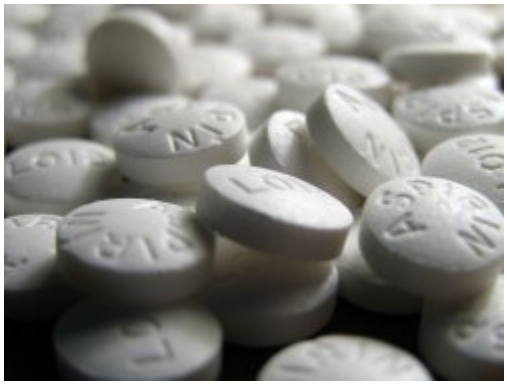
Mounting debate over aspirin use in primary prevention should prompt new talks with patients



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Oxford, UK – Physicians and consumers looking for drug-company information on aspirin need look no further than the Bayer website www.wonderdrug.com: an immodest homepage for a drug that, at least in the primary-prevention arena, has weathered a less-than-wonderful year. The **US Preventive Services Task Force** (USPSTF) says it stands by its seemingly broad recommendations for aspirin to prevent a first MI in men and stroke in women. But some experts, including regulatory groups abroad, worry that key messages on aspirin's potential harms are just not getting through to physicians and their mostly healthy patients who, for years, have taken an aspirin a day to keep heart attack at bay.

Things looked rosier early this year. In March, the USPSTF issued an update [1] to its 2002 recommendations [2] for aspirin in primary prevention. These stipulated that aspirin was likely of benefit for preventing MI in men age 45 to 79 and preventing stroke in women 55 to 79, when the benefits outweigh the gastrointestinal risks on an individual-patient basis.

But over the ensuing months, a steady stream of studies have warned against aspirin use in some of the key primary-prevention populations, including patients with asymptomatic atherosclerosis, type 2 diabetes, and peripheral artery disease. Most striking of all was the May 2009 meta-analysis, published in the *Lancet* [3], from the Oxford **Antithrombotic Treatment Trialists** (ATT)—the same group that wrote the original 2002 aspirin/primary-prevention meta-analysis, published in the *BMJ* [4], credited by many to have been the paper that cemented the role of low-dose aspirin in primary prevention in the first place. The *Lancet* paper found that while aspirin used for primary prevention may reduce the risk of nonfatal ischemic events, these benefits are offset by higher bleeding, leaving no net effect on vascular mortality.

U-turn or forward march?

Dr Eric Topol

Dr Eric Topol (Scripps Clinic, La Jolla, CA) says it's an about-face by the ATT group that's gone largely underappreciated. "The original *BMJ* article had a profound impact on the practice of medicine with respect to use of low-dose aspirin for primary prevention," he told **heart*wire***. "This is about as big a turnaround as I've seen. But I think that the more recent updated data have been largely ignored, and that's disconcerting, because now there are, just in this country alone, literally tens of millions of people taking low-dose aspirin that probably there is no basis for. . . . It's really become kind of a consumer norm. As an outgrowth of the *BMJ* study in particular, aspirin has been advocated widely in the media. It's not just the cardiologists and family doctors who are making recommendations, it's magazines and newspapers and websites. It's all over the place."

ATT investigator **Dr Colin Baigent** (Oxford University, UK) was a coauthor on both the 2002 and 2009 meta-analyses. He roundly rejects the notion that his group has done any kind of U-turn; rather, the papers represent the march of science.

Dr Colin Baigent
[Source: Oxford University Clinical Trials Service Unit]

"It's only really since the summer that it's been possible to look at the question with reliable data," Baigent told **heart*wire***. "Always in the past, recommendations have been made on a flawed appraisal of the existing trial evidence, and I would argue that it's not until now—and it took a long time to do, to get right—we can see that the balance of benefit and risk is really very marginal, especially if you give aspirin on top of safer forms of primary prevention. . . . We should be careful not to give the impression that aspirin doesn't work. It works, but the balance of benefit/hazard is not good enough for a primary-prevention situation."

Baigent also refutes suggestions that he or the ATT group as a whole championed aspirin for primary prevention at any time. "There is nothing that we've written that is in any way ambiguous about our views," he insists. "Our general policy has been to try to present the evidence without being too dogmatic about how it should be interpreted. In the 2002 paper, I think we were pretty clear that the question of primary prevention is unclear and being investigated by trials."

Can a typo be blamed?

Baigent offers one possible explanation for why aspirin for primary prevention was so heartily embraced when the 2002 *BMJ* paper came out: a critical typo in the original paper. While the online HTML and PDF versions are now correct, in the original print edition of the *BMJ* paper, the final sentence reads: "For most healthy individuals, however, for whom the risk of a vascular event is likely to be substantially less than 1% a year, daily aspirin may well be appropriate." A correction swiftly issued by the *BMJ* noted that final word should, in fact, be *inappropriate.*

Baigent says he received "a profuse apology from the *BMJ* editor at the time." Still, it's possible the misprint helped disseminate a flawed message about aspirin in primary prevention. It was never the ATT investigators intention to emphasize that daily aspirin in low-risk patients was a good idea, he says.

