

## La prevenzione primaria

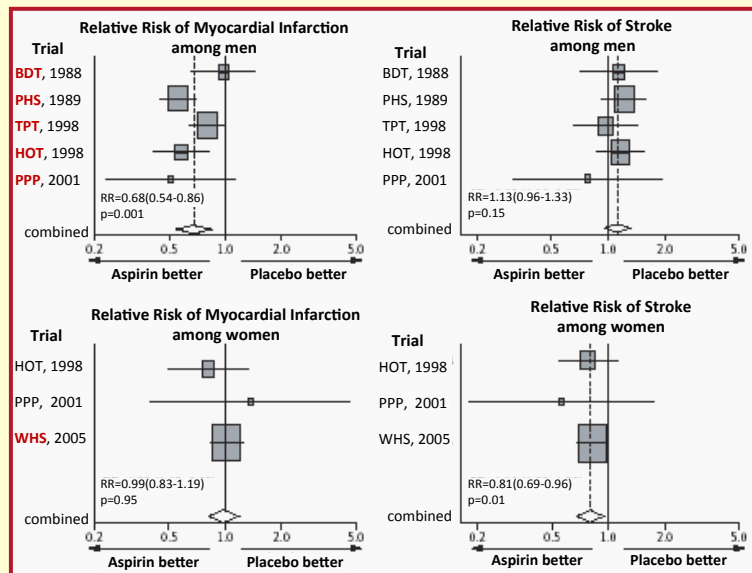
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IV Convegno Anticoagulazione.it  
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## Aspirin in the primary prevention of MI and stroke Metaanalysis of six trials



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Ridker PM, NEJM 2005, 352:1293.

## ASPIRIN IN PRIMARY PREVENTION Recommendations

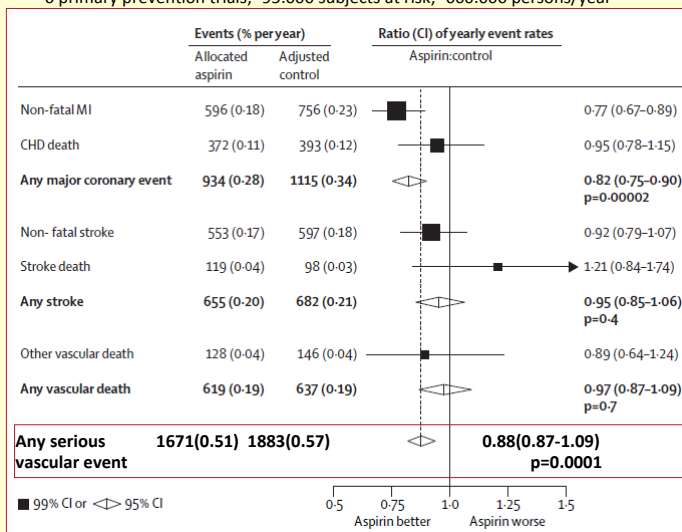
- Use aspirin (and other preventive agents) for everyone over 55 (Wald & Law, BMJ 2003, 326:1419; Elwood et al., BMJ 2005, 330: 1440)
- Encourage men 45 to 79 years and women 55 to 79 years to use aspirin when the potential benefit of a reduction in MI (men) or stroke (women) outweighs the potential harm of an increase in GI hemorrhage (US Preventive Services Task Force - 2009)

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### ASPIRIN IN PRIMARY PREVENTION OF VASCULAR DISEASE:

#### collaborative meta-analysis of individual participants data

-6 primary prevention trials; -95.000 subjects at risk; -660.000 persons/year

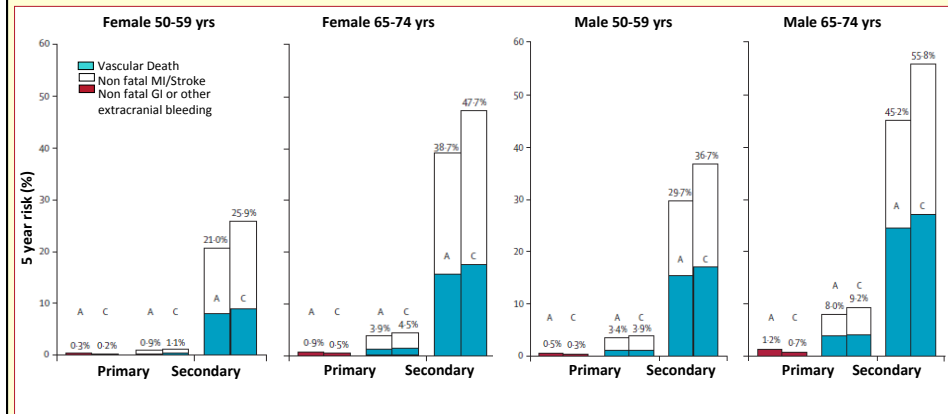


12% relative risk reduction  
 0.07% absolute risk reduction  
 NNT=1429/yr

Antiplatelet Trialists' Collaboration, Lancet 2009, 373: 1849

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## Absolute reduction of events by aspirin in primary and secondary prevention



“... in primary prevention (low risk) absolute reduction of events would be only about twice the absolute increase in bleeding irrespective of age and sex...”

