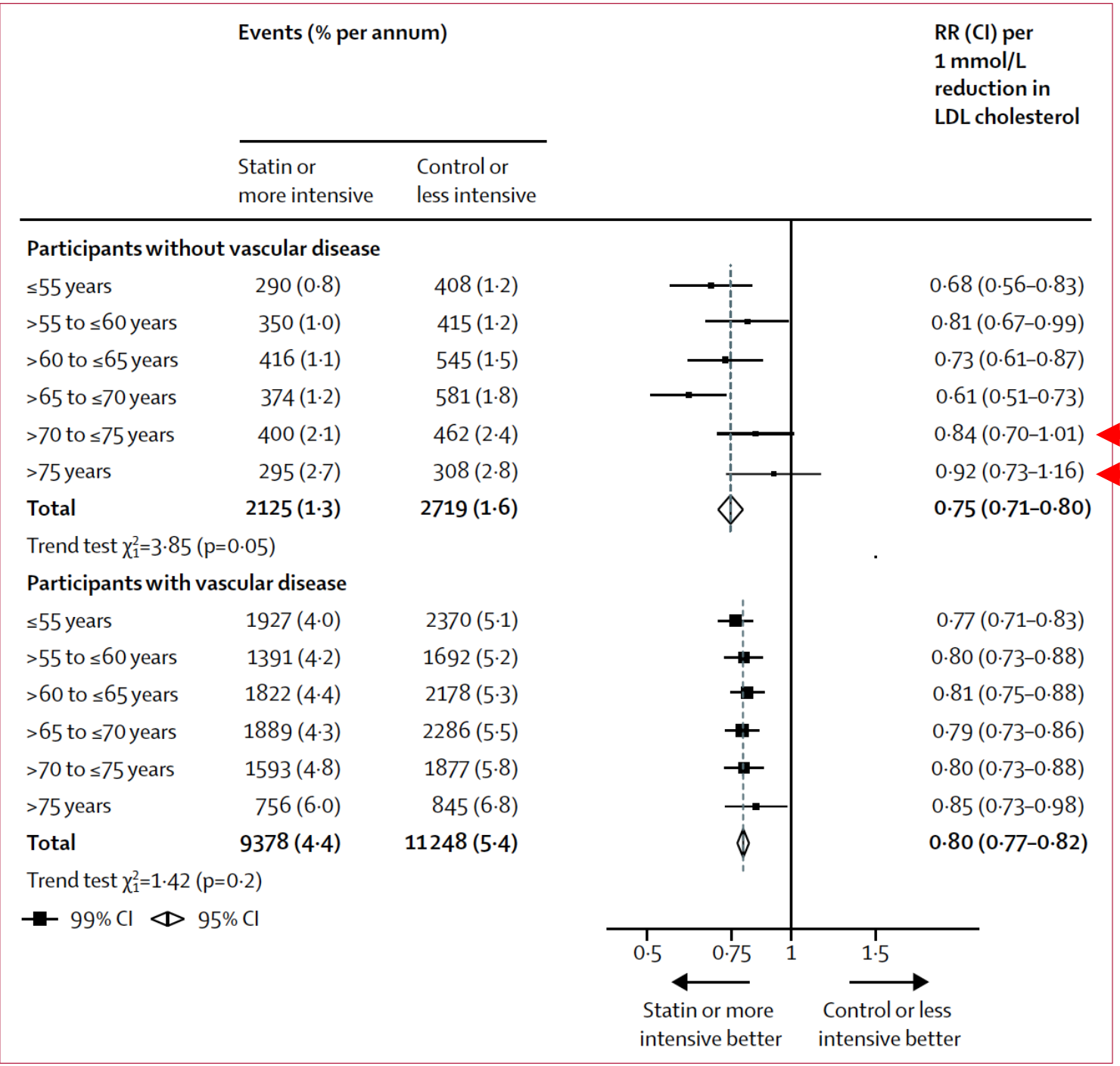
- 27 studi randomizzati con 174.149 pazienti
- 6 gruppi di età
- Il gruppo più vecchio con 14.483 pazienti

Cholesterol Treatment Trialists' Collaboration. Lancet 2019; 393: 407–15



Primary prevention: less benefit after 70 years of age, none after 75 years.

Prevenzione primaria: minori benefici dopo i 70 anni, nessuno dopo 75 anni.

