CASE 3

Data Monitoring for the Aspirin Component of the Physicians' Health Study: Issues in Early Termination for a Major Secondary Endpoint

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ABSTRACT

The Physicians' Health Study was a randomized, double-blind, placebo controlled, 2×2 factorial primary prevention trial whose primary aims were to test whether aspirin reduces risks of cardiovascular disease (CVD) mortality and beta-carotene decreases the incidence of cancer. The trial was conducted among 22,071 apparently healthy U.S. male physicians aged 40–84 years at entry. After five years of treatment and follow-up, on December 17, 1987, the independent Data and Safety Monitoring Board (DSMB) recommended unanimously the early termination of the aspirin component due principally to the emergence of a statistically extreme ($p < 0.00001$) 47% reduction in risk of a first myocardial infarction (MI), the major secondary endpoint, in the context of a far lower than anticipated CVD mortality as well as use of aspirin among the vast majority of individuals who experienced a non-fatal event. Several additional factors were involved, including little or no trend in either CVD mortality or stroke, although the numbers of events were too low to distinguish between small benefit, no effect, and small harm. These circumstances suggested clear evidence for aspirin in preventing a first MI, a major outcome of clinical and public health importance in the context of inadequate power to test the primary endpoint of CVD mortality.

INTRODUCTION AND BACKGROUND

Cardiovascular disease (CVD) is the leading cause of mortality in the United States, so primary prevention as well as treatment strategies are

crucial. While atherosclerosis is the principal underlying cause, thrombosis is the proximate cause of virtually all occlusive vascular events. Blood platelets play a crucial role in the initiation and propagation of clinical thrombotic events. The effect of aspirin on reducing the aggrebility of blood platelets has been well established, suggesting that this over-the-counter and inexpensive, widely used drug might have clinical benefit in the treatment and prevention of CVD.[1,2]

In some senses aspirin is as old as medicine itself.[1] In the fifth century B.C., Hippocrates found that an extract from the bark of the white willow tree relieved aches and pains of his patients. This extract was later found to contain an aspirin-like compound. In 1897 aspirin was synthesized by Felix Hoffmann, a chemist working in the laboratory of Friedrich Bayer. During the 20th century aspirin became the most widely used drug in the world, but its potential to decrease risks of cardiovascular disease (CVD) only became apparent during the last 30 years. In 1971, Sir John Vane demonstrated that small amounts of aspirin irreversibly inhibit platelet aggregation. Since the proximate cause of virtually all acute coronary syndromes is thrombosis, it seemed reasonable to hypothesize that aspirin might break the chain of events leading to CVD. Some, but not all, observational epidemiological studies were compatible with the possibility of small to moderate benefits of 10–50%.[3,4] For small to moderate effects, however, the amount of uncontrolled and uncontrollable confounding inherent in all observational study designs is about as big as the effect sizes. Thus, reliable data about whether aspirin reduces risks of CVD could only derive from randomized trials of sufficient size and duration to detect the postulated benefit.[5–7] During the decades of the 1970s and 1980s randomized trials were conducted among patients who had survived a prior myocardial infarction (MI), stroke, transient ischemic attacks, or unstable angina. In meta-analysis, these trials demonstrated significant benefits on subsequent MI, stroke, and CVD death.[8] There were no data, however, from large-scale randomized trials of primary prevention of CVD.

With respect to beta-carotene, basic research and observational analytic studies were compatible with a possible reduction in cancer incidence.[9] By the late 1970s it seemed important and timely to hypothesize in apparently healthy individuals that aspirin decreased CVD mortality and that beta-carotene reduced cancer incidence. Stampfer et al.[10] determined that the most efficient design was a 2×2 factorial trial to test this hypothesis.

PROTOCOL DESIGN

The Physicians' Health Study (PHS) was a randomized, double-blind, placebo-controlled, 2×2 factorial primary prevention trial among 22,071

apparently healthy male U.S. physicians aged 40–84 years at entry.[11] The PHS was funded as an investigator-initiated grant by the U.S. National Institutes of Health with the National Heart, Lung, and Blood Institute (NHLBI) supporting the aspirin component and the National Cancer Institute(NCI) the beta-carotene component. The PHS was designed and conducted as a far larger companion trial to a primary prevention trial of British doctors. A number of pilot studies were completed which demonstrated the willingness and ability of U.S. physicians to comply with their assigned regimen as well as to provide complete follow-up data. In addition, 325 mg aspirin on alternate days was demonstrated to inhibit platelet aggregation and prolong the bleeding time so this regimen was chosen to enable the participants to take one pill each day.

