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A PERSPECTIVE ON THE WOMEN'S HEALTH STUDY

Aspirin prevents stroke but not MI in women; Vitamin E has no effect on CV disease or cancer

■ ABSTRACT

Low-dose aspirin taken every other day helps prevent stroke in women aged 45 years and older, but does not prevent a first myocardial infarction (MI) or cardiovascular death among healthy women. Women receive no benefit from alternate-day vitamin E in the primary prevention of cardiovascular disease or cancer. These were the findings of the Women's Health Study, in which investigators followed 39,876 female health professionals over 10 years. The women were randomized to receive either 100 mg of aspirin or a placebo tablet every other day; they were also randomized to take 600 IU of vitamin E or a placebo capsule on the intervening days. No statistically significant differences were seen between the aspirin and placebo groups in the primary cardiovascular end point, which was the combined number of nonfatal MIs, nonfatal strokes, and cardiovascular deaths. Analysis of secondary cardiovascular end points revealed that aspirin use was associated with no significant effect on the number of total MIs, fatal MIs, and nonfatal MIs, and a nonsignificant decrease in cardiovascular mortality. However, aspirin users did experience significantly fewer strokes, in particular ischemic strokes. Vitamin E had very little impact on the primary prevention of both cardiovascular events and cancer.

LONG-TERM LOW-DOSE ASPIRIN protects women against a first stroke, but it exerts no prophylactic effect against myocardial infarction (MI) or death from cardiovascular causes.¹ Vitamin E (alpha tocopherol) does not protect women from stroke, MI, or cancer.²

These were the major findings of the Women's Health Study (WHS), a randomized, placebo-controlled, 10-year trial that included almost 40,000 women aged 45 years and older. The WHS data do not support the routine use of either aspirin or vitamin E in women for purposes of primary prevention.

Although subgroup analyses revealed that one cohort—women aged 65 years and older—did derive significant protective benefits from both aspirin and vitamin E, the WHS researchers declined to issue a blanket recommendation to routinely use these agents in older women, saying that such a decision must be made on an individual basis after consideration of each patient's risk factors and a thorough risk/benefit analysis.

This article reviews the substantial amount of morbidity and mortality data obtained during the WHS and discusses their implications for public health and everyday clinical practice.

■ RATIONALE FOR THE WOMEN'S HEALTH STUDY

Rationale for studying women only

The purpose of this study was to fill a major void in our knowledge of the primary prevention of cardiovascular events in women. Even though cardiovascular disease is the leading cause of death among women, just as it is

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among men, the vast majority of published trial data concern men. For example, prior to the publication of the WHS, five randomized trials of aspirin in the primary prevention of cardiovascular events had been reported.³⁻⁷ Three of these trials³⁻⁵ had involved men exclusively, and in the other two,^{6,7} fewer than 180 of 2,402 cardiovascular events occurred in women. As a result, recommendations for women are based on a limited amount of direct data.⁸⁻¹⁰

Another reason that such a study in women is desirable is that salicylate metabolism in women might be different from that in men.¹¹ Moreover, questions persist regarding the cardiovascular response to hormone replacement therapy.¹² Finally, there are sex-specific issues concerning the risk of stroke, particularly hemorrhagic stroke.¹³

Rationale for using aspirin

Aspirin irreversibly acetylates the active site of cyclooxygenase that is required for the production of thromboxane A₂, a powerful promoter of platelet aggregation. The inhibition of platelet aggregation lasts for the entire life of the platelet. A number of trials^{3-7,14} have shown that aspirin significantly reduces the risk of MI, but the data on stroke and overall cardiovascular risk remain inconclusive.

Rationale for using vitamin E

The hypothesis that antioxidants reduce the risk of cardiovascular events and cancer has been of great interest in recent years.

Cardiovascular events. Vitamin E has antioxidant properties that can inhibit the oxidation of low-density lipoprotein in plasma.¹⁵ It can prevent tissue damage by trapping reactive oxygen and nitrogen species. Some, but not all, studies have shown that vitamin E can retard the progression of atherosclerosis.¹⁶ In several observational studies, vitamin E supplementation was found to have positive effects on the prevention of cardiovascular disease¹⁷⁻¹⁹ and on ischemic heart disease survival.²⁰ However, there were no data from randomized trials of vitamin E for primary prevention.

