Empiric β-Blockers for the Prophylaxis of Variceal Hemorrhage: Cost Effective or Clinically Applicable?

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Current guidelines advocate the use of screening endoscopy in patients with cirrhosis to identify those who could benefit from prophylactic therapy to decrease the incidence of initial variceal hemorrhage.[1,2] The decision analysis performed by Spiegel et al. reported in this issue of HEPATOLOGY challenges this practice and illustrates the potential benefit of empiric β-blockers for all patients with compensated cirrhosis. Based on available literature, one must now decide whether these data should immediately affect clinical practice. The purpose of this editorial is to evaluate this study from an evidence-based perspective, identify key components that affect the results, and highlight unresolved issues that require further investigation.

Variceal bleeding is a major cause of mortality in patients with cirrhosis.[3] At the initial time of presentation with cirrhosis, about 30% of patients with compensated disease and 60% of those with decompensated disease have esophageal varices.[4] The annual risk of developing *de novo* varices after presentation appears to be around 8%.[5] In patients with known varices, but who have never experienced variceal hemorrhage, the annual risk of bleeding is between 2% and 70%, depending on the size of the varices, severity of liver disease, and endoscopic criteria.[6] Historically, the 1-month mortality rate associated with variceal hemorrhage has been as high as 50%; even with the advent of endoscopic therapy and the improvement in critical care, the mortality rate appears to be around 20%.[7,8] Given the high prevalence of varices, the high risk of initial hemorrhage from esophageal varices, and the high mortality rate from hemorrhage, primary prophylaxis is an attractive strategy.

Randomized controlled trials evaluating primary prophylaxis with nonselective β-blockers have been published. Based on results from these trials, 3 well-designed meta-analyses have been performed, all showing the efficacy of β-blockers in reducing the risk of a first variceal hemorrhage by about 50%; additionally, all showed a trend toward improved survival.[4,5,9] As a result, the American College of Gastroenterology and the American Association for the Study of Liver Disease have recommended screening endoscopy every 2 years in patients with cirrhosis, followed by pharmacologic prophylaxis in patients with large varices.[1,2] More recently, randomized controlled trials evaluating prophylactic endoscopic band ligation of esophageal varices have been performed. A meta-analysis showed a relative risk of variceal hemorrhage with band ligation compared with no therapy of 0.36 (95% CI, 0.26-0.50) and a relative risk for all-cause mortality of 0.55 (0.43-0.71).[10] In the same meta-analysis, 4 studies comparing band ligation with β-blockers had a pooled relative risk of bleeding with band ligation of 0.48 (0.24-0.96), but no difference in mortality. This raises the issue of whether the decreased risk of bleeding is worth the cost of multiple endoscopies, without benefit in survival. In such cases, decision analysis is an ideal study design to examine the issue.

The field of quantitative analysis has at its disposal a variety of tools designed to assess competing strategies under conditions of uncertainty. Cost-effectiveness analysis is a subset of decision analysis that compares resource use and benefit derived from different strategies under conditions of limited resources.[11-19] Quantitative analyses evaluating interventions to prevent initial variceal hemorrhage in patients with cirrhosis have previously been published. The first compared propranolol with sclerotherapy, but did not consider variceal band ligation.[20] This study assumed that 15% of participants would discontinue therapy due to adverse effects, but otherwise assumed perfect patient adherence. A second published study did not perform a formal cost-effectiveness analysis and only considered high rates of adherence to therapy.[21] Furthermore, both studies assumed that varices had already been documented by endoscopy; thus, neither examined the issue regarding initiation of screening.

More recently, Arguedas et al. created a Markov process to compare strategies of observation, empiric β-blocker without screening endoscopy, screening followed by β-blocker for appropriate patients, and screening followed by band ligation over a 5-year time horizon.[22] They assumed a 15% rate of intolerance of medications, but otherwise did not account for nonadherence to therapy. The study concluded that the preferred

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strategy depended on the severity of liver disease. In Child-Pugh class A patients, the most cost-effective strategy was endoscopic screening followed by β-blocker; in Child-Pugh class B or C, empiric β-blocker was both the most effective and most cost-effective strategy. In a sensitivity analysis, the investigators determined that important variables included the prevalence of varices, the rate of development or progression of varices, the rate of intolerance to β-blockers, and the effectiveness and cost of medications and band ligation.

The study reported by Spiegel et al. adds significant insight to the issues regarding primary prophylaxis of variceal hemorrhage. This work fulfills all requirements of a well-performed cost-effectiveness analysis. Using a 3-year time horizon and the perspective of a third party insurer (the Health Care Finance Administration, HCFA), they modeled a population of patients with Child's class A or B cirrhosis who were assumed to have no contraindication to the use of propranolol or previous investigation for varices. Briefly, they examined strategies including no prophylaxis, empiric propranolol for all subjects, screening upper endoscopy followed by propranolol if moderate or large varices were diagnosed, screening followed by band ligation if moderate or large varices were diagnosed, selective screening of high-risk patients followed by propranolol, or selective screening followed by band ligation. The investigators accounted for intolerance to propranolol, as well as for nonadherence to therapy. The primary outcome of the analysis was the incremental cost-effectiveness ratio, in this case the difference in costs divided by the difference in the number of initial variceal bleeds between competing strategies.