For the aspirin component, the primary prespecified endpoint was CVD mortality and the major secondary objectives were to assess the impact on. Additional prespecified endpoints were MI and stroke, total mortality and cause specific mortality as well as side effects, especially bleeding. Since aspirin and beta-carotene had no known beneficial or deleterious interactions, a randomized double-blind 2×2 factorial design was used to test the two hypotheses simultaneously.[10] Based on the results of previous secondary prevention trials of aspirin,[8] the hypothesis was that aspirin would reduce CV mortality by 20%. Although it was expected that such an effect might reduce total mortality by 10%, it was not expected that this trial would have sufficient power to detect this outcome. Considering cost and feasibility, a large cohort of apparently healthy U.S. male physicians between 40 and 84 years of age, having no previous CVD, was selected as the study population. The PHS design assumed that these physicians would have a lower mortality rate than the general U.S. population. Specifically, the assumption was that the cohort would have a CV mortality rate 25% of the U.S. population for the first year, 50% for the second year of follow-up, and 75% for subsequent years of follow-up. This led to the final design of 22,000 physicians being randomized to 7.5 years of follow-up. This sample size would provide 0.95 power to detect a 20% reduction in CV mortality with a one-tailed 0.05 significance level. With recruitment to start in early 1982, follow-up was scheduled to be completed in late 1990.

An independent and multi-disciplinary Data and Safety Monitoring Board (DSMB) was established jointly by the principal investigator, NHLBI, and NCI. The primary responsibilities of the DSMB were to monitor the progress of the PHS as well as the accumulating data for cogent evidence of benefit or harm. The DSMB included clinicians with expertise in aspirin, CVD, beta-carotene, and cancer as well as epidemiologists and biostatisticians, all experienced in the design, conduct, analysis, and interpretation of randomized trials. The DSMB was scheduled to meet every six months throughout the

trial. For data monitoring, the DSMB chose the method proposed by Haybittle[12] and Peto[13] to provide guidelines for early termination. This method requires that the standardized test statistic exceeds 3.0 (or three standard deviations) on any interim analysis. This corresponds to a nominal p-value of 0.0013. Since the interim analyses are conducted no more frequently than twice annually, the final p-value can be used without any further adjustment. The terms of reference for early termination included proof beyond a reasonable doubt that is likely to influence clinical practice in the context of the above-mentioned statistical guidelines.

Introductory letters and consent forms were mailed to over 261,000 U.S. male physicians aged 40–84 years. About half returned the forms and about half were willing to participate. Of these, about 33,000 were initially eligible. Interestingly, the chief exclusion criterion was regular use of aspirin. Of these, after a three-month run-in on active aspirin and beta-carotene placebo about a third were excluded because of non-compliance, leaving 22,071 willing and eligible participants who were randomized (11,037 to aspirin and 11,034 to placebo).

The DSMB recommended early termination of the aspirin arm on December 17, 1987.[14,15] The beta carotene arm continued to its completion date, which was December 31, 1995. In this report, the issues surrounding the DSMB decision to recommend early termination of the aspirin component are reviewed and implications are summarized. A more detailed discussion has been published.[14]

DATA MONITORING EXPERIENCE

As expected, with such a large number of participants randomized, the baseline risk factors were virtually identical between the aspirin and placebo arms. Compliance to the assigned trial medication was over 85% for most of the follow-up period in both the active and placebo groups. Follow-up was 100% for mortality and over 99% for major morbidity. Endpoints were classified by a separate committee blinded to the assigned intervention. These aspects were not issues in the DSMB deliberations. Bleeding problems, including bruising, gastrointestinal bleeding, and nose bleeding, were increased in the aspirin arm compared to placebo but appeared to be lower than reported in previous aspirin trials. Gastrointestinal ulcers were also higher on aspirin but not statistically significant. Thus, the DSMB did not consider these sufficient to recommend any change in the trial.

During the last 1.5 years of the PHS aspirin component, the DSMB held three formal meetings with five issues of primary concern;[14] these were—

1. Low CVD overall mortality rate resulting in reduced statistical power
2. No emerging trends in CVD mortality

3. Emerging trends in MI rate difference
4. No emerging trend in stroke rate difference
5. Placebo arm cross-over rate

Data for these key outcomes are presented in Tables 1–3, and represent a summary of what was available at each of the DSMB meetings. Relative risks (RR) are shown for each time period.