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FDA foresight barred primary-prevention indication

Despite the positive and broad-stroke primary-prevention message in the 2002 USPSTF aspirin recommendations, an **FDA** advisory panel in 2003 voted 11-3 to reject a petition by Bayer to expand aspirin's indications to be used for primary prevention in moderate-risk patients: those with a 10-year coronary heart disease risk of greater than 10%. Both Topol and Baigent actually spoke at the hearing, on behalf of the sponsor.

The question is not whether to give aspirin for primary prevention but whether to add aspirin to safer forms of primary prevention, and that's a very important distinction.

Baigent acknowledged that data from the 2002 paper formed part of his FDA presentation but emphasized that this did not include information on the sixth trial, the **Women's Health Study** [5], not published until 2005 and subsequently included in the 2009 analysis.

"What I pointed out in those hearings was that the effects of aspirin are very similar in primary and secondary prevention," he explained to **heart*wire***. "At that point in time, I felt that the effects in people who were identified at moderate risk were consistent with the effects of aspirin right across the risk range. Remember, this is quite a long time ago, before we'd actually worked out the data properly—I felt less certain about whether that absolute benefit was worthwhile. And since the time of those hearings, I've been more convinced by looking at the evidence that, particularly if you are adding aspirin to beta blockers or antihypertensives and statins, . . . it's clear that the absolute benefit is small, and it's of comparable size to the hazard and so doesn't justify using aspirin on a widespread scale."

Baigent bristles at the notion that his stint speaking on behalf of Bayer at the FDA hearing pegged him as a champion for aspirin in primary prevention and points out that he accepted no money for participating. "I don't think there is anyone who would say that I have been pushing aspirin for primary prevention. In the conversations I've had with people over the years in the field, [where] I've had concerns that the benefits may not strongly outweigh the risks, particularly in the past five years, I have never, I think, given that impression, and certainly not since we've had the analyses properly done."

Moreover, in 2009, he says, there is "overwhelming evidence" that safer drugs, such as statins and blood-pressure-lowering drugs, as well as smoking cessation, reduce the risk of MI and stroke. "So the question is not whether to give aspirin for primary prevention, but whether to add aspirin to safer forms of primary prevention, and that's a very important distinction."

The voice in the wilderness

Dr John Cleland

The loudest voice challenging the safety and efficacy of aspirin has, for years, been **Dr John Cleland** (University of Hull, UK). Indeed, he was first invited to write the editorial accompanying the original *BMJ* meta-analysis, but his views were ultimately printed as a "For Debate" article [6] appearing in the same issue, having been deemed too radical to serve as an editorial. On another occasion, he was invited to contribute to an aspirin debate article, but the counterposing group refused, because "that would give [my] opposing view too much authority," Cleland says.

Cleland believes aspirin may have a role in the first few weeks after an acute vascular event and that further study of longer aspirin usage is warranted in the setting of patients who've been treated with drug-eluting stents. But he has long warned that long-term use both as primary and secondary prevention increases the risk of hemorrhage, including plaque hemorrhage, and sudden death—an end point he believes has not been properly captured in aspirin studies.

For the first time, at least some of Cleland's views seem to be gathering support. While no one who spoke with **heart*wire*** shared Cleland's concerns about aspirin's role in secondary prevention, experts, particularly outside of the US, are rethinking its part in primary prevention. In November 2009, the UK *Drug and Therapeutics Bulletin* published a report noting that risk and benefit of aspirin for primary prevention "may be more finely balanced than previously thought" and concluded that current evidence does not support low-dose aspirin in healthy individuals for primary CVD prevention [7]. Even more strongly, advice issued in an October drug safety update by the **Medicines and Healthcare Products Regulatory Agency** in the UK reminded physicians that aspirin is not licensed for use in primary prevention and recommended that physicians review aspirin use in all primary-prevention patients who might be taking it.

Topol, once a proponent, now acknowledges he's had to revise his own views, observing to **heart*wire*** that the data in support of aspirin in primary prevention back in 2002 and 2003 "looked more convincing." As for Cleland: "I give him more kudos now for pointing out the weak spots at the time," says Topol.

Dr Ned Calonge [Source: Colorado Department of Health]

The USPSTF, however, has no plans currently to revise its guidance. According to task force chair **Dr Ned Calonge** (University of Colorado Health Sciences Center, Denver), the USPSTF looked closely at the WHS aspirin results and at the new ATT *Lancet* meta-analysis. In both instances, the task force concluded that their

recommendations still held true.