A few methodologic caveats may be noted: discounting of costs and benefits are usually performed in analyses longer than 1 year, and the time frame examined in this study, although understandably limited by available literature to provide variable inputs, may not be adequate to fully assess the impact of these strategies on patients with compensated cirrhosis whose lifespan may be longer than the period of time modeled. Additionally, the primary end point of the analysis is limited to the reduction in the incidence of initial variceal hemorrhage. The analysis does not examine overall mortality, or patient preference for different health states (utility). As a result, mortality and morbidity associated with interventions incur cost, but no decrement in overall outcome. Note that this is not merely a hypothetical problem, but a real one that has been realized in previous clinical trials such as one study reported by Angelico et al. in which, although the incidence of variceal hemorrhage rates was reduced, overall mortality was higher in one intervention group.[23]

The investigators concluded that the incremental cost-effectiveness ratio of empiric propranolol for all subjects compared with observation was $12,408 per initial variceal hemorrhage prevented. They calculated that endoscopic screening for varices was prohibitively expensive, regardless of whether propranolol or band ligation was used for prophylaxis. The incremental cost-effectiveness ratios for screening followed by propranolol and screening followed by band ligation were $175,873 and $178,400 per initial bleed prevented, respectively, compared with empiric propranolol. Likewise, they found that strategies of selective screening of high-risk subgroups of cirrhotic patients were not cost effective, because these strategies were associated with only marginal decrements in cost, but large losses in effectiveness compared with nonselective screening. In fact, selective screening was dominated by the strategy of empiric propranolol, meaning that empiric propranolol was both less costly and more effective than selective screening.

The conclusions of the analysis were dependent on several assumptions that were identified in a series of sensitivity analyses. These factors included the effectiveness of therapy to decrease the incidence of variceal hemorrhage, compliance (or adherence) to medical therapy, and the cost of therapy. One factor not varied by the investigators was the assumption that patients informed of the presence of varices at risk for bleeding by endoscopy would be more compliant with therapy than those in whom empiric therapy was undertaken. This assumption explains the curious result that reserving therapy for only those diagnosed with at-risk varices was more effective at decreasing the risk of initial variceal hemorrhage than empiric β-blocker therapy for all patients with compensated cirrhosis. Although reversal of this assumption would alter the results, it would do so by worsening the incremental cost effectiveness of endoscopic screening to detect varices, thus strengthening the argument of the investigators.

Comparison of the studies by Arguedas et al.[22] and Spiegel et al. reveals additional insight into the issue of primary prophylaxis for variceal bleeding. Spiegel et al. found that in patients with compensated cirrhosis, empiric primary prophylaxis with β-blocker was the most cost-effective strategy to prevent variceal hemorrhage. Endoscopic screening followed by either β-blockers or band ligation prevented a greater number of initial bleeds, but at a prohibitive cost. Arguedas et al. also found that empiric β-blockers constituted the most cost-effective strategy, but only in patients with decompensated cirrhosis; those with compensated disease were most efficiently managed by screening endoscopy with prophylaxis for patients with varices. The discrepancy between studies is likely based on different assumptions for the model variables. Arguedas et al. assumed a relative risk of variceal hemorrhage with band ligation compared with no therapy of 0.55, derived from individual randomized controlled trials, whereas Spiegel et al. assumed a relative risk of 0.36 based on a published meta-analysis.[10] In fact, the base-case value of the effectiveness of band ligation in the Arguedas model was outside of the 95% confidence interval reported by that meta-analysis. With the range of variable assumptions used in the sensitivity analysis, Arguedas et al. reported that band ligation would be the preferred strategy only if the relative risk of hemorrhage was less than 0.3. Finally, the Arguedas model assumed perfect adherence to medical therapy, whereas Spiegel's accounted for nonadherence, which likely resulted in band ligation becoming the most effective strategy.

Despite the fact that these studies have discrepancies in the relative cost and effectiveness of prophylactic strategies, they retain general agreement regarding the viability of a strategy of empiric β-blocker without screening. Arguedas et al. concluded that the scenarios in which screening would prevent a greater number of variceal bleeds would require the prevalence of large varices to be low (less than ~10%) or the rate of development or progression of varices to be relatively slow (less than 8% per year); otherwise, variceal hemorrhage occurring in the interval between screenings appeared to hamper the effectiveness of endoscopic screening. Paradoxically, Spiegel et al. found that selectively screening patients at high risk for varices was both more costly and less effective than empiric prophylaxis. The analysis showed that ability to predict who is at risk for varices based on clinical parameters is too inaccurate to be incorporated into management practice.

Quantitative analytic studies such as these cost-effectiveness analyses may be hypothesis generating, in that variables critical to the understanding of disease management can be identified and clinical research may be directed to pursue questions of particular relevance. In the case of primary prophylaxis of variceal hemorrhage, the important variables determining the preferred strategy include the prevalence of large varices, the relative effectiveness of β-blockers and band ligation, the costs of each, and the rate of adherence to medical therapy. The base-case assumptions made by Spiegel et al. regarding these variables were derived from the best available data; however, the conclusions were sensitive to key variables within the range reported in the literature. Importantly, the investigators have shown the viability of a strategy of empiric pharmacologic prophylaxis without screening. Whether empiric prophylaxis is more cost effective than screening followed by medical therapy or band ligation remains unresolved. The answer depends heavily on the real-life adherence rates to β-blockers by patients with cirrhosis and on the quality of life associated with β-blockers.

Although it may be premature to adopt the use of empiric prophylactic β-blocker therapy for patients with either compensated or decompensated cirrhosis, this analysis calls for a prospective study comparing empiric versus screening-directed prophylaxis. Additionally, since the downside of β-blockers is not cost, but side effects and patient adherence, it is further suggested that the trial incorporate a measure of effectiveness as well as efficacy. By this it is meant that the population studied in such a trial should not be limited to subjects fulfilling strict inclusion or exclusion criteria, but rather be representative of the population to which the results may be more broadly applied. Truly, decision analysis may not be able to tell you what to do, but rather what to think about.

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