The DSMB was aware early in the trial that the mortality event rate was far lower than the already low rate assumed in the design, and that trend persisted. By the December 1987 meeting, 733 CV deaths were expected, in contrast to the 88 that were reported and confirmed. At that time, about 68% of the reported events had been confirmed or refuted. The design had assumed the PHS rate would be between 50% and 75% of the U.S. healthy male age-matched population. However, only 12% of the assumed rate was observed. The projected mortality rates for the remaining follow-up period were also examined, but even modest increases did not alter the conclusion that the overall mortality rates would be far lower than assumed. The lower rate implied a reduced power of the trial. The DSMB conducted extensive calculations[14] which suggested that power of the trial would be only 0.50 with

Table 1 Mortality Outcome in PHS

Date*	Mortality Outcome	Aspirin	Placebo	RR
6/86	CV	28	33	0.83
	Total	58	75	0.76
1/87	CV	37	42	0.86
	Total	91	102	0.88
12/87	CV	44	44	0.99
	Total	110	115	0.95

* Date of Data Monitoring Board meeting for which analysis was presented.
Modified Table 1. *Ann Epidemiol* 1:395–405, 1991.

Table 2 Confirmed Myocardial Infarctions

Date*	Outcome	Aspirin	Placebo	RR	P-value
7/86	Non-fatal	71	111	0.61	0.003
	Total	75	122	0.61	0.0007
1/87	Non-fatal	85	137	0.60	0.0004
	Total	89	154	0.56	<0.0001
12/87	Non-fatal	99	171	0.56	<0.0001
	Total	104	189	0.53	<0.0001

* Date of DMB meeting for which analysis was presented.
Modified Table 2. *Ann Epidemiol* 1:395–405, 1991.

Table 3 Confirmed Stroke*

Date*	Outcome	Aspirin	Placebo	RR	P-value
7/86	Ischemic	31	40	0.76	0.47
	Hemorrhagic**	9	4	2.45	0.17
	(Mod–fatal)	(8)	(0)		(0.0078)
1/87	Ischemic	43	52	0.82	0.35
	Hemorrhagic	12	4	3.23	0.05
	(Mod–fatal)†	(10)	(0)		(0.0020)
12/87	Ischemic	64	61	1.05	0.79
	Hemorrhagic	13	6	2.19	0.11
	(Mod–fatal)	(10)	(2)	(5.06)	(0.02)

* Date of DMB meeting for which analysis was presented.
** Excludes strokes unclassified as to ischemic, hemorrhagic.
† Mod–fatal = moderate, severe, or fatal.
Modified Table 3. *Ann Epidemiol* 1:395–405, 1991.

the mortality rate as observed and a sample size of 22,000. In order to have 0.90 power for mortality, the effect of aspirin would have to result in a 35% reduction or greater, rather than the 20% as assumed.

In addition, Table 1 indicates that the observed difference in CV mortality between aspirin and placebo was also smaller than assumed and decreasing over time. The observed relative risk for CV mortality went from 0.83 to 0.86 to 0.99. For total mortality, the RR was initially encouraging but at the December 1987 meeting was only 0.95. Thus, the smaller intervention effect further reduced the chances of a statistically significant result at the end of the scheduled follow-up. The DSMB calculated the power of detecting a significant difference at the end of follow-up, taking into consideration the already observed intervention effects and the lower mortality rates using methods of conditional power.[16] These conditional power calculations, assuming a 20% aspirin effect for the remainder of the trial, indicated only a 0.32 chance of obtaining a significant result at the scheduled termination date in 1990. In order for the conditional power to increase to just 0.80, the aspirin effect would have to be 40%, double that of the initial assumptions.

The conclusion of both the unconditional and conditional power calculations was that the PHS aspirin component was substantially underpowered for the primary outcome of CVD mortality as well as for total mortality. Based on the mortality outcome, the choices were to (1) continue as is and hope for the best, (2) increase the sample size (but recruitment had been completed five years earlier), or (3) increase the follow-up period. In order to accumulate the desired number of primary events to compensate for the lower observed event rate, the DSMB calculated that the follow-up would have to be extended an additional 16.5 years for a total of 20.5 years of follow-up.

While the primary prespecified endpoint of CV mortality did not seem encouraging to the DSMB, the major secondary outcome of MI was of considerable interest. As shown in Table 2, the results for non-fatal MI or total (fatal and non-fatal) MI became apparent within six months and statistically extreme over the last three DSMB meetings, with a nominal p-value less than 0.0001 at the December 1987 meeting. Early in the trial, the PHS study chair and the DSMB had discussed the possibility of MI's becoming statistically significant before the primary endpoint because of the larger event rate, assuming that some portion of the hypothesized effect of aspirin would carry over to fatal MI as well as non-fatal MI. The policy was that while MI would be an endpoint of major interest, it would not by itself be sufficient to terminate the trial early. The physician participants had been advised that CV mortality was the primary endpoint. However, the MI results seemed to indicate a protective effect of aspirin for this secondary but important clinical and public health outcome.