70-75

75+

Secondary prevention: all ages benefit, RR 0.77 – 0.85

Prevenzione secondaria: tutte le età ne traggono beneficio

Cholesterol Treatment Trialists' Collaboration. Lancet 2019; 393: 407–15

Different strategies for different groups of elderly
Diverse strategie per diversi gruppi di anziani

1. **Frail older patients**, including patients with severe dementia or limited patient's life expectancy: consider stopping statin.
2. **Secondary prevention** in patients with a history of cardiovascular disease or events: continue statin
3. **Patients with diabetes** who are older than 75 years: no randomized trial data, but observational studies support continuing statins for all individuals in this group, including patients older than 85 years of age. Continue statin for most.
4. **Primary prevention for healthy adults aged 75 years and older:** since evidence is limited, and the likelihood of benefit is affected by age and risk factors, shared decision making with discussion of uncertainty of the evidence is recommended.

Skolnik N. Reexamining Recommendations for Treatment of Hypercholesterolemia in Older Adults. JAMA 2019; March 11.

Summary of Statins in Older Adults

- For secondary prevention in older patients, statins are effective
- For primary prevention in older patients, benefit is lower after 70 years and none is seen after 75
- For patients doing well on a statin may consider continuing
- Would not start patient > 75 years on a statin for primary prevention.
- Per la prevenzione secondaria nei pazienti più anziani, le statine sono efficaci
- Per la prevenzione primaria nei pazienti più anziani, il beneficio è più basso dopo 70 anni e nessuno è visto dopo i 75 anni
- Per i pazienti che stanno bene con una statina si può prendere in considerazione la prosecuzione
- Non sarebbe indicato nei pazienti > 75 anni l'utilizzo di una statina per la prevenzione primaria.

