Therapeutic Failure or Resistance to Aspirin

Gum et al. (1) recently published a highly cited study about the potential clinical consequences of aspirin resistance as assessed by aggregometry in patients undergoing elective cardiac catheterization. In a recent reply to comments raised by Steinhubl et al. (2), Topol and colleagues (3) acknowledge the real possibility of a type II error to detect an association between long-term outcomes and aspirin-resistance status as determined by the Platelet Function Analyzer (PFA-100). In fact, this is a little surprising, because previous studies indicated that PFA-100 results are highly predictive of clinical outcome in stroke patients receiving aspirin (4) and in patients with percutaneous interventions of peripheral arteries who received clopidogrel (5). It is interesting to note that, based on the percentages of aspirin-sensitive and aspirin-resistant-patients presented in Gum et al. (1), Gum et al. (6), and Topol et al. (3), the total number of patients experiencing adverse events is 35 and 43 for aggregometry and PFA-100, respectively. This inconsistency needs further clarification.

What should make the reader more concerned is the high likelihood for an alpha error regarding the main outcome of Gum et al. (1) concerning aggregometry: the total number of aspirin-resistant subjects is limited (n = 17 of 326), of whom only four (24%) experienced an adverse outcome, as compared to 10% of aspirin-responsive patients. Therefore, statistical significance (p = 0.03) relies on only four events in aspirin-resistant patients, and even one event less in this group would be likely to yield an insignificant p value. Considering that the investigators used two methods to assess aspirin resistance (6), the PFA-100 and the aggregometry, a p value correction, if done for the two end points, would also result in an insignificant p value. Thus, statistical significance is not very robust.

The late occurrence of events is conspicuous because it contrasts with what has been observed for the clinical efficacy of aspirin versus placebo, where mortality curves cross after 18 to 24 months (7). This further increases the chances for an alpha error.

Finally, Topol et al. (3) discuss the poor correlation between aggregometry and PFA-100. This is not surprising when differences between methods are considered. The PFA-100 fulfills several of the characteristics of an ideal and rather physiological platelet-function test (8,9). First, whole blood is used rather than platelet-rich plasma. Second, it is a high shear system. This is important, because the cyclo-oxygenase inhibitor aspirin and the purinergic receptor inhibitor clopidogrel are primarily used for arterial indications, which are characterized by high shear rates.

In summary, several trials (1,4,5,10) have generated interest in investigating the clinical consequences of aspirin and clopidogrel non-responsiveness, which, it is hoped, will result in adequately powered confirmatory studies with pivotal results.

REFERENCES

In response to the letter by Dr. Jilma, I believe we have fully addressed his concerns in our primary report (1) and the subsequent correspondence (2). The conclusion of our study was that “further investigation to confirm our findings... should be performed.” We fully acknowledged the relatively small sample size, number of events, and potential for alpha error (1). We also duly noted the poor correlation of the Platelet Function Analyzer (PFA) results despite Dr. Jilma’s expectations.

Rather than investigator “resistance,” we invite Dr. Jilma to perform meaningful prospective research to define further the natural history of anti-platelet drug lack of responsiveness.

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doi:10.1016/j.jacc.2004.01.012

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Angiotensin-Converting Enzyme Inhibitors, Beta-Blockers, and Mortality in Systolic Heart Failure

We read with interest the study by Johnson et al. (1). We believe that one of the key findings of this study was the relatively low rates of angiotensin-converting enzyme inhibitor (ACEI) angiotensin receptor blocker (ARB) and beta-blocker (BB) use in heart failure (HF) patients discharged from the hospital within three months, at 44.3% and 20.9%, respectively, from 1999 to 2000. Furthermore, only 11.3% of these patients received both an ACEI/ARB and a BB. The inclusion in this study of HF patients with preserved left ventricular systolic function (LVSF), or diastolic HF, may partially account for the low rates of utilization of these medications. The current American College of Cardiology/American Heart Association (ACC/AHA) HF guidelines do not have a recommendation to use either ACEI/ARB or BB in patients with diastolic HF. Lack of appropriate use of ACEI/ARB and BB in HF patients with impaired LVSF or diastolic HF indicates poor quality of care and is clearly associated with poor outcomes. Although there is pathophysiological rationale for use of ACEI/ARB and BB in patients with diastolic HF (2), lack of use of these drugs in diastolic HF is neither poor quality of care nor is it associated with poor outcomes. We believe that HF quality improvement programs should focus on increasing the use of ACEI and BB in patients with systolic HF, and studies of quality and outcomes of HF care should classify patients based on their LVSF. Furthermore, ARBs are not currently recommended in systolic HF unless patients have an absolute contraindication to ACEI (2). The U.S. Centers for Medicare and Medicaid Services in its Seventh Scope of Work (2002 to 2005) identified use of ACEI, not ARB, as a quality indicator for HF care for Medicare beneficiaries (3).

We also note with interest an apparent lack of survival benefit of combined use of ACEI/ARB and BB on one-year mortality as compared to therapy with ACEI/ARB alone (1). Most large randomized controlled trials of BBs in systolic HF enrolled patients who were already receiving an ACEI. These studies showed that use of a BB resulted in an additional 35% reduction in mortality in subjects receiving both drugs compared with those receiving an ACEI alone (4). The rate of BB use in patients with systolic HF is low (5), and we are concerned that the finding of lack of survival benefit of BBs in HF as shown in the study by Johnson et al. (1) might be perceived by some clinicians as evidence that results of clinical trials do not necessarily translate into real-life patients.

REPLY

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doi:10.1016/j.jacc.2004.01.005

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REPLY

Drs. Thornton and Ahmed have identified one important message from our population cohort study (1). We agree that beta-blockers and angiotensin-converting enzyme (ACE) inhibitors/receptor blockers were underutilized in heart failure (HF) patients in Alberta, Canada (1), and elsewhere (2–5). We found that adjusted one-year mortality was lower in seniors hospitalized for HF who were prescribed beta-blockers (18.2%; 95% confidence interval [CI] 14.2 to 22.2) or ACE inhibitor/receptor blockers (22.3%; 95% CI 20.9 to 23.7) within three months of hospital discharge than in those with no prescriptions (29.9%, 95% CI 28.8 to 31.0). The use of both beta-blockers and ACE inhibitors/receptor blockers was associated with an even lower mortality (16.6%; 95% CI 13.3 to 20.0) than ACE inhibitor/receptor blockers alone (22.3%; 95% CI 20.9 to 23.7).

The underutilization of effective therapy is not unique (6) even for therapies such as these that have been repeatedly documented to be beneficial in clinical trials that span over a decade (7). To improve the utilization of beta-blockers and ACE inhibitors/receptor blockers, their utilization has been flagged as a marker of quality of care. Our study may provide some clues as to why underutilization persists. Heart failure is not defined in terms of preservation or loss of systolic function; rather, it is a clinical constellation of symptoms (8). Both systolic and diastolic impairment in HF are independently associated with increased mortality risk (9). Clinical trials are not representative of the general population with HF, as younger, male, white, and decreased ejection–fraction patients are over-represented (10). The use of the exclusion criteria of decreased ejection fraction has the effect of under-recruitment of older female patients. In Alberta, seniors (age 65 years and older) constituted about 85% of all new diagnoses during this study period. In those age 75 years and older, women constituted over 56% of hospitalized HF patients. The population in Alberta was similar to that noted in the United States (10).

Thus, the reflective clinician may quite rightly question whether clinical trial results are generalizable to the demographically different population of hospitalized HF patients. Our study can only associate decreased mortality to the use of beta-blockers and