Cancer. Some observational studies²¹ found that antioxidants were associated with lower rates of cancer, but randomized, controlled trials^{22,23} of vitamin E have not sup-

ported those observations. In fact, one meta-analysis suggested that high-dose vitamin E might actually increase all-cause mortality.²⁴ Some trials have suggested that vitamin E may lower the risk of prostate cancer, and a large trial is currently being conducted to evaluate this possibility.

DESIGN

Between September 1992 and May 1995, we sent letters of invitation to 1.7 million female health professionals. More than 450,000 of them returned baseline questionnaires, and just over 65,000 entered a preliminary 3-month placebo run-in phase designed to identify those women who would be likely to comply with the demands of a long-term study. Upon completion of the run-in phase, 39,876 women were deemed eligible to continue the study. Among the inclusion criteria were age 45 or older at study entry; no history of coronary heart disease, cerebrovascular disease, cancer (other than nonmelanoma skin cancer), or other major chronic illness; and no current use of or contraindication to the study agents.

The 39,876 participants (mean age 54.6 years) were randomized in a 2-by-2 factorial design; women were assigned to receive either aspirin (n = 19,934) or aspirin placebo (n = 19,942) and randomized again to receive either vitamin E (n = 19,937) or vitamin E placebo (n = 19,939). In effect, the WHS was made up of four groups: aspirin and vitamin E, aspirin and vitamin E placebo, vitamin E and aspirin placebo, and two placebos.

The primary cardiovascular end point was the combined total of major events: nonfatal MI, nonfatal stroke, and cardiovascular death. Secondary end points included individual events: fatal or nonfatal MI, fatal or nonfatal stroke, ischemic stroke, hemorrhagic stroke, and cardiovascular death. The primary cancer end point was the development of any invasive cancer (other than nonmelanoma skin cancer), and the secondary end points were occurrences of the major site-specific cancers: breast, lung, and colon.

Baseline characteristics in the four groups were similar. The entire study population was quite healthy; according to the Framingham

Until now, most of the data on primary prevention of cardiovascular disease was from men

**TABLE 1****Women's Health Study data: Effects of aspirin**

END POINT	NO. OF EVENTS		RELATIVE RISK		P
	ASPIRIN (N=19,934)	PLACEBO (N=19,942)	(95% CI)		VALUE
Major cardiovascular events*	477	522	0.91 (0.80–1.03)		.13
Stroke	221	266	0.83 (0.69–0.99)		.04
Ischemic	170	221	0.76 (0.63–0.93)		.009
Hemorrhagic	51	41	1.24 (0.82–1.87)		.31
Fatal	23	22	1.04 (0.58–1.86)		.90
Nonfatal	198	244	0.81 (0.67–0.97)		.02
Myocardial infarction	198	193	1.02 (0.84–1.25)		.83
Fatal	14	12	1.16 (0.54–2.51)		.70
Nonfatal	184	181	1.01 (0.83–1.24)		.90
Death from cardiovascular causes	120	126	0.95 (0.74–1.22)		.68
Transient ischemic attack	186	238	0.78 (0.64–0.94)		.01
Coronary revascularization	389	374	1.04 (0.90–1.20)		.61
Death from any cause	609	642	0.95 (0.85–1.06)		.32

CI confidence interval

*Major cardiovascular events were defined as nonfatal myocardial infarctions, nonfatal strokes, or death from cardiovascular causes.

FROM RIDKER PM, COOK NR, LEE I-M, ET AL. A RANDOMIZED TRIAL OF LOW-DOSE ASPIRIN IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN. N ENGL J MED 2005; 352:1293–1304. COPYRIGHT© 2005 MASSACHUSETTS MEDICAL SOCIETY. ALL RIGHTS RESERVED.

risk stratification system, 84.5% of them had a less-than-5% risk of developing coronary heart disease over the next 10 years, and only 4.0% had a 10% or higher risk. With regard to other risk factors, 10.3% were 65 years of age or older, 13.1% were cigarette smokers, 18.2% had a body mass index of 30 or more, 54.4% were postmenopausal, 25.9% were hypertensive, 29.5% were hyperlipidemic, 2.6% were diabetic, and 12.9% had a parental history of MI prior to age 60 years. All told, only 23.8% of the participants had two or more cardiovascular risk factors.

