

Clevidipine, an Intravenous Dihydropyridine Calcium Channel Blocker, Is Safe and Effective for Treatment of Patients With Acute Severe Hypertension

Answers to the March 2009 Journal Club Questions

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Editor's Note: *These questions and answers refer to the Pollack et al article [Ann Emerg Med. 2009;53:329-338.] Readers should recognize that these are suggested answers and, although it is hoped that they are correct, are by no means comprehensive. There are many other points that could be made about these questions or about the article in general. Questions are rated "novice," (NOV) "intermediate," (INT) and "advanced" (ADV).*

DISCUSSION POINTS

1. In this uncontrolled, single-treatment arm study, the inclusion criteria were patients greater than or equal to 18 years, with systolic blood pressure greater than 180 mm Hg and/or diastolic blood pressure greater than 115 mm Hg. Evidence of end-organ injury was not a requirement for inclusion in this study. The investigators included left ventricular hypertrophy on ECG as a criterion for end-organ injury.
 - (NOV) A. Find this study's trial registration information at clinicaltrials.gov. Does the planned study differ in any way from that specified in the registry? Consider the inclusion criteria, exclusion criteria, outcome measures, and sample size. If any of these differ, discuss the importance of the differences.
 - (INT) B. Based on this study's inclusion criteria, an asymptomatic 23-year-old man with a blood pressure of 185/100 mm Hg would be eligible for enrollment. The authors state that clevidipine is "effective for controlling blood pressure in patients with severe hypertension requiring urgent treatment." Are patients without evidence of end-organ injury a representative sample of patients requiring urgent treatment? Include in your answer the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7 Report) and American College of Emergency Physicians treatment recommendations for patients with elevated blood pressure without evidence of end-organ damage.
2. The authors conducted an unmasked, uncontrolled, single-treatment-arm, phase III clinical trial to evaluate the safety and efficacy of intravenous clevidipine.
 - (INT) A. Why might these investigators have chosen this study design rather than comparing clevidipine to placebo or a standard treatment for hypertensive emergencies? Are randomized, placebo-controlled trials always considered the optimal study design to test new treatments? Would the inclusion of a placebo arm in this study be considered ethical research?
 - (ADV) B. Compare this study's design to a double-blind randomized trial of this agent against a standard therapy for hypertensive emergency. What additional concerns must one have about this study design compared to the randomized controlled trial?
 - (INT) C. The authors chose to use the intention-to-treat (ITT) principle to evaluate clevidipine's safety and a modified-ITT analysis for measuring drug efficacy. Define the ITT principle and the rationale for ITT in clinical trials. Imagine a randomized trial of a standard drug that cures 40% of subjects who complete standard therapy, and 95% complete therapy, versus a new drug which cures 60% of subjects who complete therapy and 60% complete therapy. The 40% who are unable to tolerate the new drug revert to the standard drug. Calculate the absolute risk difference using completer and intent-to-treat methods. What are the potential advantages and disadvantages of ITT analysis?
3. A primary study outcome was the evaluation of clevidipine's safety profile by measuring the percentage of patients whose systolic blood pressure decreased below the target range within the first 3 minutes of therapy. The investigators also recorded adverse events up to 1 week after clevidipine treatment.
 - (NOV) A. This study did not have a formal data and safety monitoring board, although a future clevidipine trial in heart failure patients (A Safety and Efficacy Study of

Blood Pressure Control in Acute Heart Failure—A Pilot Study [PRONTO], NCT00803634) intends to have periodic data and safety monitoring board review. What is the data and safety monitoring board's role, and ideally who should and should not preside on the committee?

(ADV) B. Serious adverse events were reported in 11 of the 126 (8.7%) patients who comprised the safety population. How does this adverse event rate compare with that of other commonly used agents such as β -blockers and nitrates? According to this single-treatment-arm study design, can these authors be certain that only one of the serious adverse events was possibly related to clevidipine?

4. A. What is the relationship between the investigators and the trial's sponsor? What is the relationship between the trial's sponsor and the investigational agent? What conflicts of interest could be at play? How might these conflicts of interest affect the choice of study design? How is the trial's sponsor using this study to market the drug? (Hint: see company Web site.)

