TO THE EDITOR: I read the recent clinical practice guideline on management of venous thromboembolism (1) with great interest; however, I am always suspicious when told that the use of low-molecular-weight heparin (LMWH) products results in less hemorrhagic complications than does intravenous unfractionated heparin. This is so contrary to my clinical experience. I am also well aware that, as Hippocrates noted, “Experience is delusory.”

So my question goes to the original studies analyzed for these guidelines. How many of the underlying studies had no exclusion criteria? In other words, were patients entered into protocols only after screening for chronic kidney disease, age, or other criteria that lead to a greater frequency of hemorrhagic complications? If so, should the guidelines reflect this more explicitly?

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Potential Financial Conflicts of Interest: None disclosed.

Reference

TO THE EDITOR: I am surprised that the recently published guidelines on treatment of venous thromboembolic disease (1) do not include some comments about the added safety of LMWH compared with unfractionated heparin. There is clearly a lower incidence of heparin-induced thrombocytopenia with LMWHs (2–4). The reduced likelihood of thrombocytopenia also decreases the potential for the devastating and life-threatening consequences of warfarin-induced skin necrosis (5).

Indeed, the price of 1 case of heparin-induced thrombocytopenia quickly offsets the increased initial acquisition cost of LMWH. Other savings accrue when using LMWH, such as decreased costs for intravenous solutions, laboratory tests, and nursing time, even in the inpatient setting, compared with unfractionated heparin.

In the 12 or so years that I have prescribed LMWH, I have seen 2 cases of readily reversible thrombocytopenia attributable to LMWH and no cases of thrombotic heparin-induced thrombocytopenia, whereas I routinely see at least 1 case per year of severe, sometimes life-threatening unfractionated heparin–induced thrombocytopenia. To me, the data on the safety and efficacy of LMWHs are far more convincing than as represented in the currently published guidelines. As Dr. Russell Hull told us at the 1997 ACP Annual Session, “Heparin is outdated therapy.” Why are we still using unfractionated heparin at all?

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Potential Financial Conflicts of Interest: Dr. Schreiber serves on the speakers’ bureau for Sanofi-Aventis pharmaceuticals.

References

TO THE EDITOR: In the recent guideline on management of venous thromboembolism (1), observations about the safety of heparin and warfarin during pregnancy need further clarification. Neither warfarin nor heparin is completely safe in pregnancy. The American College of Cardiology recommendations on anticoagulation for pregnant women with mechanical heart valves tell us these 3 interesting facts (2).

First, warfarin is generally safe during the first 6 weeks of gestation and in the second trimester. The risk for fetal embriopathy is at its highest between 6 and 12 weeks of gestation. The drug is also safe in the third trimester, but treatment must be discontinued after 36 weeks of gestation.

Second, unfractionated heparin is safe because it does not cross the placenta and has no clinically significant teratogenicity. However, it is associated with a higher incidence of thromboembolic complications compared with warfarin. Because levels of factor VIII and fibrinogen increase during pregnancy, the response of activated partial thromboplastin time is often blunted.

Third, LMWH lowers the incidence of thrombocytopenia, causes a more predictable response than unfractionated heparin, and is associated with a decreased risk for osteoporosis. However, an increase in the distribution of LMWH as pregnancy advances makes it necessary to monitor anti-Xa levels.

In their systematic review, Chan and colleagues (3) observed that warfarin is generally safe in pregnant women with a mechanical heart valve except between 6 and 12 weeks of gestation, during which substitution with heparin is required.

In conclusion, data from pregnant women with a mechanical prosthesis reveal that warfarin therapy is not completely harmful and heparin has its own limitations.

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IN RESPONSE: Our recommendations are based on evidence from randomized, controlled trials only. That is why the studies that were mentioned in the letters comparing the efficacy of LMWH and unfractionated heparin, as well as for safety of heparin and warfarin during pregnancy, were not mentioned in the guideline. However, LMWH is more cost-effective than unfractionated heparin. Although many studies have evaluated prophylactic use of LMWH in pregnant women, the evidence is scarce for treating deep venous thrombosis or pulmonary embolism in pregnant women.