Another key secondary outcome was the effect of aspirin on stroke. The data over the same period of time is shown in Table 3. While the number of stroke events are small and thus the data are inconclusive, the results shown are consistent with the hypothesis that aspirin is possibly beneficial for ischemic stroke and possibly adverse for hemorrhagic stroke (although the beneficial effect was not seen at the December 1987 meeting). For hemorrhagic strokes classified as moderate, severe or fatal, there were ten events in the aspirin group and two in the placebo group. While nominally significant ($p = 0.02$), the number of events is very small and not conclusive, but consistent with the available evidence from trials of secondary prevention.

Finally, the DSMB also noted that by December 17 1987 over 85% of participants who suffered a non-fatal MI were prescribed aspirin. This prescribing pattern was compatible with the results from the secondary prevention trials, and, indeed, the U.S. Food and Drug Administration (FDA) had labeled aspirin for this indication. The effect of the treatment cross-over or "drop-in" phenomenon was that individuals at higher risk for having a primary outcome were now on active aspirin treatment and future intervention effects of aspirin were likely to be diminished. Thus, this situation further lowered the ability of the PHS to reach its primary objective during the funded follow-up period.

After considering all of the issues in much more detail than described here, the DSMB recommended to the study chair at its December 1987 meeting that he be unblinded and consider the options listed below.[14]

1. Extend the length of follow-up.
2. Increase the study population.

3. Continue as planned with no change.
4. Terminate the trial early and report the results.

Extension of follow-up for a considerable period was considered, assuming funding could be obtained. However, ethical issues suggested that the participants needed to be told about the MI results so they could make an informed decision whether to continue in their assigned study arm. This information might have the effect of increasing the cross-over to aspirin. The DSMB did not believe extension with immediate disclosure of the MI results was a viable option. Additional recruitment was not feasible. Continuing as planned for another three years could be achieved with little additional effort but also with very little gain at the expense of not sharing the MI and stroke results. The DSMB recommended unanimously on December 17, 1987, to the study chair that the aspirin component be terminated early.

Following the unanimous recommendation of the DSMB, the principal investigator spoke with the Steering Committee and prepared a preliminary report. A manuscript was submitted for expedited review to the *New England Journal of Medicine* (NEJM) on December 23, 1987, and accepted for publication on December 30, 1987.

Interestingly, of seven independent experts chosen by the editor of NEJM to review the manuscript, six concurred with the decision of the DSMB concerning early termination of the blinded aspirin component of the PHS. The preliminary report was published on January 25, 1988.[15]

Unblinding of PHS Participants

Letters were written, printed, and mailed to all participants to arrive on or before January 25, 1988, together with reprints of the preliminary report. Of those assigned to aspirin, over 99% elected to remain on the drug. Over the 2–3 years following termination, 74% of the physicians who were assigned to the placebo arm elected to take aspirin with an additional 15% already on aspirin. Thus, 89% of the placebo arm physicians elected to take aspirin, suggesting that these individuals accepted and endorsed the recommendations of both the DSMB and the study's advisory committee. In addition, the CV mortality rate remained low and confirmed the DSMB recommendation that this primary outcome would not likely yield definitive results.

Postscript

The results of the PHS were accompanied by the simultaneous publication of the results of the British Doctors Trial (BDT) on January 28, 1988, in the British Medical Journal. The BDT showed no significant effect of aspirin on first MI.[17] Considerable confusion occurred among health care providers

and the general population, so the principal investigators of both trials along with the chairs of their DSMB's published a meta-analysis of the two trials. For non-fatal MI, the PHS showed a significant benefit of 42% ± 9% and the BDT showed a non-significant benefit of 3% ± 19%. Not surprisingly, due to the far larger sample size of the PHS the meta-analysis of the two trials showed a 33% ± 9% reduction in first MI whose p-value is less than 0.00002.[18] In the final report of the PHS, with 100% of reported events confirmed or refuted, aspirin reduced the risk of a first MI by 44% ($p \leq 0.00001$).[19]

Starting in 1999, three additional randomized trials of aspirin in the primary prevention of CVD have been completed and published. The Thrombosis Prevention Trial (TPT),[20] Hypertension Optimal Treatment Trial (HOT),[21] and Primary Prevention Project (PPP)[22] all showed significant benefits of aspirin on first MI. In fact, the PPP was also terminated early based on the recommendation of its DSMB. A meta-analysis of the five trials provides conclusive evidence to corroborate the initial finding from the PHS that aspirin significantly reduces the risk of a first MI by 32% ($p \leq 0.00001$).[23] Further, even after randomization of over 55,000 subjects, of which about 12,000 are women, there are non-significant effects on stroke and CVD mortality. The beta-carotene component of the PHS ended as scheduled on December 31, 1994. At that time there were an additional seven years of observational aspirin use. In the analyses of 12 years of aspirin (five randomized and seven observational) there was a significant reduction in CVD mortality of about 20% among aspirin takers.[24,25]