(INT) B. A journal's editor must weigh the pros and cons of publishing each submitted article. Consider the list of pros and cons that might be at play here. What do you think of the article's title?

(INT) C. The Editor's Capsule Summary published with this article states: "Comparative randomized trials will be required before this investigational agent is considered for routine clinical practice." This drug was approved by the Food and Drug Administration in August 2008. Attempt to reconcile these facts. Would you use this drug at this time? What additional information would you desire before using this drug?

ANSWER 1

In this uncontrolled, single-treatment arm study, the inclusion criteria were patients greater than or equal to 18 years, with systolic blood pressure greater than 180 mm Hg and/or diastolic blood pressure greater than 115 mm Hg. Evidence of end-organ injury was not a requirement for inclusion in this study. The investigators included left ventricular hypertrophy on ECG as a criterion for end-organ injury.

Q1.a Find this study's trial registration information at clinicaltrials.gov. Does the planned study differ in any way from that specified in the registry? Consider the inclusion criteria, exclusion criteria, outcome measures, and sample size. If any of these differ, discuss the importance of the differences.

We initially found this trial by going to clinicaltrials.gov and typing "clevidipine," but we also found it by typing "Clevidipine clinical trials" in Google, where the fourth selection was clinicaltrials.gov. The trial's registration page documents that the trial was registered 1 month before patient recruitment began—a good thing—and that the study population, the inclusion and exclusion criteria, and outcome measures reported in the article were identical to those described in the trial registry—another good thing. The only difference

between the registered protocol and the actual study was the sample size. The protocol states "Estimated enrollment: 100," whereas the study enrolled 131 patients during a 5-month period.¹ In the article, the authors state that the sample size was "determined by clinical judgment without formal power calculation" and "no formal statistical hypothesis testing" was performed during the study design phase. Although sample size need not be based on an anticipated hypothesis test—in question 3 of the March 2008 *Annals of Emergency Medicine* Journal Club, we discussed how it can be guided by the desired precision—it is a good idea to use some explicit method to determine the size of one's study.² In the EVALuation of the Effect of ULtra-ShOrt-Acting Clevidipine In the Treatment of Patients With Severe Hypertension (VELOCITY) trial there were 2 primary considerations: estimating the frequency of common undesirable effects such as relative hypotension with adequate precision and detecting rare adverse effects. We will not go into the mathematics of determining sample size to detect rare events, but readers should understand that there are methods that can determine how many subjects are needed to be relatively certain that an adverse effect occurs in less than 1 in (some number) of patients and that without going through such an exercise, it is difficult to say that a study "proves" that a drug is safe.

We do not know why the study recruited 31 more subjects than planned. Perhaps the investigators planned to go 5 months, assuming 20 patients per month, but recruitment went better than expected. If the investigators were conducting a comparative trial and the difference between the active drug and control was small, it would be to the advantage of the drug's manufacturer to enroll more patients to increase the likelihood of getting a "statistically significant" difference. However, in a single-limb trial, the more patients enrolled, the more likely that rare adverse effects would be found. In this regard, it is to the advantage of the sponsor to keep the study small. Thus, it remains unclear why the study was larger than planned.

Q1.b According to this study's inclusion criteria, an asymptomatic 23-year-old man with a blood pressure of 185/100 mm Hg would be eligible for enrollment. The authors state that clevidipine is "effective for controlling blood pressure in patients with severe hypertension requiring urgent treatment." Are patients without evidence of end-organ injury a representative sample of patients requiring urgent treatment? Include in your answer the JNC-7 and American College of Emergency Physicians (ACEP) treatment recommendations for patients with elevated blood pressure without evidence of end-organ damage.

When critically reviewing a study about a therapy, a physician must decide whether the study results should change his or her clinical practice. To make an informed decision, readers should ask 3 questions originally described by Guyatt et al³: What were the results? Are the results of the study valid? Will the results help me in caring for my patients?