Participants were mailed their assigned white pills (aspirin 100 mg or placebo) and amber capsules (vitamin E 600 IU or placebo) in calendar packs once a year. They were instructed to take the pills and capsules on alternate days without skipping any days. Participants completed questionnaires every 6 months during the first year and once yearly thereafter to report compliance and any occurrence of study end points and adverse

effects. We attempted to confirm the occurrence of every reported study end point and were successful in more than 97% of cases. We included only confirmed reports in our data analysis. All analyses were performed on an intention-to-treat basis. The study was closed on March 31, 2004. The mean duration of the trial was 10.1 years (range 8.2 to 10.9 years).

RESULTS

Cardiovascular events

Aspirin vs placebo. With respect to the primary end point, 999 major cardiovascular events were confirmed—477 in the aspirin group (47.7%) and 522 in the placebo group (52.3%), which translated into a nonsignificant 9% reduction in risk (TABLE 1).

A large number of strokes were reported—221 (45.4%) in the aspirin group and 266 (54.6%) in the placebo group. Aspirin use significantly lowered the incidence of total stroke (–17%), ischemic stroke (–24%), and

Aspirin significantly lowered the incidence of total, ischemic, and nonfatal stroke

TABLE 2

Women's Health Study data: Lack of effect of vitamin E

END POINT	NO. OF EVENTS VITAMIN E (N=19,937)	NO. OF EVENTS PLACEBO (N=19,939)	RELATIVE RISK (95% CI)	P VALUE
Major cardiovascular events*	482	517	0.93 (0.82–1.05)	.26
Myocardial infarction	196	195	1.01 (0.82–1.23)	.96
Nonfatal	184	181	1.02 (0.83–1.25)	.87
Fatal	12	14	0.86 (0.40–1.85)	.70
Stroke	241	246	0.98 (0.82–1.17)	.82
Nonfatal	220	222	0.99 (0.82–1.19)	.93
Fatal	21	24	0.88 (0.49–1.57)	.66
Ischemic†	194	197	0.99 (0.81–1.20)	.88
Hemorrhagic†	44	48	0.92 (0.61–1.38)	.68
Cardiovascular death	106	140	0.76 (0.59–0.98)	.03
Total invasive cancer	1,437	1,428	1.01 (0.94–1.08)	.87
Breast	616	614	1.00 (0.90–1.12)	.95
Lung	107	98	1.09 (0.83–1.44)	.52
Colon	107	107	1.00 (0.77–1.31)	.99
Cancer death	308	275	1.12 (0.95–1.32)	.17
Total mortality	636	615	1.04 (0.93–1.16)	.53

CI confidence interval

*Defined as a composite end point comprising the first of any of these events: nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

†Stroke type was not known for 3 women in the vitamin E group and 1 in the placebo group.

FROM LEE I-M, COOK NR, GAZIANO JM, ET AL: VITAMIN E IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE AND CANCER. THE WOMEN'S HEALTH STUDY: A RANDOMIZED CONTROLLED TRIAL. JAMA 2005; 294:56–65.

Women older than 65 got a significant benefit from aspirin for cardioprotection

nonfatal stroke (–19%). The differences between the aspirin and placebo groups in terms of total and ischemic stroke became evident early on and continued throughout the study. As expected, the aspirin group experienced a 24% increase in the incidence of hemorrhagic stroke, but the difference was not statistically significant because of the small number of cases.

Of the 391 MIs that were confirmed throughout the study, 198 (50.6%) occurred in the aspirin group and 193 (49.4%) in the placebo group. Aspirin had no statistically significant impact on the total number of MIs or the number of fatal and nonfatal MIs that occurred during any point during the study.

Additional analyses revealed that aspirin was associated with a significant 22% reduction in transient ischemic attacks, but aspirin had no effect on the need for revascularization or all-cause mortality.

Age. Although the women aged 65 and older accounted for 10.3% of the WHS population, they experienced 30.6% of the major cardiovascular events. Unlike the group as a whole, this subgroup of older women did attain a significant benefit from aspirin in terms of the primary end point, total major cardiovascular events (–26%; $P = .008$). Also, these women had significantly fewer ischemic strokes (–30%; $P = .05$), and they were the only group in which aspirin conferred a significant cardioprotective effect, as their incidence of MI was 34% lower than that of the participants younger than 65 years ($P = .04$). The older women also had a 22% lower incidence of all stroke, but the difference was not statistically significant.