Omega-3 Fatty Acids for Primary CV Prevention

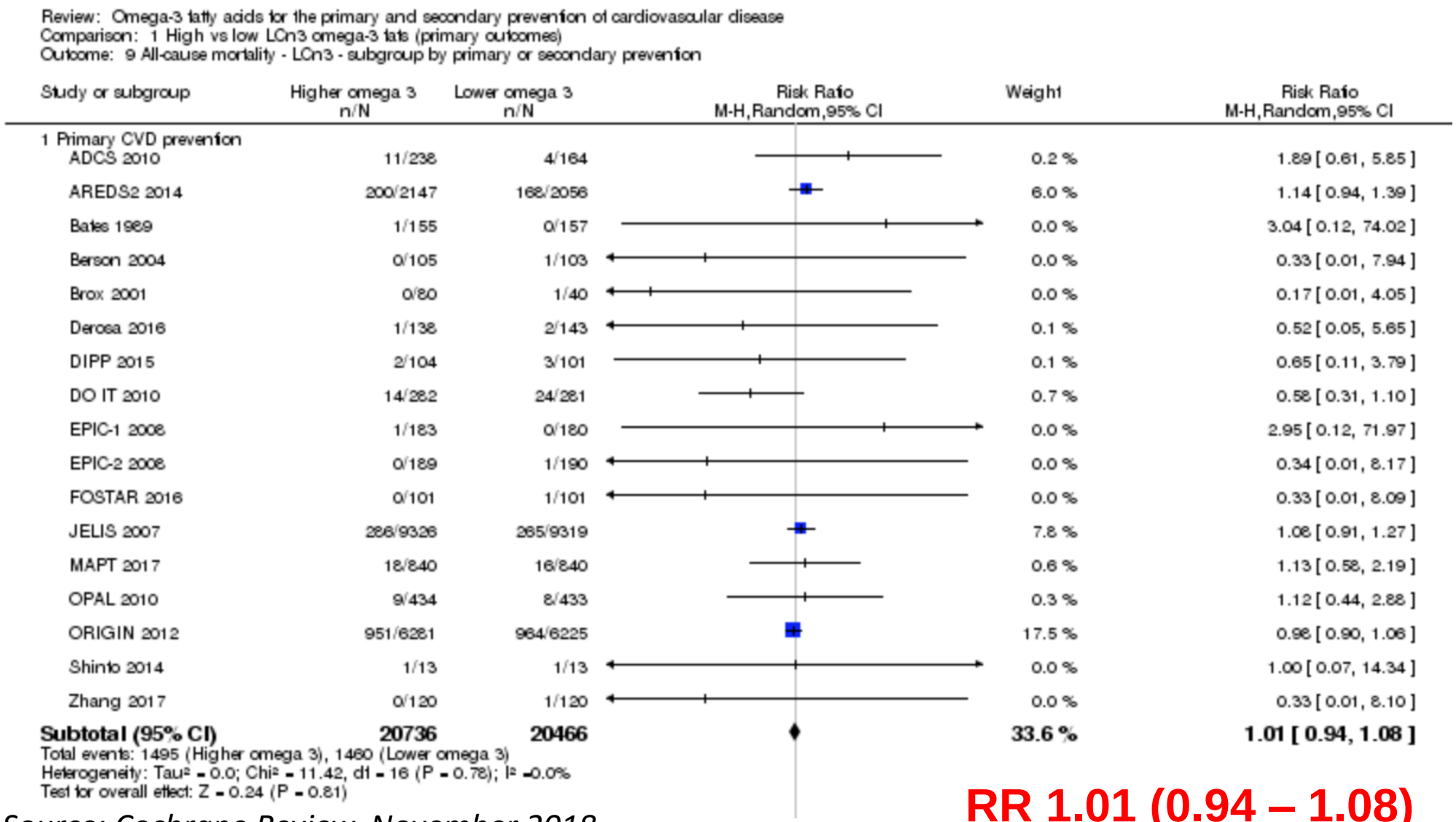
Omega-3 Fatty Acids

Brief review of evidence regarding eicosapentaenoic acid and docosahexaenoic acid (EPA/DHA) for primary prevention: Cochrane review and 2 new studies

Cochrane Review (2018):

- 79 studies, 112,059 patients
- 745 pages long!!!
- Reported primary prevention separately

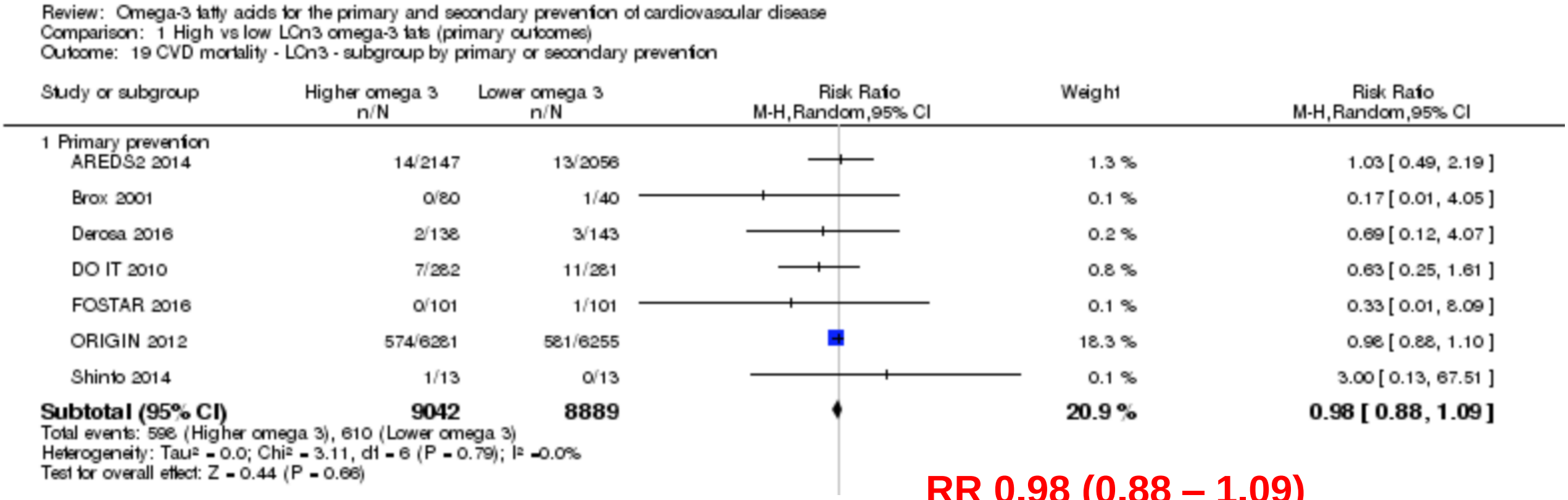
Omega-3 for Primary Prevention: No Change in All Cause Mortality



RR 1.01 (0.94 – 1.08)

Source: Cochrane Review, November 2018

Omega-3 for Primary Prevention: No Change in CV mortality



RR 0.98 (0.88 – 1.09)