Research questions are composed of 3 critical elements: a target population (ie, the domain), a determinant (eg, the

intervention in an interventional design, the grouping variable in an observational study), and 1 or more predefined outcomes.⁴ The domain is the patient population to whom the study results and conclusions may be applied. When one interprets the literature, it is important to consider all 3 elements. In VELOCITY, the determinant was the intravenous administration of clevidipine. The outcomes included predefined systolic blood pressure changes, pulse fluctuations, and dosing. The authors intended the domain to be patients with “acute severe hypertension requiring urgent treatment,”¹ but are the participants in this study representative of that domain? The stated inclusion criteria were patients aged 18 years or older and with persistent severe hypertension, defined as systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 115 mm Hg, assessed on 2 successive readings at least 15 minutes apart. The presence of evidence of acute or chronic end-organ injury was not required for inclusion in this study.

According to the stated inclusion criteria, a 23-year-old man with 2 successive blood pressure measurements of 185/100 mm Hg, with no signs of acute end-organ damage, and without any of the exclusion criteria, was eligible for study inclusion and therefore received continuous intravenous clevidipine infusion for at least 18 hours. Would such aggressive antihypertensive treatment be in line with national recommendations?

The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7 Report), states that marked increases of blood pressure without signs of target end-organ damage usually do not necessitate hospital admission, and such patients may benefit from oral, short-acting antihypertensive regimens.⁵ Furthermore, the JNC-7 report states “there is no evidence to suggest that failure to aggressively lower [blood pressure] in the emergency room is associated with any increased short-term risk to the patient who presents with severe hypertension.”⁵ According to the ACEP “Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients with Asymptomatic Hypertension in the Emergency Department,” “initiating treatment for asymptomatic hypertension in the ED [emergency department] is not necessary when patients have follow-up” and, further, “rapidly lowering blood pressure in asymptomatic patients in the ED is unnecessary and may be harmful in some patients.”⁶ In 2008, *Annals of Emergency Medicine* published a supplement dedicated to the management of hypertension that reiterated these recommendations. Slovis and Reddi⁷ recommended that oral antihypertensive treatment be considered in patients with systolic blood pressure greater than 180 mm Hg or diastolic greater than 110 mm Hg and further that “administering antihypertensive therapy in the ED to acutely decrease blood pressure in patients without end-organ damage is discouraged.”

In defense of the VELOCITY study, 81% of the patients enrolled presented with severe hypertension and end-organ injury. However, left ventricular hypertrophy on ECG was the

sole end-organ injury for 21% of those deemed to have end-organ injury. Although left ventricular hypertrophy can certainly result from untreated hypertension,⁵ most emergency physicians do not believe that hypertension with left ventricular hypertrophy but no other signs of end-organ injury requires aggressive treatment. Furthermore, the JNC-7 report cautions that current ECG algorithms for defining left ventricular hypertrophy overestimate its prevalence in blacks,⁵ a group that accounted for 77% of patients enrolled in VELOCITY.¹ If hypertension with left ventricular hypertrophy alone does not qualify as a hypertensive urgency, then only 76 of 126 (60%) VELOCITY participants had an indication for acute treatment. To measure clevidipine’s efficacy and safety in the target population, it would be prudent to reanalyze the data in only those patients with signs of acute end-organ injury and severe hypertension.

ANSWER 2

The authors conducted an unmasked, uncontrolled, single-treatment-arm, phase III clinical trial to evaluate the safety and efficacy of intravenous clevidipine.

Q2.a Why might these investigators have chosen this study design rather than comparing clevidipine to placebo or a standard treatment for hypertensive emergencies? Are randomized, placebo-controlled trials always considered the optimal study design to test new treatments? Would the inclusion of a placebo arm in this study be considered ethical research?