More clinical research is required for patient populations with a moderately increased CV risk

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Antiplatelet Trialists' Collaboration, Lancet 2009, 373: 1849

## Guidelines on aspirin use for primary prevention

- EUROPEAN GUIDELINES ON CARDIOVASCULAR DISEASE PREVENTION IN CLINICAL PRACTICE

(Piepoli MF, Eur Heart J 2016, 37:2315)

Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.

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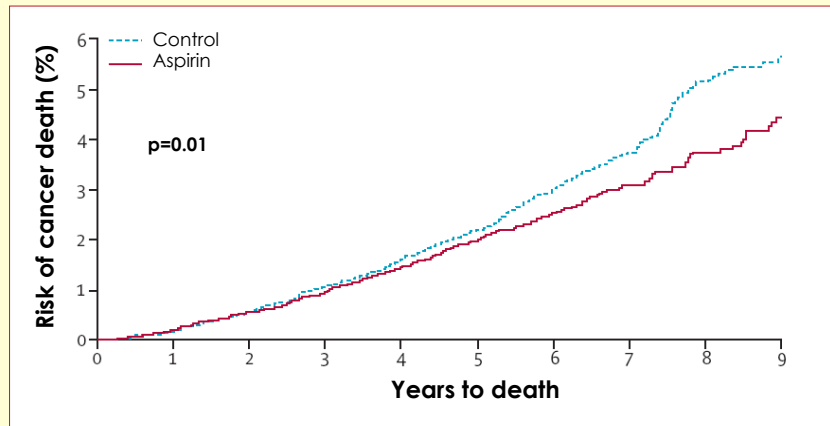
- US PREVENTIVE SERVICES TASK FORCE (USPSTF) RECOMMENDATION STATEMENT

(Bibbins-Domingo K, Ann Intern Med 2016, 164:836)

Population	Adults aged 50 to 59 y with a $\geq 10\%$ 10-y CVD risk	Adults aged 60 to 69 y with a $\geq 10\%$ 10-y CVD risk	Adults younger than 50 y	Adults aged 70 y or older
Recommendation	Initiate low-dose aspirin use. Grade: B	The decision to initiate low-dose aspirin use is an individual one. Grade: C	No recommendation. Grade: I (insufficient evidence)	No recommendation. Grade: I (insufficient evidence)

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## Effect of allocation to aspirin versus control on risk of death due to cancer



*A pooled analysis of 25535 patients in seven trials*

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Rothwell PM et al., Lancet 2011, 377: 31

## Evidence-based clinical practice guidelines ACCP-9th Ed

- **For persons aged 50 years or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B) based on:**

every 10 years treatment

low risk (10 year risk ~5%):	6 fewer MI/1000 pts 4 more major bleeds /1000 pts
moderate risk (10 year risk ~15%):	19 fewer MI/1000 pts 16 more major bleeds /1000 pts
high risk (10 year risk ~25%):	31 fewer MI/1000 pts 22 more major bleeds/1000 pts
in All:	~20 fewer cancer deaths/1000 pts

Vandvik PO et al., Chest 2012, 141:e637

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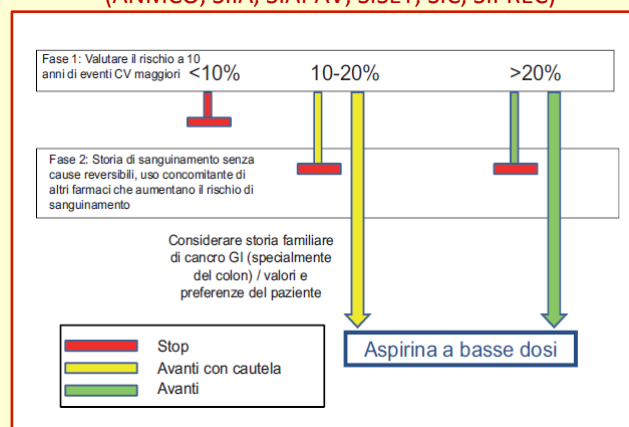
## Limitations to the observations on aspirin effects on cancer mortality