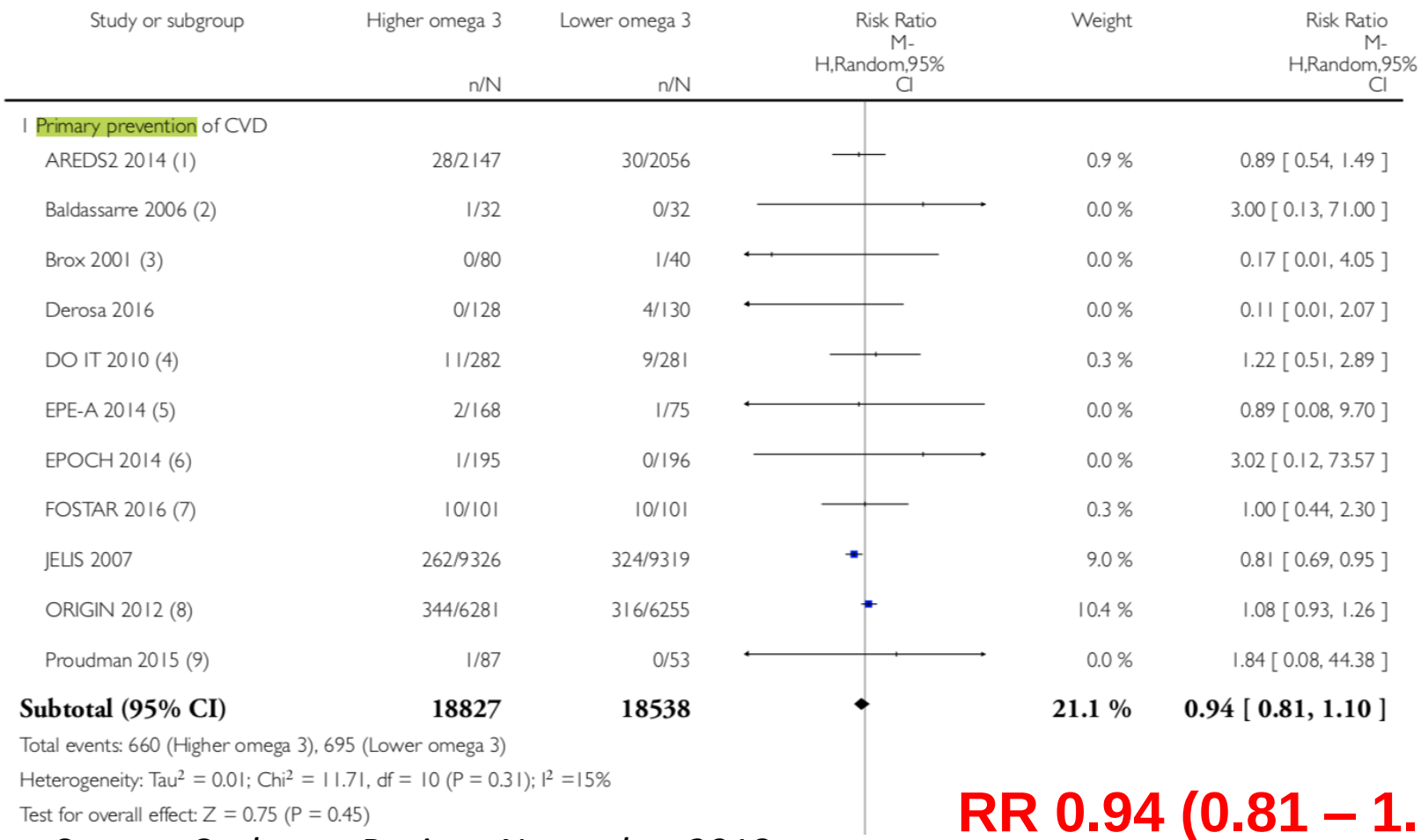
Source: Cochrane Review, November 2018

Omega-3 for Primary Prevention: No Change in CHD Events

Review: Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 1 High vs low LCn3 omega-3 fats (primary outcomes)