The investigators do not explain their choice of study design in the article or in the clinicaltrials.gov registry. One plausible line of reasoning goes as follows: (a) the Food and Drug Administration (FDA) requires 2 independent statistically significant at $P < .05$ placebo-controlled trials to establish a drug’s efficacy; (b) clevidipine had already been shown to be superior to placebo in controlling blood pressure in the Efficacy Study of Clevidipine Assessing Its Preoperative Antihypertensive Effect in Cardiac Surgery (ESCAPE) I (preoperative) and ESCAPE II (postoperative) trials⁸; (c) there was little impetus for The Medicines Company to perform another randomized trial; a third positive trial would not add much to the story, but a negative trial could be devastating; (d) The Medicines Company presumably wanted their drug approved for use in the ED and ICU; (e) aware that one of the big safety issues in this environment is “bottoming out” (decreasing the blood pressure too low), the company planned an open-label single-limb observational study to chronicle the frequency of untoward outcomes.

Although the decision to conduct a single-limb open-label trial is wholly in compliance with FDA regulations and provides insight into the drug’s safety profile, such a trial cannot answer the question most important to emergency physicians: is this drug better than the ones I currently use? This question can be answered only through randomized trials testing clevidipine against the relevant agents.

Randomized, blinded, controlled trials are considered the zenith of biomedical therapeutic research because they are the

design least likely to produce a biased result. Provided that a large number of subjects are enrolled (see answer to question 2b of the May 2008 Journal Club [answers published in November 2008] for a discussion of this),⁹ randomization helps ensure that groups are similar with respect to measured and unmeasured characteristics that could affect the outcome and bias the study. The blinding of patients, providers, outcome assessors, and data analysts helps ensure that the 2 groups receive equivalent intervention (except for the therapy being tested) and equal assessment.

The remaining issue is whether the control group should receive a placebo or a currently used intervention. The advantage of a placebo-controlled trial is that this is the only design that asks whether using the drug is better than doing nothing. This is the most fundamental question we can ask about an intervention. The disadvantage is that if there is reason to believe that the currently accepted standard therapy is better than placebo, it may be unethical to give placebo. The advantage of a comparison against standard therapy is that it is the only study design that can answer the question, is the new agent better than the standard one? The disadvantage is that unless the standard therapy has been tested against placebo, we are at risk of endorsing a series of drugs, each of which is shown equivalent to the other but none of which are any better than placebo.

We have already discussed that this study treated patients who may not have required treatment. A placebo limb would certainly be justifiable and desirable in patients who did not have a clear indication for immediate decreasing of the blood pressure. However, for those patients with a true hypertensive urgency/emergency (eg, hypertensive encephalopathy), it would be unethical to give only placebo.

Q2.b Compare this study's design to a double-blind randomized trial of this agent against a standard therapy for hypertensive emergency. What additional concerns must one have about this study design compared to the randomized controlled trial?

This was a single-limb unblinded study of clevidipine, designed to measure the efficacy and safety of the drug. The absence of a control group makes it impossible to know how these patients would have fared if given nothing or a different agent. When a study's outcomes are "soft" or subjective measurements (eg, physician assessment of patient pain relief), the absence of blinding increases the likelihood that outcome reporting could be biased. In the VELOCITY trial, the measurements of blood pressure are not prone to bias, but the counting of adverse events and, even more so, the determination of whether such adverse effects were due to clevidipine could be biased in the absence of blinding. To determine whether this drug is better than standard therapy, one really needs an randomized controlled trial against an appropriate alternative therapy.

But what about questions of safety? Although blinding might increase the validity of adverse event reporting, there are advantages to single-limb studies. First, they are less expensive

and patients are enrolled at least twice as quickly. Consequently, one can generate a larger N, which increases the likelihood of seeing rare adverse events. One can think of many drugs such as Vioxx and Phen-fen that seemed fine in randomized trials but whose adverse effects became apparent only in postmarketing studies when the drug was given to tens of thousands of patients.

Q2.c The authors chose to use the intention-to-treat (ITT) principle to evaluate clevidipine's safety and a modified ITT analysis for measuring drug efficacy. Define the ITT principle and the rationale for ITT in clinical trials. Imagine a randomized trial of a standard drug that cures 40% of subjects who complete therapy and 95% complete therapy, versus a new drug that cures 60% of subjects who complete therapy and 60% complete therapy. The 40% who are unable to tolerate the new drug revert to the standard drug. Calculate the absolute risk difference with completer and ITT methods. What are the potential advantages and disadvantages of ITT analysis?

