Letters

Possible Benefit to Survival from Early Invasive Strategies in Patients with Acute Coronary Syndromes

TO THE EDITOR: In their systematic review (1), Qayyum and colleagues report that there is no mortality benefit or reduction in nonfatal myocardial infarction from an early invasive strategy compared with conservative management for patients with non–ST-segment elevation acute coronary syndromes. We conducted 2 systematic reviews on this topic (2, 3) and demonstrated a statistically significant improvement in mortality and nonfatal myocardial infarction in the same population over a mean follow-up of 2 years. Specifically, in an analysis of 7 trials with 8375 patients, we noted that the incidence of all-cause mortality was 4.9% in the early invasive group versus 6.5% in the conservative group (risk ratio, 0.75 [95% CI, 0.63 to 0.90]; P = 0.001), and the incidence of nonfatal myocardial infarction was 7.6% in the invasive group versus 9.1% in the conservative group (risk ratio, 0.83 [CI, 0.72 to 0.96]; P = 0.012) (2). Men and troponin-positive patients had the most benefit (3).

The main reason for this discrepancy stems from the fact that 3 of the trials included in the authors’ meta-analysis (VANQWISH [Veterans Affairs Non–Q-Wave Infarct Strategies in Hospital], MATE [Medicine versus Angiography in Thrombolytic Exclusion], and TIMI [Thrombolysis in Myocardial Infarction] IIIb) were done before the era of glycoprotein IIb/IIIa inhibitors and coronary stents and therefore do not reflect current standards of care. Both glycoprotein IIb/IIIa inhibitors and stents statistically significantly increase event-free survival in patients with acute coronary syndromes, and the former is associated with a statistically significant survival advantage (4, 5). Moreover, as the authors note, a large proportion of patients in VANQWISH and TIMI IIIb also received fibrinolysis, which are no longer considered first-line therapy for acute coronary syndromes when percutaneous coronary intervention is easily available (1). In fact, we noted in our meta-analysis a statistically nonsignificant increase in mortality (risk ratio, 1.31 [CI, 0.98 to 1.75]) at 6 to 12 months when these 3 trials were analyzed separately (2).

We are reminded again that it is critically important for systematic reviews to reflect current practice. In doing so, we strongly believe that the current body of evidence demonstrates a mortality benefit and therefore supports early invasive therapy compared with conservative management in patients with non–ST-elevation acute coronary syndromes.

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Potential Financial Conflicts of Interest: None disclosed.

References

3. Bavry AA, Kumbhani DJ, Quiziz R, Ramchandani SR, Kanchalia S, Antman EM. Invasive therapy along with glycoprotein IIb/IIIa inhibitors and intracoronary stents...


IN RESPONSE: We appreciate Drs. Kumbhani and Bavry’s interest in our systematic review. They suggest that excluding 3 trials (TIMI IIIb, VANQWISH, and MATE) that were performed before the current era of glycoprotein IIb/IIIa and coronary stenting would yield different results. When we excluded these 3 trials from meta-analyses, our results did not change (relative risk for death, 0.88 [95% CI, 0.72 to 1.07]; for nonfatal myocardial infarction, 0.82 [CI, 0.57 to 1.17]; and for combined death and nonfatal myocardial infarction, 0.84 [CI, 0.63 to 1.10]).

The discrepancy between our results and the 2 meta-analyses (1, 2) by Bavry and colleagues is due not to inclusion of older trials but to differences in study inclusion criteria. The 2 meta-analyses by Bavry and colleagues included the ISAR-COOL (Intracoronary Stenting with Antithrombotic Regimen Cooling OH) trial (3). We excluded that trial because it did not compare routine invasive with selective invasive strategy. Instead, it compared 3 to 5 days of antithrombotic treatment with less than 6 hours of treatment before coronary intervention. Because almost all patients in this trial underwent angiography within 5 days of randomization, it does not have a selective invasive strategy group and, in our view, should not be included in a comparative systematic review of the 2 strategies.

