

## ***Aspirin Not Recommended For Heart Disease Anymore***

*by Dr. John G. F. Cleland 1/2002*

Despite the vast size of these meta-analyses, **the evidence in support of aspirin preventing atherosclerotic events**

**is still inconclusive.** The third meta-analysis from the Antithrombotic Trialists' Collaboration contains data on over 100,000 patients at high risk of atherosclerotic events, representing more than 250, 000 patient years of follow up. (1)

This meta-analysis and its predecessors form the major argument for the current widespread fashion of prescribing aspirin to such patients. (2, 3) It is an enormous body of research and the collaboration is to be congratulated for having gathered so much data. However, quality as well as quantity matters. And the quality is such that the results can only be inconclusive.

### **Summary Points:**

- The series of meta-analyses on the anti-platelet activity of aspirin overvalues aspirin's effectiveness and safety.
- All the large long term trials of aspirin after myocardial infarction show no effect on mortality.
- Aspirin may change the way vascular events present rather than prevent them.
- This may lead to a "cosmetic" reduction in non-fatal events and an increase in sudden death.
- Data on the safety and cost-benefit of aspirin are inadequate.
- Advocating the use of aspirin for preventing atherosclerotic events diverts attention from other, more effective, drugs.

### **Trials Do Not Show That Aspirin Saves Lives**

Meta-analysis is increasingly viewed either as a way of verifying that the outcome of an individual trial is consistent with the rest of the known data or as a way of generating a hypothesis. However, in the absence of a definitively positive trial, many consider meta-analysis inadequate evidence for clinical decision making. The series of metaanalyses from the trialists' collaboration contains serious additional flaws.(3-6) It is remarkable and probably statistically significant how seldom trials of anti-platelet agents have shown benefit on their selected primary outcome. The choice of the primary endpoint by the Antithrombotic Trialists' Collaboration is arbitrary and suspect.

Antiplatelet agents seem to be substantially more effective in reducing the incidence of non-fatal events than in reducing death. Indeed, among large long-term trials after myocardial infarction **there is no evidence that aspirin saves lives.**

An intervention can reduce non-fatal events in three ways: by genuinely reducing them, by concealing them, or by converting non-fatal events into fatal ones. The failure of aspirin to reduce mortality despite a reduction in non-fatal events in many studies suggests that **aspirin may conceal, rather than prevent, vascular events.** (6)

Epidemiological data suggest that 25% of non-fatal myocardial infarctions are silent.(4,5) As aspirin, even at low doses, is an analgesic and because it **may provoke dyspepsia**, which may create confusion about the cause of chest pain, it is not difficult to believe that aspirin could increase the proportion of silent events from 25% to 30%. This could explain all the benefits of antiplatelet agents on non-fatal myocardial in the meta-analysis.

**Aspirin increased the risk of sudden death in every long-term study after myocardial infarction that reported such events.** 38

This increase was from 4.4% on placebo to 5.6% on aspirin in the persantine-aspirin reinfarction (PARIS) study; from 2.0% to 2.7% in the aspirin myocardial infarction study (AMIS); and from 2.0% to 2.4% in the persantine-aspirin reinfarction study (PARIS-II).(9)

This could reflect an increased risk of sudden death among concealed, and therefore untreated, events. Another possible mechanism by which aspirin may convert non-fatal events into fatal ones is by increasing the risk of hemorrhagic conversion of cerebral and myocardial infarctions.

All cause mortality and, arguably, disabling stroke are the only robust markers of benefit with an antiplatelet agent. It is not clear that antiplatelet agents reduce the risk of either.

Some trials that were included lost more than a quarter of their patients to follow up(10) In similar circumstances, with other agents, it has been suggested that all patients lost to follow up in the active treatment group should be considered to have died and none of those in the control arm. Such an analysis would neutralize the benefit observed in one of the few seemingly convincingly positive studies of aspirin, the ISIS-2 trial.(11)

### **Bias In Interpretation**

The Antithrombotic Trialists' Collaboration shows bias in the analysis and interpretation of their results. We are given

scant detail on how the numbers of events credited to each trial changed between meta-analyses. (2, 3) Trials were retrospectively reanalyzed, resulting in resurrection of a number of apparently dead patients and the discovery of a number of new deaths.

