Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 46, No. 6, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.10.082

Aspirin Use in Chronic Heart Failure

What Should We Recommend to the Practitioner?

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There has been ongoing controversy as to whether aspirin should be used in patients with chronic heart failure (CHF). The argument for aspirin is that many patients have underlying coronary disease, and aspirin prevents reinfarction and other vascular events. Arguments against the routine use of aspirin are that many CHF patients do not have underlying coronary disease, and that the benefit of aspirin lessens after the first 6 to 12 months after infarction. Also, several analyses suggest that aspirin may actually worsen outcomes in CHF patients, possibly because it inhibits prostaglandins, with resulting adverse hemodynamic and renal effects. Two recent prospective randomized studies have found that aspirin is associated with more frequent hospitalizations for worsening heart failure, although it did not have an adverse effect on vascular events. These results suggest that aspirin should not be routinely used in CHF patients and be avoided in those with refractory CHF, but that it may be beneficial in patients with recent infarction or multiple vascular risk factors. (J Am Coll Cardiol 2005;46:963–6) © 2005 by the American College of Cardiology Foundation

Coronary artery disease (CAD) is the primary etiology in the majority of patients with chronic heart failure (CHF) due to systolic dysfunction, and aspirin is generally recommended for patients with CAD (1,2). Therefore, it would be reasonable to expect that aspirin would be beneficial and widely used in CHF patients with underlying CAD. Instead, there has been continuing controversy and confusion as to whether aspirin is beneficial or possibly harmful in CHF patients (3). In this brief review, I will summarize the sources of this controversy, comment on pertinent information that has become available recently, including the study by Masoudi et al. (4) in this issue of the *Journal*, and provide my personal perspective on how aspirin should, and should not, be used in CHF patients.

IS ASPIRIN BENEFICIAL IN CHF PATIENTS?

The argument for using aspirin in heart failure patients is its efficacy for patients with CAD, and this is primarily based on the 1994 Antiplatelet Trialists' Collaboration and the updated 2002 Antithrombotic Trialist Collaboration meta-analyses (1,5). Two points relevant to the present discussion should be made concerning these analyses. First, although it is very apparent that aspirin is effective in preventing vascular death and other vascular events when administered early after acute coronary events, the data are more limited and less convincing when taken from trials in which aspirin was initiated in patients with chronic CAD who have not had recent acute coronary events or symptomatic angina. As a result, the most recent American College of Chest Physicians Consensus Conference on Antithrombotic Therapy provided only a weak recommendation for aspirin in patients with chronic CAD (level of evidence 2C) (6). This is the group in which CHF patients with CAD most commonly fall. Second, there is sparse information available about the numbers of heart failure patients who may have been included and their outcomes. With regard to the limited information that is available, patients with heart failure included in post-myocardial infarction (MI) trials of aspirin demonstrated, if anything, an adverse trend (7,8).

Thus, the existing antiplatelet trials and the large meta-analyses do not contribute specific outcome data to support the use of aspirin in CHF patients. Nonetheless, we all must recognize the validity of the oft-used maxim that "the absence of evidence is not evidence of absence." The strongest argument for using aspirin in the CHF population, or at least that subgroup of it with known CAD, is the recognition that these patients remain at risk for vascular events, and specifically for MI, which is known to have a markedly adverse effect on the prognosis of CHF patients (9). However, the incidence of MI has been consistently low in CHF patients enrolled in clinical trials enrolling CHF patients with moderate to severe systolic dysfunction (usually 1% to 2% per year) and substantially lower than the mortality rates in the same trials. Even recognizing that MI may be underdiagnosed in heart failure patients (10), the absolute benefit of aspirin may be low and its benefit-to-risk ratio may not be favorable if counterbalancing adverse effects were present.

IS ASPIRIN POTENTIALLY HARMFUL IN HEART FAILURE PATIENTS?