For the ATT meta-analysis, Calonge says USPSTF has written a letter to the *Lancet* editor expressing their concerns. "The problem is that if you take both genders and throw them together, because the women don't get a benefit from MI, you lose the stroke benefit, and because men don't get a benefit from stroke, you lose the MI benefit," he told **heart*wire***. "We believe if you really separate [events] by gender and age groups and into strokes vs heart attacks, the evidence is still very strong that we can have substantial net benefit through aspirin chemoprophylaxis."

Moreover, there is not "adequate evidence" to tease out the incremental benefit—or lack thereof—of adding aspirin in a patient already on a statin, he added.

"We still believe that a clinician could look at, for example, the 10-year heart-disease risk for men and look at the GI bleed risk in the different age categories that we have in the article and pick the cutoff point where the averted events from heart disease offset or are greater than the number of events from a GI bleed." USPSTF risk calculation tables for women and stroke are also available online.

Bayer: Talk to your doc

In a statement provided to **heart*wire***, a Bayer spokesperson pointed out that many experts "support the use of low-dose aspirin" to reduce MI and stroke risk for primary prevention in "individuals at sufficient risk" for these events.

"Current clinical-practice guidelines are widely consulted for clinical decision-making regarding safe, effective, and appropriate aspirin use at this time. The **American Heart Association**, **American Diabetes Association**, and the USPSTF all recommend that aspirin should be discussed with men and women over the age of 45 and 55, respectively, and may be used when the benefits are deemed to outweigh the risks."

As to the kinds of media messages reaching consumers, Bayer says: "In all US communications efforts, including advertising, Bayer consistently emphasizes the importance of individuals speaking to their doctors before starting or stopping an aspirin regimen and that the decision on whether to recommend aspirin for prevention resides with the physician."

Confusion and debate

Topol blogged about the *Lancet* meta-analysis after it was published but says he worries physicians aren't listening. "I think actually most cardiologists are still prescribing aspirin: for every patient that they see this should be a topic of discussion," he says. "I'm not aware of any significant effort that's being made in the cardiology community to get this on track and to get patients off low-dose aspirin or to stop starting it. I think whereas the [original] *BMJ* paper really had a profound impact, I don't know if there's anything going on to promote the updated data."

> **To say, in the present state of knowledge, that we know what the best dose of aspirin is, and that we know it's effective, and that we know the benefit is just a lie.**

Cleland, not surprisingly, has even stronger views. "It's important that the message gets out. I think it will cause some violent argument in the cardiology community, and I think that's healthy. . . . I'm glad that people are confused and talking about this. It's just possible that aspirin is effective and that we haven't done the trial to show that it's safe and effective. But to say, in the present state of knowledge, that we know what the best dose of aspirin is, and that we know it's effective, and that we know the benefit is just a lie. The honest answer is that we don't know and we should not be thrusting a medication on patients where we don't know the benefits and the safety."

Baigent, for his part, has given interviews in the UK warning patients against *stopping* aspirin abruptly.

"The appropriate step would be for people who have any concerns about this to talk to their doctors about the benefits and hazards and what it means for them. I've never suggested that people should just come off aspirin without any kind of conversation with their doctors. . . . It's very important that people don't just stop

treatment."

Baigent also emphasizes that future analyses will be fleshed out by the several major randomized trials of aspirin in primary prevention still ongoing: **Aspirin in Reducing Events in the Elderly** (ASPREE), **Aspirin and Simvastatin Combination for CV Events Prevention Trial in Diabetes** (ACCEPT-D), and **A Study of Cardiovascular Events in Diabetes** (ASCEND).

According to Calonge, the USPSTF will consider these trial results as they are published and, if they are radically at odds with the current task-force advice, will push up what is usually a five-year cycle for reviewing recommendations. The task force will even take the step of incorporating new data prior to publication—if investigators permit—if the new information is deemed urgent.

Baigent, meanwhile, says he keeps an open mind for whatever new information these trials add. "I've never pretended that I've known all the answers at any one time," he told **heart*wire***. "It's taken a long time to get all the evidence together from the aspirin trials, and I think that perhaps we were optimistic when we didn't have all the evidence in 2003."

*Baigent disclosed receiving no personal payments from industry; Oxford is heading up the ASCEND trial, which is supported in part by Bayer. Cleland has previously disclosed serving as an advisor or consultant for Medtronic; receiving grants for clinical research from Medtronic and Otsuka; and owns stock, stock options, or bonds in AstraZeneca. Topol is editor-in-chief of **theheart.org** and has previously disclosed serving as a consultant for HUYA Biosciences and Sanofi-Aventis. Calonge has previously disclosed having no conflicts of interest.*

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