Outcome: 51 CHD events - LCn3 - subgroup by primary or secondary prevention



Study or subgroup	Higher omega 3 n/N	Lower omega 3 n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Primary prevention of CVD					
AREDS2 2014 (1)	28/2147	30/2056		0.9 %	0.89 [0.54, 1.49]
Baldassarre 2006 (2)	1/32	0/32		0.0 %	3.00 [0.13, 71.00]
Brox 2001 (3)	0/80	1/40		0.0 %	0.17 [0.01, 4.05]
Derosa 2016	0/128	4/130		0.0 %	0.11 [0.01, 2.07]
DO IT 2010 (4)	11/282	9/281		0.3 %	1.22 [0.51, 2.89]
EPE-A 2014 (5)	2/168	1/75		0.0 %	0.89 [0.08, 9.70]
EPOCH 2014 (6)	1/195	0/196		0.0 %	3.02 [0.12, 73.57]
FOSTAR 2016 (7)	10/101	10/101		0.3 %	1.00 [0.44, 2.30]
JELIS 2007	262/9326	324/9319		9.0 %	0.81 [0.69, 0.95]
ORIGIN 2012 (8)	344/6281	316/6255		10.4 %	1.08 [0.93, 1.26]
Proudman 2015 (9)	1/87	0/53		0.0 %	1.84 [0.08, 44.38]
Subtotal (95% CI)	**18827**	**18538**		**21.1 %**	**0.94 [0.81, 1.10]**

Total events: 660 (Higher omega 3), 695 (Lower omega 3)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 11.71$, df = 10 (P = 0.31); $I^2 = 15\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Source: Cochrane Review, November 2018

RR 0.94 (0.81 – 1.10)

Also no change in:

Stroke: 0.97 (0.86, 1.09)
Arrhythmia: 1.11 (0.97, 1.28)

Figure 3

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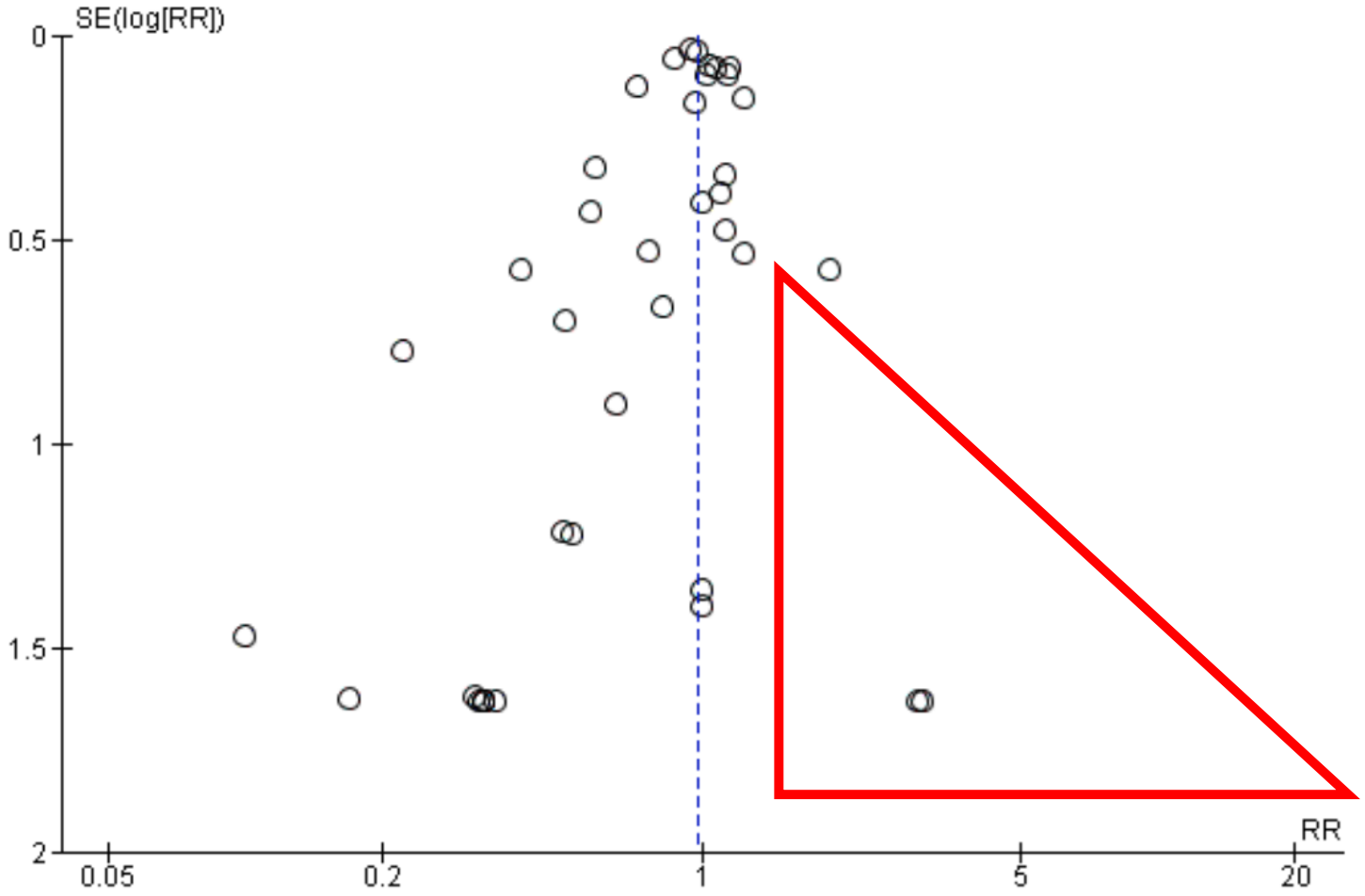