Drs. Kumbhani and Bavry contend that we should have included only trials that performed coronary intervention according to current standards of care. One can extend this and argue that only trials that meet current standards of care for both coronary intervention and pharmacologic therapy should be included in a systematic review. This would leave only 1 trial, ICTUS (Invasive versus Conservative Treatment in Unstable Coronary Syndromes) (4), which used both glycoprotein IIb/IIIa and coronary stents and had more than 90% of patients receiving statins. This trial, which provided the currently accepted standard of care to enrolled patients, found a statistically significant benefit for the selective invasive strategy over currently accepted standard of care to enrolled patients, found a statistically significant benefit for the selective invasive strategy over

References


Review of Comparative Effectiveness of Treatments to Prevent Fractures

TO THE EDITOR: I greatly enjoyed the systematic review (1) by MacLean and colleagues on treatments for osteoporosis. However, I disagree with 1 point. Although it is true that they “identified 1 trial on the efficacy of alendronate fracture prevention in patients with renal insufficiency compared with those without renal insufficiency” (2), the authors did not mention another similar analysis documenting the efficacy of risedronate for prevention of fractures in patients with renal insufficiency (3). The article on efficacy of risedronate in patients with chronic kidney disease is especially important, because it documented fracture efficacy of risedronate in patients with glomerular filtration rate less than 30 mL/min per 1.73 m² or stage 4 chronic kidney disease, whereas the article that the authors cited reported on patients with glomerular filtration rates as low as 30 to 45 mL/min per 1.73 m².

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Potential Financial Conflicts of Interest: None disclosed.

References


TO THE EDITOR: MacLean and colleagues did not mention musculoskeletal adverse effects associated with bisphosphonates in their review of osteoporosis treatments (1). Although most adverse effects are gastrointestinal, bisphosphonate use may also induce musculoskeletal side effects. Postmarketing reports describe severe disabling
and incapacitating musculoskeletal pain, which may occur up to 4 years after taking alendronate or risedronate (2).

Retrospective cohort studies have examined the prevalence of musculoskeletal adverse effects of alendronate and risedronate (3, 4). Among 840 patients receiving either of these bisphosphonates (84.5% received alendronate), the prevalence of musculoskeletal adverse effects (bone pain, arthralgia, and myalgia) was 2.3% for those receiving alendronate and 3.1% for those receiving risedronate (3). A study of 612 patients in an osteoporosis clinic (4) revealed that 5.6% experienced musculoskeletal adverse effects, including myalgia, arthralgia, back pain, and generalized bone pain, with alendronate and risedronate. Unlike in the former study, all cases of musculoskeletal adverse effects occurred in patients receiving once-weekly formulations of alendronate or risedronate (20.1% and 25% of alendronate and risedronate users, respectively).

Although not as frequent as gastrointestinal side effects, possible musculoskeletal adverse effects may be associated with oral bisphosphonate therapy; clinicians need to be alert for this and counsel patients appropriately.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: We read with interest the recent comprehensive systematic review on osteoporosis therapies by MacLean and colleagues (1), and we would like to bring 3 issues to your attention.

The article describes an increased risk for “mild cardiac events” with raloxifene, based on a combination of 4 events (tachycardia, chest pain, palpitations, and vasodilatation) across 6 studies (n = 2686). Criteria for selecting these particular events and trials are not given. The trials selected do not include pivotal randomized, placebo-controlled trials, such as the MORE (Multiple Outcomes of Raloxifene Evaluation, n = 7705) (2) and RUTH (Raloxifene Use for the Heart, n = 10101) (3) trials, which form the basis of the U.S. Food and Drug Administration (FDA)—approved indications and safety profile for raloxifene. In addition, the term vasodilatation corresponds to hot flashes or flushes, which are not mild cardiac events. If vasodilatation is not included, only 8 “mild cardiac events” remain across the 6 trials, all of which were reported as “chest pain,” with 4 events each in the raloxifene and placebo groups. If “mild cardiac events” includes only the adverse events of tachycardia, chest pain, and palpitations, the numbers of these events do not differ between the raloxifene and placebo groups in the MORE and RUTH studies (data available by request from Dr. Charlie Liu; e-mail, liuch@illy.com).

Second, although the focus of the systematic review is bone agents, no mention is made of the primary efficacy and safety trials (2–4), which had a total of 37,000 participants. The findings of these studies support the more recent U.S. Food and Drug Administration—approved indications for raloxifene: the reduction in risk for invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for breast cancer, in addition to postmenopausal osteoporosis prevention and treatment.

Finally, the authors conclude that the available data are insufficient to determine the relative efficacy or safety of osteoporosis agents because of the lack of head-to-head comparisons. One such comparative study was published on 15 November 2007, 5 days after the end of the specified literature search period. This 18-month, randomized, double-blind trial compared teriparatide with alendronate in 428 patients with glucocorticoid-induced osteoporosis, with a change in lumbar spine bone mineral density as the primary outcome and safety and incidence of fractures as secondary outcomes (5).