Controversy concerning the use of aspirin in CHF patients began with post-hoc analyses of the Studies Of Left Ventricular Dysfunction (SOLVD). In reviewing the rela-

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Manuscript received August 2, 2004; revised manuscript received October 14, 2004, accepted October 25, 2004.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CAD = coronary artery disease
CHF = chronic heart failure
MI = myocardial infarction
NSAIDs = non-steroidal anti-inflammatory drugs
SOLVD = Studies Of Left Ventricular Dysfunction
WASH = Warfarin/Aspirin Study in Heart Failure
WATCH = Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial

tionship of several baseline characteristics to outcomes, Pitt and Yusuf (11) noted a significant interaction between antiplatelet therapy (primarily aspirin) and enalapril effect, in which the angiotensin-converting enzyme (ACE) inhibitor benefit on survival was not observed in patients receiving antiplatelet agents. A subsequent and more extensive analysis of the combined SOLVD treatment and prevention trials confirmed this interaction, with enalapril treatment reducing all-cause mortality by 23% (hazard ratio 0.77, 95% confidence interval 0.67 to 0.87) in patients not taking antiplatelet agents, versus a trend toward higher mortality in those taking antiplatelet agents (hazard ratio 1.10, 95% confidence interval 0.93 to 1.30) (12). Subsequent analyses of other long-term ACE inhibitor trials that exclusively or preferentially enrolled patients with known vascular disease (three post-MI trials and the Heart Outcomes Prevention Evaluation [HOPE] as well as the SOLVD prevention trial) also suggested lesser benefit in patients receiving aspirin (13,14). However, despite the size, extensive prospective data collection, and highly significant p values of several of these analyses, non-randomized observational cohort analyses have important limitations that preclude causal attribution (15). Furthermore, with the salient exception of the HOPE trial, patients who were taking aspirin had lower mortality rates than those not taking aspirin, whether they were assigned to the active or placebo treatment groups. Thus, these post-hoc analyses cannot answer the question of whether aspirin is beneficial (or harmful) in CHF patients.

Recently, two prospective randomized studies evaluated the effect of aspirin in well-defined CHF populations with reduced ejection fractions. Although both were limited in size, their methodology makes them the most rigorous assessment of the efficacy of aspirin in this setting. The Warfarin/Aspirin Study in Heart Failure (WASH) was a prospective, randomized, unblinded trial comparing no antithrombotic therapy with aspirin 300 mg/day and warfarin titrated to a target international normalized ratio of 2.5 conducted as a pilot study for a potential larger trial (16). A total of 279 CHF patients with ejection fractions ≤35% were enrolled in the United Kingdom and U.S. End points were adjudicated by a committee unaware of the treatment assignments. The primary composite end point of death, MI, or stroke was experienced by similar proportions of patients assigned to no antithrombotic therapy, aspirin, and warfarin (26%, 32%, and 26%, respectively). A secondary end point, all-cause hospitalizations, was seen more frequently in the aspirin patients (64%) than either no therapy or warfarin (48% and 47%, respectively, $p = 0.044$). This difference primarily reflected a higher rate of heart failure admissions in the aspirin group.

The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial was presented at the March 2004 American College of Cardiology Scientific Sessions; the WATCH trial was a prospective, randomized trial of open-label warfarin titrated to a target international normalized ratio of 2.5 and double-blind aspirin 162 mg or clopidogrel 75 mg, with a primary end point of death, MI, and stroke. The primary hypotheses were that anticoagulation with warfarin would be superior to antiplatelet therapy with aspirin and that antiplatelet therapy with clopidogrel would be superior to antiplatelet therapy with aspirin (17). The latter hypothesis was designed to determine whether aspirin itself or as a result of an interaction with ACE inhibitors has an adverse effect in CHF. The trial was originally designed to enroll 4,500 patients to provide power to test each pairwise hypothesis at an alpha of 0.017. Unfortunately, the trial was terminated prematurely because of lagging enrollment, with a total of 1,587 patients followed for a minimum of 12 months and a mean of 23 months. No significant differences were observed for the primary outcome; however, because of its early termination, the study only retained 41% power to detect a 20% difference. Of note is that 27% fewer patients were hospitalized for worsening heart failure in the warfarin group compared to the aspirin group ($p = 0.01$), with a 31% lower overall rate of heart failure hospitalizations. The clopidogrel group exhibited a statistically non-significant trend toward fewer hospitalizations compared with aspirin. Thus, the findings of the WASH and WATCH trials are quite consistent, demonstrating that aspirin, compared to no therapy or warfarin, was not associated with either an increase or a reduction in death, MI, and stroke. On the other hand, both studies found a substantial excess of hospitalizations for worsening heart failure, and neither study nor the two combined include sufficient numbers of events to exclude a difference in major vascular events.