Funnel plot of comparison: 1 High vs low LCn3 omega-3 fats (primary outcomes), outcome: 1.1 Aall-cause mortality (overall) – LCn3.

Evidence of Publication bias

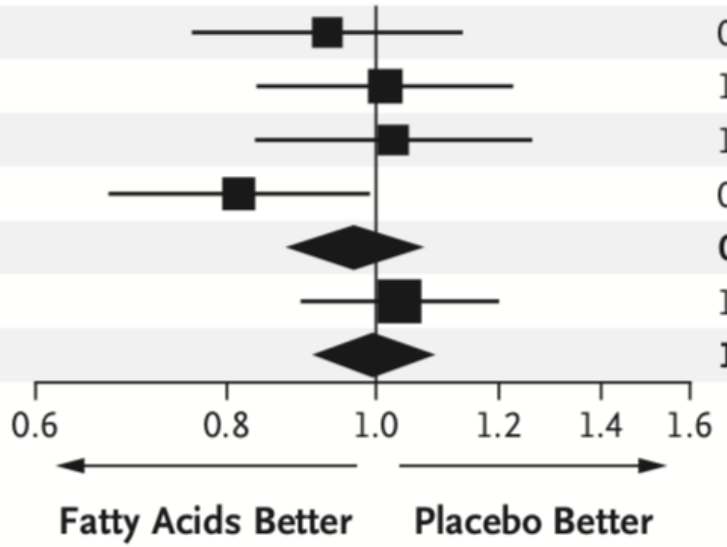
Small negative studies are missing

Source: Cochrane Review 2018

Omega-3 fatty acids for primary prevention in T2DM: The ASCEND trial (2018)

- 15,480 persons randomized to 1 gm omega-3 daily or olive oil
- Mean age 63 years, 94% with type 2 diabetes, no pre-existing vascular disease, mean follow-up 7.4 years
- No benefit for any composite outcome (small decr. vascular death)

Type of Event	Fatty Acids (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)
	no. of patients with event (%)		
Nonfatal myocardial infarction	186 (2.4)	200 (2.6)	0.93 (0.76–1.14)
Nonfatal ischemic stroke	217 (2.8)	214 (2.8)	1.01 (0.84–1.22)
Transient ischemic attack	185 (2.4)	180 (2.3)	1.03 (0.84–1.26)
Vascular death	186 (2.4)	228 (2.9)	0.81 (0.67–0.99)
Serious vascular event	**689 (8.9)**	**712 (9.2)**	**0.97 (0.87–1.08)**
Any revascularization	368 (4.8)	356 (4.6)	1.04 (0.90–1.20)
Serious vascular event or revascularization	**882 (11.4)**	**887 (11.5)**	**1.00 (0.91–1.09)**



N Engl J Med 2018;379:1540-50.