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References

TO THE EDITOR: Gandhi and colleagues (1) report the results of a randomized, controlled trial on the effect of intensive intraoperative insulin therapy after on-pump cardiac surgery. The authors conclude that the application of an insulin sliding scale that fails to consistently maintain blood glucose levels between 4.4 and 5.6 mmol/L (80 and 100 mg/dL) does not reduce mortality or morbidity in nondiabetic and diabetic patients after a variety of cardiac procedures. An increased incidence of death and stroke in the treatment group prompted the authors to caution against the routine use of insulin therapy during cardiac surgery.

Several aspects of the paper merit further comment. A study paradigm supposedly designed to examine the clinical value of a therapeutic concept in the operating room without considering important principles of surgical and anesthetic care is prone to flaws. Gandhi and colleagues’ paper does not provide the required information for interpretation and understanding of outcomes observed in relatively few patients undergoing interventions of high surgical, physiological, and pharmacologic complexity, such as operations on the heart. What exactly were the surgical procedures performed? What were the patients’ baseline cardiac function and risk assessment? Which anesthetics and narcotics were used, and how was inotropic and vasopressor therapy decided? Was there an attempt to reduce aortic manipulation and embolization? What were the methods of cardiopulmonary bypass, and did they differ by group, surgeon, and procedure? What cardioplegia solutions were used? Was it administered cold, warm, antegrade, retrograde, or both? How was temperature management decided? What were the details of the cardiopulmonary bypass circuitry? Was cardiotomy suction blood reinfused directly, or was it processed through a “cell saver” before reinfusion? What were the nadir hematocrits? Was the transfusion requirement? What was the extent and incidence of bleeding and reoperation? How was heparin therapy managed? Were antifibrinolytics administered, and at what dosages? Were patients’ blood volumes hemocoagulated or ultrafiltered? Did patients receive perioperative antibiotics or steroids? What was the incidence of intraoperative pacing or mechanical assistance?

The authors chose the primary and secondary study outcomes because of their “clinical relevance.” We think that selecting factors that are potentially modifiable by insulin therapy would have increased the clinical relevance of the study results. Atrial fibrillation, heart block, stroke, and postoperative ventilation are outcomes with primarily a surgical or anesthetic cause. It seems very unlikely, for example, that normoglycemia would shorten the action of anesthetics or analgesics, counteract the functional consequences of the type or size of aortic valve inserted (2), or counteract the placement of an aortic crossclamp over an unknown ascending aortic atheroma—arguably one of the most important risk factors for poor cerebrovascular outcome (3).

We must emphasize that normoglycemia was not achieved in the trial. Furthermore, hyperglycemia was not prevented through use of an insulin sliding scale based on blood glucose measurements every 30 minutes (that is, mean blood glucose level after separation from cardiopulmonary bypass was 6.8 mmol/L [SD, 1.3] [123 mg/dL [SD, 24]] in nondiabetic patients and 7.3 mmol/L [SD, 1.6] [132 mg/dL [SD, 29]] in diabetic patients). Considering the well-documented evidence on the importance of tight glycemic control (blood glucose level, 4.4 to 6.1 mmol/L [80 to 111 mg/dL]) (4) and the authors’ ambitious goal to maintain glycemia between 4.4 and 5.6 mmol/L (80 and 100 mg/dL), a more aggressive insulin regimen, including more frequent blood glucose measurements, would have been expected. It is therefore debatable whether insulin therapy was as intensive as stated in the title.