- There is no evidence from prospective, randomized studies that regular aspirin use protects against cancer
- Cancer incidence and mortality were not perspecified end-points of the CV trials included in the metaanalyses on cancer prevention
- Two large primary prevention trials (PHS, WHS) have been excluded from the matanalyses
- Most of the effect occurred after the trials were completed and randomized treatments had been stopped

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## Aspirina a basse dosi nella prevenzione cardiovascolare primaria

Italian intersociety consensus document  
(ANMCO, SIIA, SIAPAV, SISET, SIC, SIPREC)



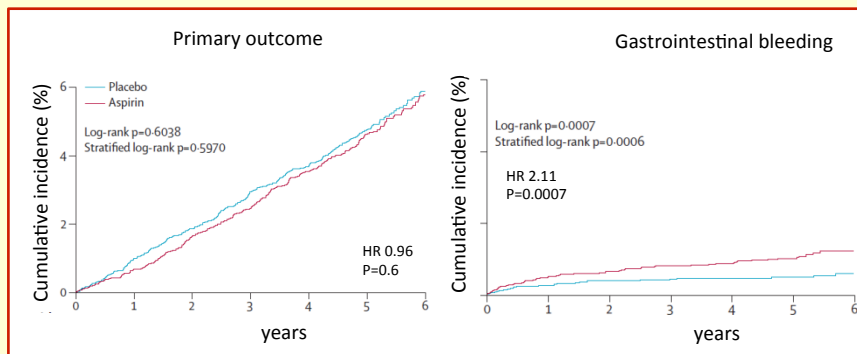
..."area di incertezza a livello di rischio da 10 a 20%/10 anni"...

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Volpe M et al., G Ital Cardiol 2014;15:442

## Aspirin to reduce risk of vascular events in patients at moderate risk

### The ARRIVE Trial



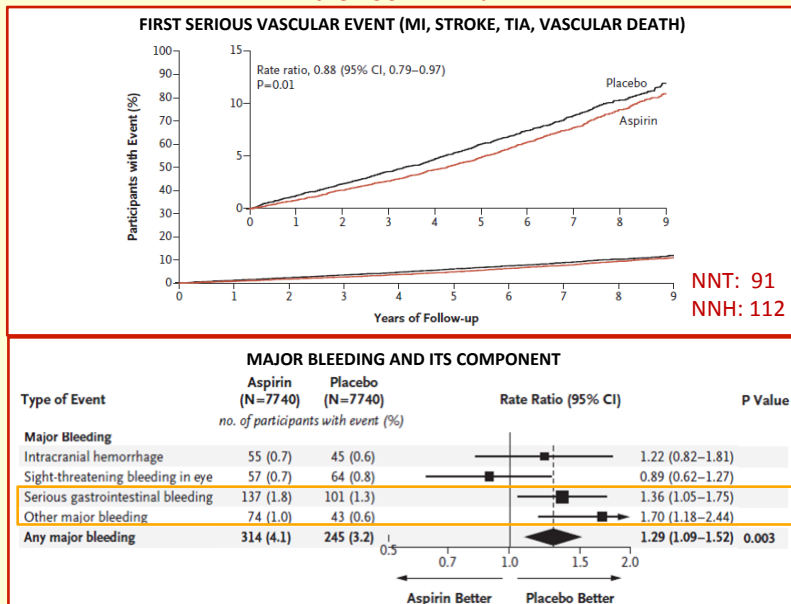
-12,546 subjects at moderate risk (10-20%/10yr)  
-median follow-up=60 months  
-lower than anticipated event rate: expansion of primary end-point (UA, TIA), extended follow-up

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Gaziano JM et al., Lancet 2018; 392: 1036

## Effect of aspirin for primary prevention in persons with diabetes

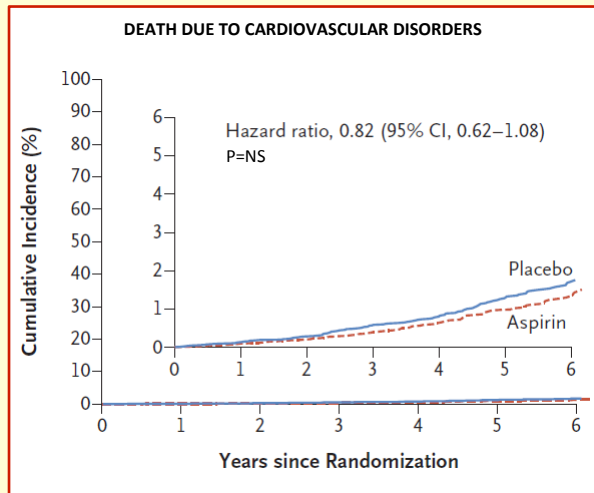
### the ASCEND Trial



-15,480 patients with DM  
-mean follow-up: 7.4 years

The ASCEND Study Collaborative Group, N Engl J Med 2018;379:1529

## Effect of aspirin on mortality in the healthy elderly the ASPREE Trial



-death from any cause: HR 1.14 (1.01-1.29): 1.6 excess deaths per 1000 person/years in the aspirin group