There are a number of ways one might analyze a randomized trial. One could analyze subjects categorized by the intervention they actually received (a treatment analysis), one could restrict the treatment analysis to those subjects who completed that treatment (a completer analysis), or one could analyze subjects according to the group to which they were assigned by randomization, regardless of whether they received the intervention or completed the treatment specified for that group (an ITT analysis). Those who favor ITT analysis reason that randomization controls for baseline differences between the study groups and that excluding patients who drop out, cross over to a different therapy, or do not complete the intervention defeats the randomization and potentially introduces systematic bias.¹⁰ For example, in this study, all patients enrolled should be included, even if some of them never received clevidipine, started receiving clevidipine but stopped for whatever reason, started receiving clevidipine but received additional antihypertensive agents, etc. If we analyzed only those who received a full course of clevidipine and no additional antihypertensive therapies, we might get an overly optimistic impression of the drug's performance. This can be particularly important when a drug is highly effective, but because of adverse effects or other problems many cannot tolerate the drug. A "completer" analysis might indicate that 90% of patients who complete treatment are cured, whereas an ITT analysis on the same data could conclude that 65% of people are cured if only half the patients completed therapy and the cure rate was 40% in those who did not.

In randomized trials, ITT analysis ensures that whatever equivalence was achieved through the randomization remains, but there is a cost: results of an ITT analysis represent a comparison of those who were randomized to one therapy or another. Depending on circumstances, this could be a very different comparison from that between those who actually had one therapy or the other. Although the first comparison is likely unbiased, it answers the wrong question. The second

comparison answers the right question but can provide a highly biased answer.

The benefit of the ITT analysis for randomized controlled trials is evident in the example posed in question 2c. A completer analysis (a study of only those who completed the prescribed course) of an randomized controlled trial of these therapies would find that the new drug was $60\% - 40\% = 20\%$ better than the old drug. This finding answers the question, if one can tolerate the new drug, how much better is it than the standard drug? An ITT analysis finds that the new drug cures $0.6 \times 60\% + 0.4 \times 0.95 \times 40\% = 51.2\%$ versus $0.95 \times 0.4 = 38\%$ for the standard drug, a difference of 13.2%. This finding answers the effectiveness question, if you give the new drug to 100 persons (followed by the standard drug if they cannot take it), how many will be cured (compared with giving 100 persons the standard drug)? We see how the completer analysis grossly overestimates the drug's effectiveness compared with the ITT analysis. Both values are important, however, because the completer analysis says "if we can find a way to eliminate the adverse effects, the new drug is potent," whereas the ITT value provides a more realistic estimate of the drug's effect in practice.

These examples demonstrate the strength and weaknesses of "actual treatment," "completer," and "ITT" analyses and show that there are many situations in which none of these, alone or in combination, provides a good estimate of a treatment's effect. As we have said in previous Journal Club articles, our main recommendation for such situations is that authors should present the actual data so that readers can calculate any measure they like. If each stratum of patients (eg, those who were randomized to treatment but dropped out) is identified and counted and their outcomes are reported, then readers can make what they like of the data. Readers should also be aware that there are advanced techniques that use Bayesian methods or instrumental variables to explicitly model dropout and crossover phenomena. The methods can provide estimates that have higher validity than treatment, completer, or ITT approaches.¹¹

ANSWER 3

A primary study outcome was the evaluation of clevidipine's safety profile by measuring the percentage of patients whose systolic blood pressure decreased below the target range within the first 3 minutes of therapy. The investigators also recorded adverse events up to 1 week after clevidipine treatment.

Q3.a This study did not have a formal data and safety monitoring board, although a future clevidipine trial in heart failure patients (A Safety and Efficacy Study of Blood Pressure Control in Acute Heart Failure—A Pilot Study [PRONTO], NCT00803634) intends to have periodic data and safety monitoring board review. What is the data and safety monitoring board's role and ideally who should and should not preside on the committee?