Omega-3 fatty acids for primary prevention: The VITAL trial (2019)

- 25,871 persons randomized to 1 gm omega-3 daily or placebo
- Mean age 67 years, 14% type 2 diabetes, no pre-existing vascular disease, median follow-up 5.3 years

End Point	n–3 Group (N=12,933)	Placebo Group (N=12,938)	Hazard Ratio (95% CI)
	no. of participants with event		
Cardiovascular disease			
Primary end point: major cardiovascular event†	386	419	0.92 (0.80–1.06)
Cardiovascular event in expanded composite end point‡	527	567	0.93 (0.82–1.04)
Total myocardial infarction	145	200	0.72 (0.59–0.90)
Total stroke	148	142	1.04 (0.83–1.31)
Death from cardiovascular causes	142	148	0.96 (0.76–1.21)
Death from cancer	168	173	0.97 (0.79–1.20)
Death from any cause	493	485	1.02 (0.90–1.15)

Only benefit was small reduction in total MI (1.1% vs 1.5%, NNT = 250 over 5 years

Also small reduction in vascular events if low fish consumption

My Interpretation

- In the modern (statin) era, aspirin should not be recommended for primary prevention
- The decision to continue a statin in patients older than 70 years for primary prevention should be individualized; do not initiate a statin for primary prevention over age 75
- Eat fish!

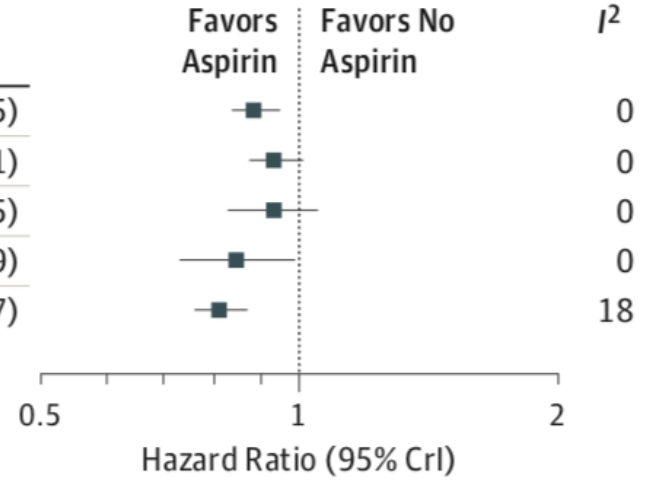
- Nell'era moderna (statine), l'aspirina non dovrebbe essere raccomandata per la prevenzione primaria
- La decisione di continuare una statina in pazienti di età superiore a 70 anni per la prevenzione primaria deve essere individualizzata; non iniziare una statina per la prevenzione primaria oltre i 75 anni
- Mangia pesce!

Grazie!

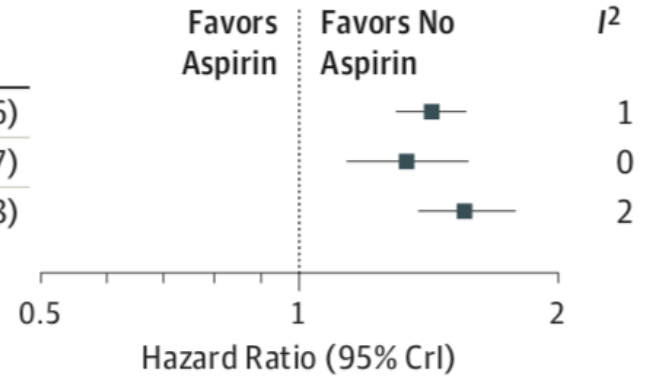
New meta-analysis (JAMA 2019): combined all studies regardless of year, statin vs no statin

Figure 1. Cardiovascular and Bleeding Outcomes in all Participants

Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Composite CV outcome	11	2911	79717	3072	78147	0.38 (0.20 to 0.55)	0.89 (0.84-0.95)
All-cause mortality	13	3622	81623	3588	80057	0.13 (-0.07 to 0.32)	0.94 (0.88-1.01)
CV mortality	13	995	81623	997	80057	0.07 (-0.04 to 0.17)	0.94 (0.83-1.05)
Myocardial infarction	13	1469	81623	1599	80057	0.28 (0.05 to 0.47)	0.85 (0.73-0.99)
Ischemic stroke	10	831	65316	942	63752	0.16 (0.06 to 0.30)	0.81 (0.76-0.87)



Bleeding Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Increase, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Major bleeding	11	1195	74715	834	73143	0.47 (0.34 to 0.62)	1.43 (1.30-1.56)
Intracranial bleeding	12	349	80985	257	79419	0.11 (0.04 to 0.18)	1.34 (1.14-1.57)
Major GI bleeding	10	593	70336	380	70465	0.30 (0.20 to 0.41)	1.56 (1.38-1.78)



JAMA 2019;321(3):277-287