Most interventions probably help some people some of the time and harm others some of the time. A small benefit could reflect a small overall benefit in a large population or a substantial benefit in some patients and harm in others.

Aspirin could exert a short-term benefit followed by long term harm, in which case the benefits and safety of aspirin could be increased by using only a short term course of therapy. (14) Aspirin may be harmful in patients with coronary disease and heart failure.(5, 6, 12)

The evidence for an adverse interaction between aspirin and angiotensin converting enzyme inhibitors observed in the SOLVD (studies of left ventricular function) and HOPE (heart outcomes prevention evaluation) trials is also a matter for concern.(6, 12) These are important issues that have not been adequately addressed.

### **Neither Safe Nor Cheap**

Many believe that, even if aspirin is not effective, it is safe. Aspirin does appear to be relatively safe for the patients included in clinical trials, but as these studies excluded by design patients at risk of adverse events with aspirin and tended to include younger patients with lower multiple morbidity it is likely that aspirin is not as safe as suggested.

**Low dose aspirin for cardiovascular prophylaxis may account for more than 30% of all major gastrointestinal hemorrhage in patients (4, 6, 15) and may also be associated with an increased risk of renal failure.**

Finally, there is a widespread view that aspirin is cheap. However, when evaluating the costs of treatment the amount and type of benefit and the costs of managing adverse effects also need to be evaluated. Very few economic appraisals of aspirin have been done.

One such analysis, recently commissioned by the chief scientist's office in Scotland, suggested it may cost more than £80 000 to prevent one event with aspirin for primary prevention and more than £3000 for secondary prevention. (16) These analyses have assumed that aspirin is as effective as the meta-analyses suggest, which may not be true.

**A Diversion:** Perhaps the greatest potential detriment of aspirin on health care, however, is that it diverts attention away from treatments that are of unequivocal benefit to many groups of patients. The reader should not accept the conclusions of the Antithrombotic Trialists' Collaboration

uncritically but rather read the original papers on which their conclusions are based.

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### **Aspirin & Tylenol:**

*Linked to Kidney Failure*

*Reference: New England Journal of Medicine, December 20, 2001;345:1801-1808*

Individuals who have kidney disease or other ailments who regularly take aspirin or acetaminophen may be boosting their risk of developing kidney failure.

Researchers report that such patients who were regular users -- those who took these painkillers at least **twice a week**

**for 2 months -- were two to three times more likely to have the beginning stages of chronic kidney failure,**

compared with individuals who did not use these painkillers on a regular basis.

This study and others have found that the risk is minimal in those without pre-existing kidney disease.

Individuals who used either drug regularly were 2.5 times more likely to be diagnosed with chronic renal failure, compared with individuals who did not use these painkillers. The risk rose in tandem with the amount of either drug taken over a lifetime, the investigators found.

In looking at only participants with diabetes -- a major underlying cause of kidney failure -- **regular aspirin and acetaminophen use were still linked to an increased risk.**

The results support those of other studies that have found an association between regular use of painkillers and an increased risk of chronic kidney failure in susceptible individuals.

The results are consistent with exacerbating effects of acetaminophen and aspirin on chronic renal failure, practically regardless of accompanying disease.

#### **OUR COMMENT:**

About **15% of the people on dialysis** today are there as a **result of the damage that Tylenol and/or aspirin** did to their kidneys. In addition, about **20% of those with heart failure** are also the **result of taking NSAIDs** (nonsteroidal anti-inflammatory drugs), such as aspirin, Tylenol, etc. These drugs may also be associated with diverticular disease of the colon.

**Pain is actually a wonderful gift** – it tells us that something is wrong. Pain is a clear signal given to us to provide immediate feedback from our body so we can take appropriate action to correct the problem. To mask the pain with drugs makes about as much sense as turning off a fire alarm – so you won't hear it -- when your house is burning down. The alarm is warning you that if you don't take action, damage is imminent.

Worldwide research now tells us that **many diseases** that we once thought were from genetics or poor lifestyle causes (eating junk food, etc.) are **really caused from infection**. If you have any type of pain, it may be important to begin the use of both **immune system builders**, such as whole, pesticide-free **colostrum** as well as **natural anti-infective agents**, such as **olive leaf extract, hyssop, virgin coconut oil, wild yew extract** and many others.