Gandhi and colleagues’ paper is accompanied by an editorial by van den Berghe (4), the principal author of the Leuven trial (2), which demonstrated superior survival with strict glycemic control in critically ill patients, most after cardiac surgery. As all patients in the Leuven study received parenteral or enteral nutrition, it remains unknown whether reduced mortality in the treatment group was due to the benefits of feeding while maintaining normoglycemia using insulin or to the harm inflicted with hyperalimentation and hyperglycemia in the conventional group (5). The results of Gandhi and colleagues’ study, in context with the current body of literature on glycemic control and glucose–insulin–potassium infusions, clearly emphasize the need for trials designed to dissect the clinical effects of insulin therapy, nutrition, and normoglycemia in cardiac surgery. Until the results of such studies are available, we are hesitant to accept that a therapy that seems to be effective in postoperative...
critical care can be harmful intraoperatively. However, we believe that the efficacy of metabolic therapies depends on the nutritional state of the persons studied—that is, whether they are fed or not. Currently, it is too early to speculate what diet, if any, is best for patients undergoing open heart surgery, but we do know that studies conducted during surgery are not performed in a black box, also known as the operating theatre.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: In their recent article comparing intensive intraoperative insulin therapy and conventional glucose management during cardiac surgery, Gandhi and colleagues (1) did not discuss the medications used during induction of anesthesia, specifically whether etomidate was used. This is important for 2 reasons. First, Edelman and colleagues (2) showed that etomidate administration in humans resulted in cerebral deoxygenation and enhanced hypoxic risk in the setting of cerebral ischemia. Second, the adrenal counterregulatory hormones are inhibited by etomidate, which can last 8 to 12 hours (3), and could have contributed to more morbidity—especially in the intensive insulin-treated group, where the brain is more vulnerable at lower blood glucose levels (4).

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References

TO THE EDITOR: The results of a nicely planned and performed randomized, controlled trial were recently published in the article by Gandhi and colleagues (1). The study has a relevant message for routine clinical practice, preventing clinicians from introducing tight blood glucose control during cardiac surgery. We agree with the main conclusions from the study about the lack of benefit of intensive insulin therapy during cardiac surgery, although it is not a surprising finding, as stated in the editorial by Van den Bergh (2).

As the editorialist pointed out (2), the increase in mortality is not significant and may be attributable to chance. Furthermore, the study was neither designed nor powered to answer such a question. However, when the data are carefully examined, concern arises about some differences in the baseline characteristics of the 2 study groups that may explain, at least in part, the occurrence of more deaths and strokes in the intervention group. The main difference is in the use of aspirin: 89 (48%) patients in the intensive treatment group versus 112 (60%) in the conventional treatment group. This difference is significant ($P < 0.025$) and may have some relationship with the different event rate detected. Furthermore, if taken together, some additional differences between the groups, although not statistically significant, may have a relevant influence on the outcome: More male patients were included in the intensive treatment group (134 vs. 123 patients), fewer received angiotensin-converting enzyme inhibitors (65 vs. 72 patients) and β-blockers (96 vs. 103 patients), and more had a history of cerebrovascular disease (20 vs. 13 patients). Among patients with diabetes, 20 (vs. 11 in the control group) were previously treated only with oral drugs. The heterogeneity in the baseline characteristics of the study groups is most likely due to a random effect, but we feel that this factor may explain an important part of the excess event rate reported in the intensive treatment group. We strongly believe that further clinical research on this important issue is warranted.

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Potential Financial Conflicts of Interest: None disclosed.

References
IN RESPONSE: Drs. Carvalho and Schricker ask for several details on the surgical interventions pertaining to the applicability of study findings to other settings rather than to the validity of results. It is important to realize that the degree of intraoperative glycemic control was the only difference in study intervention between the 2 groups. The beauty of randomization with allocation concealment is that all known and unknown prognostic variables should be equally distributed between the 2 study groups. Specific surgical details can be provided by personal communication but are beyond the scope of our response.