Smoking. Among the past and never smokers, aspirin lowered the incidence of major cardiovascular events (–20%; $P = .003$),



all stroke (-25% ; $P = .006$), and ischemic stroke (-33% ; $P = .001$), but not MI. Among the current smokers, aspirin users had an apparent increase in all of these measures, particularly with regard to the primary end point ($+30\%$; $P = .03$) and the incidence of MI ($+50\%$; $P = .02$). While this must be viewed in the context of multiple comparisons, since resistance to aspirin may be more prevalent among smokers, it is possible this may have played some role in the increased risk observed among current smokers,²⁵ although this was in no way definitively demonstrated. The entire issue of aspirin resistance requires much more study.

Other variables. There was no evidence that any of the cardiovascular risk factors considered, except smoking and age, modified the effect of aspirin on the primary cardiovascular end point. Aspirin was no more or less effective in high-risk patients than in low-risk patients.

Adverse effects. As expected, the aspirin group experienced significantly more episodes of gastrointestinal bleeding that required transfusion ($+40\%$; $P = .02$). Aspirin use also led to significant increases in the incidence of peptic ulcer ($+32\%$; $P < .001$), hematuria ($+6\%$; $P = .02$), easy bruising ($+40\%$; $P < .001$), and epistaxis ($+16\%$; $P < .001$), but there was no significant difference in gastrointestinal upset in general.

Vitamin E vs placebo. The data on vitamin E were much more clear: it had very little effect in preventing any cardiovascular events.

Of the 999 major cardiovascular events, 482 (48.2%) occurred in the vitamin E group and 517 (51.8%) in the placebo group; the difference in risk was a nonsignificant 7% (TABLE 2). No significant reductions in total stroke, fatal stroke, nonfatal stroke, ischemic stroke, or hemorrhagic stroke were seen in the vitamin E group. Likewise, there were no significant differences in the number of fatal MIs, nonfatal MIs, and total MIs.

The lack of an effect of vitamin E on the incidence of hemorrhagic stroke is noteworthy because there has been some concern that vitamin E supplementation might increase the risk of hemorrhagic stroke. Such a finding

was observed in an earlier trial in men.²⁶ In our trial, however, we actually saw no significant difference in the incidence of hemorrhagic stroke with vitamin E.

Even though the rates of fatal stroke and fatal MI were not significantly different in the two groups, the rate of cardiovascular mortality was 24% lower in the vitamin E group than in the placebo group ($P = .03$). This finding was unexpected, and has not been seen in other studies. Vitamin E was also associated with a nonsignificant 4% higher rate of total mortality.

Age. While vitamin E's lack of prophylactic benefit extended across virtually all of the previously mentioned subgroups, baseline variables, and risk factor categories, one subgroup did receive some benefit. Again, women 65 years of age and older had significantly fewer major cardiovascular events (-26% ; $P = .009$), MIs (-34% ; $P = .04$), and cardiovascular deaths (-49% ; $P < .001$).

Adverse effects. Aside from a small but significant increase in the incidence of epistaxis ($+6\%$; $P = .02$), there were no significant differences in adverse effects, including GI bleeding. This is an important finding because vitamin E may inhibit platelet function. Nor were there any differences in other symptoms such as fatigue, hematuria, easy bruising, gastrointestinal upset, nausea, diarrhea, and constipation, which is noteworthy because the participants had taken vitamin E for such a long time.

Interaction of aspirin and vitamin E. Aspirin and vitamin E had no effect on each other in terms of any cardiovascular outcome.

Cancer

The development of a first cancer was confirmed in 2,865 women (7.2%); 1,437 cases (50.2%) occurred in the vitamin E group and 1,428 (49.8%) in the placebo group—not a significant difference (TABLE 2). In fact, not a single statistically significant difference was observed between the vitamin E and placebo groups in any aspect of the cancer portion of the study. The null finding was consistent across every subgroup, baseline variable, and risk factor.