-19,114 subjects 70 years of age or older  
-mean follow-up: 4.7 years

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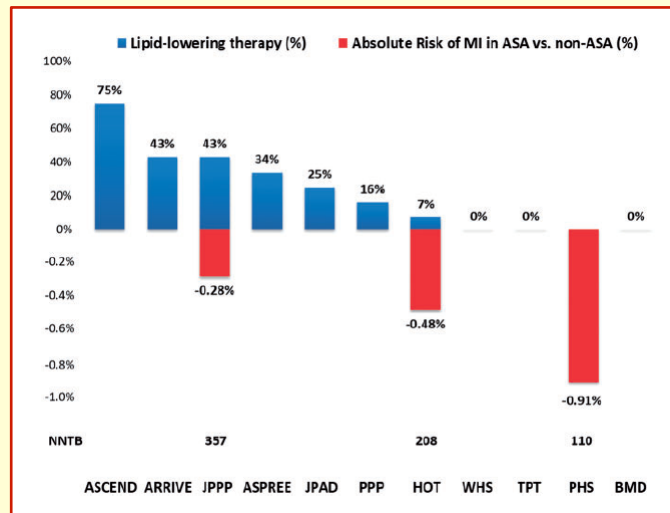
McNeil JJ et al., N Engl J Med 2018; 379:1519

## Recent, large primary prevention trials with aspirin Incidence of MACE in the placebo group

Trial	Type of patients	10 year incidence
ARRIVE	Moderate CV risk	8.9%
ASCEND	T2DM	11.4%
ASPREE	>70 years old	11.1% (total mortality)

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## Concomitant use of statins and prevention of MI by aspirin in primary prevention trials



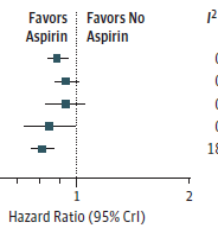
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Valgimigli M et al., Eur Heart J 2018; ePub

## Aspirin for primary prevention a systematic review and meta-analysis

### CARDIOVASCULAR OUTCOMES

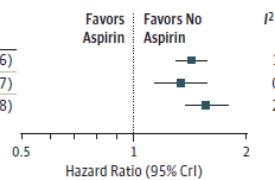
Outcome	HR (95% CrI)
Composite CV outcome	0.89 (0.84-0.95)
All-cause mortality	0.94 (0.88-1.01)
CV mortality	0.94 (0.83-1.05)
Myocardial infarction	0.85 (0.73-0.99)
Ischemic stroke	0.81 (0.76-0.87)



**NNT: 265**  
**NNH: 210**  
**CV RISK: 9.2%/10 yr**

### BLEEDING OUTCOMES

Outcome	HR (95% CrI)
Major bleeding	1.43 (1.30-1.56)
Intracranial bleeding	1.34 (1.14-1.57)
Major GI bleeding	1.56 (1.38-1.78)



-13 primary prevention trials  
-164,225 participants  
-1,050,511 participant/years

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Zheng SL et al., JAMA 2019, 321:277



## Bleeding Risks With Aspirin Use for Primary Prevention in Adults

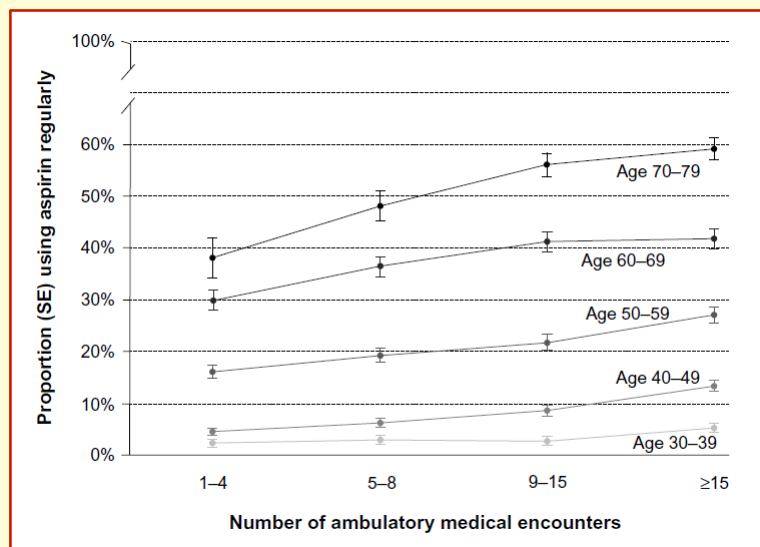
### Rate ratios for bleeding among different subgroups