IS THERE A PLAUSIBLE MECHANISM FOR AN ADVERSE EFFECT OF ASPIRIN IN CHF?

It is difficult to reach definitive conclusions from observational studies, post-hoc analyses of non-randomized subgroups in trials designed to address other questions, and underpowered randomized clinical trials—which constitute the totality of the published data examining the efficacy and safety of aspirin in CHF patients. However, biological plausibility can add a greater degree of credibility to these kinds of observations, and there are plausible mechanisms that could explain the previously summarized findings.

Aspirin inhibits cyclooxygenase, thereby not only inhibiting platelet thromboxane synthesis, the presumed mechanism of its vascular protection, but also generation of prostacyclin and other prostanoids in blood vessels and other organs. In heart failure patients, prostaglandins play an important role in counteracting excessive vasoconstriction associated with neurohormonal activation in this syndrome (18,19). Administration of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, even in low doses, can cause hemodynamic deterioration and impair renal blood flow and renal function (18,20–23). Indeed, observational studies have implicated NSAIDs as increasing the risk of heart failure by up to 10-fold in older patients with a history of heart disease (24,25). If the effect of aspirin is primarily a hemodynamic one, this could also explain why the primary finding in the prospective randomized trial is an increase in episodes of worsening heart failure with no or relatively little change in the incidence of death, MI, or stroke.

One of the mechanisms by which ACE inhibitors improve systemic and renal hemodynamics is through increased synthesis of prostaglandins (26). As a result, some of the effects of ACE inhibitors in CHF are exquisitely sensitive to cyclooxygenase inhibition. Thus, aspirin in doses used for cardioprotection can abolish the vasoconstrictive effects of an ACE inhibitor, whereas similar effects are not seen when with antiplatelet agents whose actions are not mediated by cyclooxygenase inhibition (27). These data have been used to support the hypothesis that there is an interaction between aspirin and ACE inhibitors, which could explain the previously cited findings from the SOLVD trial and other studies (28). However, it is likely that, if aspirin does play an adverse role in heart failure, it would not be restricted to patients taking ACE inhibitors, although it might be more apparent in this group.

The stimulus for this state-of-the-art perspective was the observational analysis of a large cohort of CHF patients examining the relationship of aspirin to outcomes by Masoudi et al. (4) in this issue of the *Journal*. These investigators used data from a national sample of Medicare beneficiaries who were hospitalized for a primary diagnosis with heart failure in 1998 to 2001, which was collected as part of a quality improvement project. They restricted their study population to the 24,012 discharged patients with coexisting CAD, because their objective was to examine aspirin use in this population and determine the relationship between aspirin prescription and subsequent one-year mortality. Of these, 54% were prescribed aspirin at discharge. The primary outcome variable was death at one year. One-year readmission rates for all causes and for heart failure were also examined.