We want to bring these 3 points to your readers’ attention so that they are aware of the current available efficacy and safety data.

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References

TO THE EDITOR: The meta-analysis by MacLean and colleagues (1) is interesting and comprehensive, but we question 1 methodological
aspect: the use of previous meta-analyses and their combination with individual trials. The Methods section is unclear as to how previous meta-analyses were chosen or combined, and this may have led to inconsistent results. For example, for alendronate, 2 meta-analyses are listed for patients who are at high risk (defined in Table 1) for hip fracture (Table 4). One meta-analysis includes 2 trials in high-risk patients. The other includes 6 trials: 2 overlap with the first meta-analysis, whereas the other 4 do not meet the authors’ high-risk criteria. How were these 2 meta-analyses combined and the non–high-risk studies incorporated in order to achieve the overall assessment? We suggest that greater consistency and clarity would be gained in building meta-analyses from relevant individual trials.

This inconsistent use of meta-analyses and individual trials could lead to inconsistent results. For example, for hip fractures in high-risk patients, alendronate is assigned “good” efficacy, whereas zoledronic acid is assigned “fair” efficacy. The justification for these categorizations is unclear. Both drugs have 2 trials in high-risk patients. The 2 alendronate studies had hip fracture as secondary outcome. The first showed marginal statistical significance ($P = 0.047$), and the second was very small (4 hip fractures total) and showed no statistical significance. For zoledronic acid, the first study (2) had hip fracture as a primary end point, with very statistically significant results ($P = 0.002$) and the second had a beneficial trend (with 56 hip fractures) (3). It is not clear how these 2 zoledronic acid studies were combined to yield the overall assessment “fair efficacy” because no meta-analysis yet exists, but we performed a pooled analysis to yield a hazard ratio of 0.6 ($P < 0.01$). Thus, evidence for hip fracture efficacy for zoledronic acid is at least as strong as that for alendronate and should support a similar overall efficacy. This inconsistency would have been alleviated by building the meta-analysis from individual studies.

We would like to know what criteria were used to choose meta-analyses for inclusion and how they were combined with each other and with individual trials. We strongly believe that the use and combination of previous meta-analyses is confusing, and it is not always consistent with the authors’ stated methods, and has led in at least 1 case to an illogical efficacy assessment. We suggest that future meta-analyses rely solely on individual studies that meet their specific criteria.

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References

TO THE EDITOR: MacLean and colleagues (1) inappropriately use the same data in 2 mutually exclusive categories, thereby increasing the statistical significance in both of these categories.

Figure 4 in the article concerns hip fractures in high-risk patients. The data source for 3021 of these patients is the review article by Stevenson and colleagues (reference 22). In Table 15 of the review by Stevenson and colleagues, it is evident that the original data are found in the 1996 FIT (Fracture Intervention Trial) of 2027 patients (2) and the 1995 study by Liberman and colleagues of 994 patients (3).

Appendix Figure 3 of the article addresses hip fractures in non–high-risk patients. The data source for 5426 of these patients is the review article by Stevenson and colleagues (reference 22). In Table 15 of the paper by Stevenson and colleagues, the original data come from the 1998 FIT of 4432 patients and the same 994 patients from the 1995 study by Liberman and colleagues.

These 994 patients don’t all belong in both the high-risk and non–high-risk categories. Furthermore, none of the 3 original articles are referenced in the article by MacLean and colleagues, which I think is not good practice.

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Potential Financial Conflicts of Interest: None disclosed.
IN RESPONSE: Dr. Rosen is correct. The study he references (1) was included in our analysis but was not called out in the section on renal insufficiency. This trial reported the effect of risedronate on fractures among participants with varying degrees of renal insufficiency. This study, which combined data from 9 randomized, double-blind, placebo-controlled trials, reported a reduced incidence of vertebral fractures with risedronate compared with placebo in participants with severe, moderate, and mild renal insufficiency.

Although not reported in our paper, we did collect data and calculate pooled estimates for all adverse events reported in all studies reviewed. Details on musculoskeletal and other adverse events can be found in the appendices to the full report (2). We identified between 1 and 3 studies that compared the effect of alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid on myalgias, cramps, or leg pain. Statistically significant risks were observed for ibandronate (2.25 [CI, 1.57 to 3.29]) and zoledronic acid (3.67 [CI, 2.01 to 7.18]) compared with placebo.