The issue of aspirin resistance requires much more study

■ IMPLICATIONS FOR CLINICAL PRACTICE

Aspirin

The role of aspirin in primary prevention is not settled, and therefore we conclude that the decision to use it as a prophylactic agent must be based on the totality of a given patient's individual circumstances, particularly risk factors. Prior to embarking on any prophylactic regimen, we need a clear idea of what we are facing in terms of risk and benefit, and we must weigh the two carefully.

Combined cardiovascular major events.

Overall, for the primary cardiovascular end point of combined total major events, aspirin failed to show any significant benefit for primary prevention. For secondary prevention and treatment of evolving acute MI, the benefits of aspirin had been consistent across genders.²⁷ However, the WHS found a benefit in the prevention of stroke, so further exploration of aspirin's role in primary prevention in women is certainly warranted.

Stroke. Our findings on aspirin and stroke were particularly intriguing. Women are more likely to experience a stroke than an MI (by a ratio of 1.4 to 1), while the converse is true in men (0.4 to 1).³ Therefore, our finding that aspirin protects women from stroke is important.

MI. Another intriguing finding was that aspirin exerted no protection against MI, except for a subgroup of women, those over the age of 65. We wondered if this lack of benefit might be attributable to the low dose or to the alternate-day regimen. Although we cannot rule out these possibilities, we believe they are unlikely for several reasons. First, the results of a previous study we conducted showed that a dosage of 100 mg every other day reduced thromboxane A₂ levels by 93% and prostacyclin levels by 85%; the reductions were similar in men and women.²⁸ Second, our aspirin regimen resulted in a significant increase in GI hemorrhage requiring transfusion as well as a large (+24%) although not statistically significant increase in hemorrhagic stroke, so platelet aggregation appears to have been appropriately inhibited and the dosing regimen appears to have been adequate.

We also wondered if there is a sex-based

difference in the response to aspirin and concluded that there probably is not. It is difficult to hypothesize that women are somehow more resistant to aspirin when we did see benefit for stroke prevention.

Finally, we know that the lack of cardio-protection was not the result of suboptimal compliance. Compliance in this study was good and it was consistent, partly because we made a concerted effort to educate the WHS participants about what it means to be in a clinical trial for 10 years, how important it is to adhere to the protocol, and how worthwhile the results will be for public health. Healthy people are not used to taking a medication every day, and they might have become lax about compliance, so motivation was key. Also, by sending our subjects calendar packs, we made it as easy for them as we could. Our efforts were rewarded because compliance, defined as the taking of at least two thirds of the study agents, was approximately 73% for aspirin and 76% for vitamin E. As expected, compliance did diminish somewhat as the study progressed, but when we compared outcomes between the most compliant participants and the entire group, we saw constant patterns over time.

When we combined our data with those from the previously mentioned trials in 55,580 patients,³⁻⁷ we found that, overall, aspirin did significantly reduce the risk of MI, but it had no significant effect on stroke. However, when stratified by sex, there were statistically significant differences in that for men, there were significant reductions in the risk of MI and nonsignificant increases in the risk of stroke, while for women there were significant reductions in risk of stroke but no reductions in MI risk.

Vitamin E

We do not recommend vitamin E supplementation for the primary prevention of cardiovascular disease or cancer. The absence of a protective effect in the WHS is consistent with the findings of other large trials and meta-analyses. But just as vitamin E did not lower the total mortality rate, neither did it increase it.^{29,30} Concerns about increased mortality had been expressed following a recent meta-analysis, especially with higher

Whether to use aspirin must be based on the patient's total risks and possible benefits

doses.²⁴ Biologically, however, there is no plausible mechanism that has been raised for vitamin E's increasing the risk of mortality overall.

Older women

Both aspirin and vitamin E conferred significant cardiovascular benefits on women aged 65 years and older, but we are not sure what this means. Subgroup analyses tend to raise more questions than they answer. For example, do the biological changes that occur with aging have an impact on the response to aspirin or vitamin E? Or is it simply that women younger than 65 years just have such a low risk for cardiovascular events that taking a preventive agent does not matter? Until we

can acquire more data, we cannot issue a blanket recommendation that older women should be taking either aspirin or vitamin E. Again, the decision must be made on an individual basis.

Future study

Even though the administration portion of the WHS has closed, follow-up will continue for at least another 5 years. We expect to see and report more end point events as the study population grows older.

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