The primary purpose of a data and safety monitoring board, also known as a data monitoring committee, is to ensure the safety of participants in the study and prevent them from incurring harm resulting from unnecessary continuation of a

doomed study.¹² The data and safety monitoring board has further obligations to the investigators, trial sponsor, and drug or device regulatory agencies.¹² The study investigators rely on the data and safety monitoring board to protect their subjects from adverse treatment effects. The trial's sponsor depends on the data and safety monitoring board to independently monitor the trial's progress and make informed decisions about whether to continue enrollment or stop a trial early. Early study termination might be determined when the interim results demonstrate a significant harm or benefit or statistical futility in continuing the trial. This topic will be discussed in a future Journal Club article.

A previous phase III clevidipine trial was temporarily suspended in March 2005 after an interim analysis demonstrated more frequent reports of atrial fibrillation in the clevidipine arm than other treatments.¹³ Enrollment was suspended and a detailed assessment of the data by an independent data and safety monitoring board showed no actual significant increase in risk and the trial was resumed. This is an example of how a data and safety monitoring board protects the participants in a trial and also maintains the integrity of the study.

The data and safety monitoring board should be composed of a multidisciplinary team of experts that often includes specialists in clinical trials, biostatistics and study design methodology, epidemiology, and pharmacy for drug trials.¹² The committee that monitors a trial should be independent of the study's investigators and sponsor to avoid conflicts of interest so that the data and safety monitoring board can act solely to protect study subjects.

Q3.b Serious adverse events were reported in 11 of the 126 (8.7%) patients who composed the safety population. How does this adverse event rate compare with that of other commonly used agents such as β -blockers and nitrates? According to this single-treatment-arm study design, can these authors be certain that only 1 of the serious adverse events was possibly related to clevidipine?

In this trial, approximately 40% of patients experienced an adverse event, with 8.7% of patients having at least 1 serious event. The site investigators assessed that only 9.5% of these events were related to the clevidipine treatment.

Medication adverse events are available in electronic resources such as Micromedex and DrugDex.¹⁴ A search for serious and common adverse events for clevidipine, labetalol, nitroglycerine, and nitroprusside shows similar safety data. Serious adverse effects, including ventricular arrhythmia, hyperkalemia, and hepatotoxicity, occur in less than 1% of patients receiving labetalol.¹⁴ Clevidipine's package insert reports that less than 1% of patients with severe or essential hypertension sustained a myocardial infarction, cardiac arrest, syncope, or dyspnea.⁸

A compilation of the common adverse reactions in trial patients treated with clevidipine includes headache (6.3%), nausea (4.8%), and vomiting (3.2%). Nearly 5% (4.8%) of patients with severe hypertension had adverse events resulting in

clevidipine discontinuation.⁸ A review of labetalol's adverse event profile shows that 5% develop orthostatic hypotension, 9% to 20% experience lightheadedness or bradyarrhythmias, and 13% experience nausea after intravenous dosing. Sixty percent of patients receiving nitroglycerine report headache.¹⁴ Prolonged and large infusions of nitroprusside have been associated with hypothyroidism, metabolic acidosis, and cyanide toxicity.¹⁴

Clevidipine's safety profile appears similar to that of other commonly used hypertensive emergency/urgency treatments. However, postmarketing phase IV research studies should continue to monitor the safety of clevidipine and all newly approved medications to ensure that no potential long-term adverse effects were missed in the relatively short follow-up periods of the phase II and III trials or that no rare but major adverse effects were missed because of the small number of subjects involved in the studies.

The single-treatment-arm, uncontrolled study design makes it difficult for investigators to determine with reasonable certainty that only 1 of the serious adverse events was related to clevidipine. The lack of blinding creates the possibility of bias in judging what events were causally related to clevidipine.

ANSWER 4

Q4.a What is the relationship between the investigators and the trial's sponsor? What is the relationship between the trial's sponsor and the investigational agent? What conflicts of interest could be at play? How might these conflicts of interest affect the choice of study design? How is the trial's sponsor using this study to market the drug? (Hint: see company Web site.)

