

Draft editorial for Annals of Internal Medicine

Aspirin for disease prevention – public policy or personal choice?

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988 (limit 1000) words + Table + references

After a mammoth review of the available evidence, in this issue the United States Preventive Services Task Force (USPSTF) outlines its new recommendations on the use of aspirin for the primary prevention of cardiovascular disease and colorectal cancer.¹ It recommends (grade B) low-dose aspirin in individuals of both sexes who are aged 50-59, with predicted risk of a myocardial infarction or stroke of at least 10% over 10 years, who do not have an increased risk of bleeding, and who are willing to take aspirin for at least 10 years. For the analogous group aged 60-69, the recommendation for aspirin is 'optional' (grade C). The group aged 50-59 at increased cardiovascular risk is a relatively small one: it can be estimated (from NHANES data ² - see Table 13 of online supplement) at around 14% of US men and 4% of women (although the 'optional' group aged 60-69 would be much larger – 77% and 22% respectively).

In order to assess the value of this new work it is worth considering what new evidence has emerged since the previous recommendations in 2009. In that year, the Antithrombotic Trialists' (ATT) Collaboration reported a collaborative meta-analysis of individual data from 6 primary prevention trials among 95,000 people, which included a detailed assessment of how the cardiovascular benefits and bleeding risks compared in different prognostic groups.³ The new work from USPSTF considers a further 5 primary prevention trials among around 25,000 people, of whom the majority were low-risk. The relative risk estimates for nonfatal myocardial infarction (22% reduction), stroke (no significant effect), mortality (no significant effect), and serious gastrointestinal bleeding (58% increase) were almost identical to those reported by the ATT. Perhaps not surprisingly, therefore, the ATT and USPSTF are aligned in the finding that aspirin yields small cardiovascular benefits (ie, a reduction in nonfatal myocardial infarction) and small bleeding risks (serious gastrointestinal bleeding, and much less commonly, haemorrhagic stroke), and that the 'net'

benefit (cardiovascular benefit minus bleeding risk) of about 1-2 fewer events per 1000 treated per year is also small. The ATT analysis showed that the absolute risks of cardiovascular disease and of bleeding are positively correlated, so the net benefits of aspirin are likely to remain small even among people with several risk factors for cardiovascular disease. Given that risk factors for cardiovascular disease and bleeding overlap substantially, it seems unlikely that meta-analyses that include new trials, even the ongoing trials, will yield well-defined groups in whom cardiovascular and bleeding risks are uncoupled.

The judgement about the value of aspirin is, however, altered by the emergence since 2009 of new evidence that daily aspirin might prevent colorectal cancer (and possibly other types of cancer).^{4,5} Long-term follow-up information from eight trials of a daily aspirin regimen indicated that such treatment may reduce the risk of colorectal cancer incidence and mortality, with benefits emerging within about 5-10 years of commencing aspirin.⁴ But many uncertainties about the effects of aspirin on cancer remain. The largest primary prevention trials of aspirin assessed alternate day regimens. Whilst recent long-term follow-up from the Women's Health Study suggested that aspirin 100mg on alternate days reduced the risk of colorectal cancer, with benefits emerging 10 years after commencing aspirin,⁶ the results of further follow-up of the Physicians' Health Study (which previously reported no effect of aspirin 325mg alternate days on colorectal cancer after 12 years' follow-up⁷) are unknown. The magnitude of the effect of aspirin on overall cancer risk, the chronicity of any effect, and how the absolute effects of aspirin vary among different types of people, all remain to be determined reliably. Updated analyses of data from trials of aspirin are currently in progress under the auspices of the Non-vascular outcomes on Aspirin (NoVA) Collaboration.⁴

Whilst the work of the NoVA Collaboration will go some way towards addressing these uncertainties, it seems more likely that we will have to wait for completion of some of the large ongoing trials before the effects of aspirin on cancer among people at low risk of cardiovascular disease are really well understood (Table). Over the next few years, ongoing primary prevention trials of aspirin in people

with diabetes (ACCEPT-D, ASCEND) people at elevated cardiovascular risk (ARRIVE, TIPS-3), and persons 70 years or over (ASPREE) will report their (within-trial) findings, with over 3500 incident cancers (with perhaps 10% of these colorectal). They will therefore substantially increase the currently available information on cancer. Over the next decade, depending on whether those trials can obtain reliable post-trial follow-up of incident cancers and cancer deaths, increasingly reliable estimation of the long-term effects on cancer of about 5 years' of aspirin in different categories of people will become possible.

The incidence rates of cancers in the completed trials will vary substantially depending on geographical location and the era in which they occurred (since historically cancer rates have varied with time). In comparison, however, the proportional effects of a given aspirin regimen (eg, low-dose daily aspirin) should be relatively stable, so the absolute effects of aspirin on cancer will be estimable by applying the relevant statistics from a meta-analysis of the trials to contemporary rates in any given region. Future models might consider the possibility that aspirin would be best directed at healthy individuals with above average risk of cancer (eg, those who are overweight). It will be important, moreover, to incorporate contemporary estimates of event rates for cardiovascular disease, which are falling in many regions, and rates of gastrointestinal bleeding, which are also falling (perhaps in part due to H pylori eradication and wider use of proton-pump inhibitors).

In summary, the evidence from trials does not yet seem to merit a general recommendation for lifelong aspirin in any specific low-risk group. In my view, it would be better not to rush to judgement with inadequate data, but instead encourage completion (and long-term follow-up) of the outstanding trials so that the quality of the evidence in future years provides a firm foundation for public policy.

Table: Ongoing randomized trials of aspirin vs placebo in low-risk populations providing information on cancer outcomes

Study	Regimen(s)	Treatment duration	Sample size (actual or target)	Recruitment complete	Eligibility	Primary endpoint	Estimated total of all cancers	End date (estimated)
ACCEPT-D	A100 vs open control; simvastatin for all	5 y	5170	Y	Diabetes, no CVD	CV death, non-fatal stroke, nonfatal MI, other CV hospitalisation	~300	Unknown (completed 2015)
ARRIVE	A100 enteric coated vs P	5y	12,000	Y	10-20% estimated 10y risk of CHD	MI, stroke, CV death, unstable angina, TIA	~800	2016
ASPREE	A100 vs P	5 y	19,000	Y	Elderly, no diabetes or CVD	Death, dementia or significant disability	~1000	2018
ASCEND	A100 vs P (ω 3FA vs P)	7.5 y	15,500	Y	Diabetes, no CVD	MI, stroke or TIA, or CV death	~1400 in trial (then more in registry follow-up)	2018
TIPS-3	A75	5y	5000	N	No CVD, elevated risk	CV events and cancer	NA	2020

References

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