Baseline Characteristic	Adjusted Incidence Rate Ratio (95% CI)		
	Major GI or Extracranial Bleeding*	Hemorrhagic Stroke†	Hospitalization for Major Bleeding Event‡
<b>Age (per decade)</b>	<b>2.15(1.93-2.39)</b>	<b>1.59(1.33-1.90)</b>	<b>1.05(1.05-1.05)</b>
Diabetes (yes vs. no)	1.55 (1.13-2.14)	1.74 (0.95-3.17)	1.36 (1.28-1.44)
Mean BP (per 20 mm Hg)	1.32 (1.09-1.58)	2.18 (1.62-2.87)	
BMI (per 5 kg/m <sup>2</sup> ):	1.24 (1.13-1.35)	0.85 (0.71-1.02)	
PPI	-	-	0.84 (0.80-0.88)

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Whitlock EP et al., Ann Intern Med 2016, 164: 826

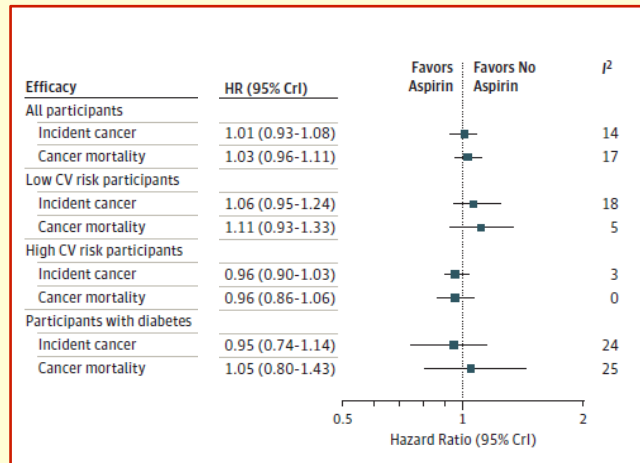
## Inappropriate aspirin use for primary prevention of cardiovascular disease in the USA



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Van Wormer JJ et al., Clin Epidemiol 2014;6:433

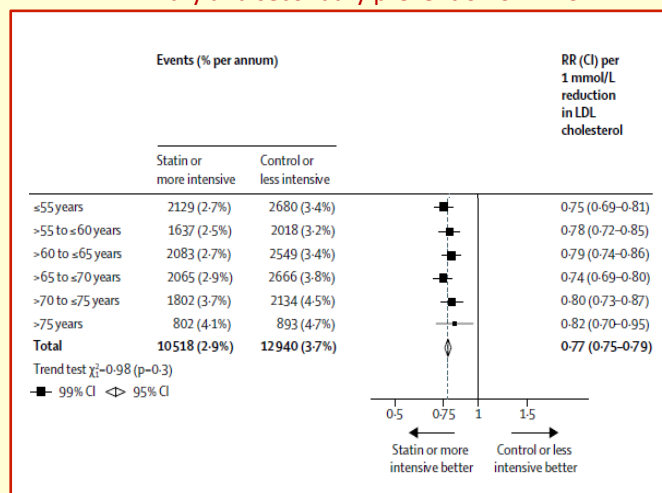
## Aspirin for primary prevention a systematic review and meta-analysis Exploration cancer outcomes



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Zheng SL et al., JAMA 2019, 321:277

## Efficacy of statin therapy in older people Primary and secondary prevention of MACE



...statin therapy produces significant reduction in MACE irrespective of age,  
but less direct evidence of benefit in primary prevention...

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Cholest Treatm Trial, Lancet 2019; 393:407

## Conclusions

- The recent large primary prevention trials have failed to explore the grey area of intermediate cardiovascular risk
- In primary prevention aspirin is of uncertain net value, as the reduction of CV events is largely balanced by an increase of major bleeds
- Aspirin may be considered on an individual basis in patients at high CV risk and low bleeding risk
- The benefit of aspirin in cancer prevention requires confirmation by prospective studies and the long term follow-up of recently completed studies
- Correction of risk factors, and maybe statins, are preferred to aspirin in primary prevention

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