Within the limitations of observational analyses, this study has much to recommend. It includes a large number of patients with a robust database that included 195 variables collected from medical record reviews. Appropriate statistical analyses were employed, and the results are interpreted with reasonable caution. However, the limitations of these types of analyses require emphasis. The use of aspirin was not random, and, not surprisingly, there are major differences between patients who were and were not prescribed aspirin. As was the case in this and in the other cohort studies discussed earlier, those given aspirin tended to be healthier and have fewer comorbid conditions. To list a few, aspirin-treated patients were: slightly younger; less likely to have been admitted from a skilled nursing facility; and less likely to have concomitant atrial fibrillation, chronic lung disease, or dementia. They were substantially more likely to be discharged on ACE inhibitors and beta-blockers and less likely to be discharged on diuretics. They were also more likely to have been treated at a teaching hospital and by a cardiologist. As might be expected, they were more likely to have had a previous MI or revascularization procedure. The investigators attempted to minimize the impact of these imbalances using appropriate adjustment procedures, but such adjustments may not be adequate, and the pattern of differences suggests that there are others that were not measured, which could confound the results. The large discrepancy between the 20% lower unadjusted mortality rate for the aspirin-treated patients (31% vs. 39% for the no-aspirin group) and the adjusted 6% lower relative risk is indicative of the potential impact of additional differences that may not have been taken into account. Another problem inherent in post-discharge studies, and an important potential cause of confounding, is that nothing is known of their post-discharge status and management. Thus, it is uncertain whether the discharge medicines, including ACE inhibitors and beta-blockers or even aspirin, were continued. The inherent assumption that quality and intensity of post-discharge care is equal in patients treated with and without aspirin is probably not valid, given the differences observed in-hospital.

The primary result was a slightly lower adjusted relative risk of death associated with aspirin treatment (hazard ratio 0.94, 95% confidence interval 0.89 to 0.99). Although this figure is reassuring in that it does not show an adverse effect of aspirin, in light of the relatively small reduction in relative risk and the high potential for confounding, it should not be considered robust evidence that aspirin is beneficial. There were similar proportions of the composite of death or readmissions for all causes and heart failure, although information is not provided on heart failure outcomes themselves or whether there is an adverse effect in those at highest risk for worsening heart failure, such as those with moderately or severely reduced ejection fraction or abnormal renal function. Importantly, this study does not provide any information about the safety or efficacy of aspirin in heart failure patients without coronary disease.

ASPIRIN AND HEART FAILURE: WHAT ADVICE SHOULD WE GIVE TO THE PRACTITIONER?

So what should we tell the practitioner? I do not believe there is sufficient data to make an evidenced-based recommendation. With that qualification, I can only present my

personal view of the data and my approach to patients. In reviewing the totality of the data in CHF patients that I have touched upon, including the study by Masoudi et al. (4), I am less concerned that aspirin has an adverse effect on major vascular events (death, MI, or stroke), but I am also not convinced that it is beneficial, even in CHF patients with known CAD. I strongly suspect that aspirin is associated with more frequent episodes of worsening heart failure, but I recognize that the evidence for this is not conclusive.

With regard to patient treatment, I will restrict my comments to heart failure patients with reduced systolic function, because the data, such as they are, are primarily derived from this group. For patients with no evidence of coronary or other atherosclerotic vascular disease, I see no reason to use aspirin for primary prevention and purposefully avoid doing so, even in the presence of most risk factors. My approach to patients with known vascular disease is more individualized. I use aspirin in those with recent coronary events or procedures or current angina, but not necessarily in those with a distant history MI. Given the potential to worsen heart failure, I use aspirin in low doses (81 mg). However, in patients with advanced or refractory heart failure, especially if it necessitates frequent hospital admissions despite optimal medical therapy (and patient adherence to it), I believe it makes sense to consider an alternative antithrombotic agent to aspirin in patients with known CAD because both WASH and WATCH trial patients receiving warfarin had fewer hospitalizations for heart failure, and in the WATCH trial there was a similar trend for clopidogrel that did not reach statistical significance.

Will this issue ever be resolved? Our best hope is the ongoing Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, sponsored by the National Institute of Neurological Disease and Stroke. This study is randomizing 2,860 patients with ejection fractions ≤35% who are in sinus rhythm. The primary end point is death or stroke, but MI and hospitalization for heart failure are two prespecified secondary end points. This trial is well powered to determine whether one of these agents should be preferred in the CHF population, but it may not answer the question of whether aspirin should be used.

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