The prescribing information for this drug indicates that it is manufactured by the Hospira Corporation and marketed by The Medicines Company.⁸ It appears from the conflict of interest statement that 3 of the 6 authors are consultants for The Medicines Company and that The Medicines Company sponsored the trial.¹ Much has been written lately about conflicts of interest inherent in the development and evaluation of new therapeutic agents. We encourage readers to peruse the referenced articles.¹⁵⁻¹⁸

Because The Medicines Company is a for-profit entity, its trustees have a fiduciary responsibility to make decisions that optimize conditions for their shareholders. When shown 2 designs that will evaluate one of their drugs in development, one that maximizes that amount of knowledge that will be gleaned and one that maximizes the likelihood that their drug will be approved by the FDA and brought to market, they are obligated to choose the latter. As discussed in question 2a, even though the open-label single-arm trial is not the study an emergency physician would want to conduct—he or she would want to know how this drug does against commonly used agents such as nitroprusside or labetalol in a double-blind randomized trial—one can understand why the company might choose this design.

The drug's Web site (<http://www.cleviprex.com/>) has 3 main clinical sections: operating room, critical care, and ED. The ED section uses the VELOCITY trial considered in this Journal

Club article as evidence that the drug rapidly decreases blood pressure without overshooting the target blood pressure. It also cites the open-label ECLIPSE trial, which showed that the drug had “comparable safety and efficacy” to nitroprusside, nitroglycerin, and nicardipine in perioperative cardiac surgery patients.¹⁹

What the drug's Web site does not say is that:

(a) at least 40% of patients in the VELOCITY trial had no indication for the acute lowering of their blood pressure; and

(b) there are no published studies comparing clevidipine to placebo or another commonly used agent with respect to efficacy, adverse effects, or, most important, patient outcomes for patients with hypertensive urgencies and emergencies.

Q4.b A journal's editor must weigh the pros and cons of publishing each submitted article. Consider the list of pros and cons that might be at play here. What do you think of the article's title?

This article is a great example of the dilemma that journal editors often face. Journals want to inform readers about new, promising agents that might improve patient outcomes. The VELOCITY trial makes a pretty good case that clevidipine is biologically active and, in this oddly defined group of patients, decreases blood pressure in a controllable, predictable manner. These are desirable characteristics. By publishing this article, *Annals* is making its readership aware that this drug exists and that it has promise.

The danger is that this article will be misinterpreted by readers or misrepresented by marketers and used as evidence that emergency physicians should use clevidipine routinely in the treatment of ED patients with hypertensive urgencies and emergencies. *Annals* cannot control this, but it is hoped that the content of the capsule summary that appears with the article, “Comparative randomized trials will be required before this investigational agent is considered for routine clinical practice,” puts the article in its proper context.

Finally, some *Annals* editors might have edited the article's title as follows: “Clevidipine, an Intravenous Dihydropyridine Calcium Channel Blocker, Appears Safe and Effective for Treatment of Patients With Acute Severe Hypertension.” We say this because (a) a 131-patient study is a bit small to render a drug safe (what if the 132nd patient had died?), (b) a single-limb trial is not the best way to establish efficacy or effectiveness, and (c) not all patients had “acute severe hypertension.”

Q4.c The Editor's Capsule Summary published with this article states: “Comparative randomized trials will be required before this investigational agent is considered for routine clinical practice.” The FDA approved this drug in August 2008. Attempt to reconcile these facts. Would you use this drug at this time? What additional information would you desire before using this drug?

The answer to this question should now be clear according to answers to the other questions. The drug's performance against placebo gained it FDA approval. The VELOCITY trial's results were sufficient to convince the FDA of its safety for ED patients and were likely the basis for the FDA granting this indication.

That said, establishing that a drug is better than placebo and safe is not the same as saying it should be used. Although the VELOCITY trial suggests that clevidipine is safe and effective for this indication, the rationale for a switch is not compelling because existing agents are already known to be effective and have far better established safety profiles. Although this does not mean that there is not a clinical situation (nonresponse to traditional treatments or factors [asthma, medication allergies, concerns about cyanide with nitroprusside] that preclude the use of standard agents when we might consider clevidipine), we will not change our routine practice until there is a high-quality double-blind randomized trial that shows that clevidipine is superior to (or equivalent to but less costly than) existing agents.

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