LESSONS LEARNED

1. The PHS DMB experience confirms what the Coronary Drug Project investigators described earlier: that the decision process is complex and hard to define in advance.[26] While statistical procedures such as the Peto-Haybittle group sequential boundary are useful in interpreting interim analyses of the primary prespecified endpoint cautiously, they provided little help to the DSMB for most of the issues under discussion in the PHS. They did, however, help interpret the "significance" of the MI finding.

2. Secondary endpoints can play a major role in the decision. The DSMB did anticipate in advance that MI (fatal and non-fatal) might become significant, using the Peto-Haybittle criteria, before the primary outcome of CVD mortality. At the beginning of the PHS, the participants were clearly informed that the primary outcome was CV mortality. However, this does not assure that those participants would not respond to the significant MI results. In fact, over 99% of those assigned to aspirin remained on the active drug, and 89% of those assigned to placebo choose to take active aspirin after the results were disseminated.

3. The role of a DSMB in addressing a non-significant primary endpoint in the context of a statistically extreme finding on the major secondary endpoint is a very challenging task. Any DSMB recommendations or comments must be based on unblinded or partially blinded interim data, and thus subject the trial to possible bias. Yet, this DSMB had to struggle with the fact that the CV mortality rate, the primary outcome, was less than half the rate assumed, which reduced the power to be far less than 0.50 at the same time that a secondary endpoint, MI, was becoming more and more significant with time. Extending or expanding the trial was considered but determined to be not feasible.

4. Conditional power methods were used to assess whether the primary outcome could ultimately be statistically significant, given the observed data, projected mortality rates, and a range of hypothesized aspirin effects for the remainder of the trial. None of the calculations with reasonable variations in the assumptions indicated that the primary mortality outcome would be significant in the next several years. This methodology was helpful.

5. The DSMB did not formulate the recommendation to terminate at the meeting on December 17, 1987. Rather, the discussions about terminating early began much earlier as the observed trends began to emerge and gained momentum at the last three meetings with the data as summarized in Tables 1–3. The DSMB was interested in observing whether the trends would become stronger, fluctuate, or weaken. The fact that the CVD mortality rate did not increase and that fatal and non-fatal MI results were apparent by six months and became statistically extreme over time helped the DSMB in their deliberations. Thus, over the last three meetings the DSMB became increasingly convinced that nothing more would be gained by continuing the aspirin component. In this case, tracking the emerging trends was important.

6. The principal investigator found the advice of external reviewers useful in dealing with the DSMB recommendations. In the PHS, the external experts came by way of the editorial process of the New England Journal of Medicine but served the useful purpose of a second opinion.

7. Despite the PHS results for fatal and non-fatal MI, the endorsement of the aspirin as a primary prevention strategy has been mixed. The physician participants in the PHS overwhelmingly accepted the results by taking aspirin themselves. Other later trials[22,23] have suggested similar results. In early 2002, the United States Preventive Services Task Force (USPSTF) issued guidelines that all apparently healthy individuals with ten-year risk of a first CHD event of greater than 6% should be considered for aspirin prophylaxis to prevent a first MI.[27] Later that year the American Heart Association (AHA) issued similar guidelines for all apparently healthy individuals whose ten-year risks are greater than 10%.[28]

Nevertheless, the Food and Drug Administration has not as yet labeled aspirin to prevent a first MI. In 1989, following the publication of the final report of the PHS as well as the BDT, the Cardio-Renal Drugs Advisory Committee (CRDAC) to the U.S. FDA voted 6–2 to label aspirin to prevent a first MI. The FDA did not act on this recommendation, citing the apparently discrepant results of the PHS and BDT. In 2003, CRDAC reviewed the evidence from all five published trials and their meta-analysis, and voted not to approve aspirin for primary prevention of a first MI. One recently completed and two ongoing trials should provide important relevant information. The recently completed Women's Health Study of about 40,000 apparently healthy female health professionals provides relevent important information.[29] The recently begun ASPREE trial in Australia among the elderly (Mark Nelson, personal communication) is evaluating the high risk primary prevention subjects for which regulatory authorities are requiring further data.

Monitoring committees should bear in mind the likely impact of the results on clinical and public health practice when considering early termination but should still give the participants in a trial the highest priority.

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