As pointed out by Dr. Stock and colleagues, a limitation of our methods is that we did not specifically search for adverse events, but rather collected data on the adverse events that were reported in the context of our defined search strategy. However, data from the MORE trial (3) and the referenced study by Vogel and colleagues (4) are included in our analyses.

Regarding questions about the use of previously published meta-analyses, our methods do not describe pooling across meta-analyses because we did not pool across meta-analyses. All meta-analyses relevant to the study questions were sought, and we described pooled estimates from these meta-analyses as reported by the original authors. When no meta-analyses were available, we pooled data if at least 3 studies were available; otherwise, we reported the results of the 1 or 2 studies identified. Also, as stated in the Methods section of our article, the studies included in each of the meta-analyses are enumerated in the complete report.

Dr. Black and colleagues erroneously state that we assigned a ratings of “good efficacy” and “fair efficacy” for the prevention of hip fractures to alendronate and zoledronic acid, respectively. We reported that each of these agents reduced the risk for hip fracture and that the level of evidence to support this assessment was good for alendronate and fair for zoledronic acid. The criteria used to define the level of evidence are detailed in the Methods section of our article. Per these criteria, however, the level of evidence for both alendronate and zoledronic acid is good, and we thank Dr. Black and colleagues for bringing this error to our attention.

With regard to the data reported in the figures for high-risk populations included in the paper and the data reported in the Appendix Figures for populations not described as high-risk, we would point out that these categories are not necessarily mutually exclusive. In addition, some meta-analyses included in this systematic review reported risk estimates for different risk groups that are not mutually exclusive. Such is the case with the meta-analysis (5) by Stevenson and colleagues. The risk estimates from this meta-analysis for high-risk groups are included in the “high-risk” figures; those for other groups are in the “not described as high-risk” group. It is possible that some of the same patients were included in the overlapping risk groups described in the report by Stevenson and colleagues. However, we do not feel that it was inappropriate for the meta-analysis by Stevenson and colleagues or our review to include data from the same patients in the non–mutually exclusive risk groups. This approach simply provides several different ways to look at the data.

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Potential Financial Conflicts of Interest: None disclosed.

References
Circumstances is it ethical for a physician to be used as an instrument of government to weaken the physical or mental resistance of a human being, nor should a physician participate in or tolerate cruel or unusual punishment or disciplinary activities beyond those permitted by the United Nations Standard Minimum Rules for the Treatment of Prisoners. Physicians must not conduct, participate in, monitor, or be present at interrogations,* or participate in developing or evaluating interrogation strategies or techniques. A physician who becomes aware of abusive or coercive practices has a duty to report those practices to the appropriate authorities and advocate for necessary medical care. Exploiting, sharing, or using medical information from any source for interrogation purposes is unethical.

* Interrogation is defined as a systematic effort to procure information useful to the purposes of the interrogator by direct questioning of a person under the control of the questioner. Interrogation is distinct from questioning to assess the medical condition or mental status of an individual.

We hope that clinicians, policymakers, and the public will find this revision and the rest of the content of the 2005 edition of the ACP Ethics Manual helpful.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

CORRECTIONS

Correction: Comparative Effectiveness and Harms of Treatments for Clinically Localized Prostate Cancer

In a recent systematic review (1) evaluating the comparative effectiveness and harms of treatments for clinically localized prostate cancer, the second sentence in the Data Synthesis section of the abstract should have read: “One [randomized, controlled trial] RCT enrolled mostly men without prostate-specific antigen (PSA)–detected disease and reported that compared with watchful waiting, radical prostatectomy reduced crude all-cause mortality (24% vs. 30%; P = 0.04) and prostate cancer–specific mortality (10% vs. 15%; P = 0.01) at 10 years.”

Reference

Correction: Emerging Antimicrobial Resistance in Neisseria gonorrhoeae

In a recent article (1) on prevention strategies for Neisseria gonorrhoeae, there was a misprint regarding a new type of azithromycin therapy. The sentence describing the delivery method should read: “However, a recently developed extended-release microsphere formulation delivers 2 grams of azithromycin by sachet.”

Reference

Correction: Screening for Osteoporosis in Men

A recent clinical practice guideline from the American College of Physicians (1) and its systematic review (2) contained errors. On pages 681 and 682 of the guideline (1), the criterion for low body weight as a risk factor for osteoporosis in men should have been only body mass index less than 20 to 25 kg/m², not both this body mass index and “weight less than about 40 kg,” as originally stated. The same criterion should have been printed in the Discussion section of the systematic review (2).

References