Although we appreciate the concerns of Drs. Assaly and Habib, we did not use etomidate for induction of anesthesia in our study patients. We chose the study outcomes not only because of clinical relevance, but also because other studies showed that glycemic control, insulin use, or both affected death (1, 2), stroke (3), prolonged mechanical ventilation (1, 2, 4), acute renal failure (2, 4), sternal wound infections (2), atrial fibrillation (2), and heart block requiring pacing (2).

We never claimed that normoglycemia was achieved during cardiac surgery. We were able to achieve as strict glucose control as was safely feasible by monitoring glucose levels every 30 minutes in the operating room (intensive by most standards). A hyperinsulinemic, normoglycemic clamp can achieve normoglycemia (5), but measurement of glucose concentration every 5 minutes with constant titrating of dextrose levels to clamp glucose levels at goal would not be practically feasible outside of a study protocol. Although a more aggressive insulin infusion protocol may have further decreased intraoperative glucose concentrations, it also may have resulted in a greater frequency of hypoglycemia. Identification of hypoglycemic symptoms is especially challenging in an unconscious patient, and the prognosis of hypoglycemia remains unclear.

Drs. Rius and Mauricio noted a difference in some patient characteristics between the 2 study groups at baseline (for example, aspirin use), which may be a reasonable explanation for the increased incidence of strokes and deaths in the intensive treatment group. The small number of events makes it difficult to draw firm conclusions about stroke and death despite the fact that these reached statistical significance. The issue in interpreting the data, we believe, is not whether the distribution of events is too extreme to have occurred by chance alone, but rather whether such few events should drive clinical policy. We clearly think this would be misguided until more trials or a much larger trial become available.

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References
Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We thank Drs. Shastri and Stein for their comments and their very relevant questions, which provide us with an opportunity to address several important clinical issues. First, our comment on “systematic evaluation” refers to the automated developed and quantitative immunochemical FOBT. As Drs. Shastri and Stein point out, they, we, and others have evaluated the office-developed immunochemical FOBT (1, 2). However, the test uses a fixed threshold set by the manufacturer, and the hand development is not conducive for large-scale population screening. Evaluating the immunochemical FOBT as a laboratory test, with a quantified result, allows the treating physician to decide whether the test is positive or negative, and whether further evaluation is required. Second, the number of requested stool samples definitely influences screening adherence. In our study population, which is used to collecting 3 guaiac-based FOBTs, this was not an issue. However, we are now completing a study on an average-risk population, which will allow us to evaluate adherence in persons in this population who, to date, have not participated in FOBT screening. Third, the maximum cost of FOBT screening is set by our Ministry of Health because this test is available for the total population through their own health maintenance organization. The $20 cost is the total cost per patient that was estimated by the local health insurance agency for up to 21 days in the Gårdlund study, although the mean duration was 8.2 days. However, Gårdlund’s figure shows that the 4-fold difference in fatal PE at 21 days had completely disappeared 2 weeks later. Heparin, thus, may have delayed some events by a few days in the study, but it did not prevent events, and selection of the 21-day time point dramatically distorts the study’s overall findings. Dentali and colleagues never mention their alteration of the original data.

Third, Mahé and colleagues reported 27 PEs (10 heparin, 17 control) that were “discovered at autopsy,” with no indication that any were clinically important. Dentali and colleagues included these cases, which favored heparin, as “fatal” PEs, but excluded identical cases from Gårdlund’s study, which favored the control (33 heparin, 12 control). Dentali and colleagues exclude any other laboratory test. Second, the number of requested stool samples definitely influences screening adherence. In our study population, which is used to collecting 3 guaiac-based FOBTs, this was not an issue. However, we are now completing a study on an average-risk population, which will allow us to evaluate adherence in persons in this population who, to date, have not participated in FOBT screening. Third, the maximum cost of FOBT screening is set by our Ministry of Health because this test is available for the total population through their own health maintenance organization. The $20 cost is the total cost per patient that was estimated by the local health insurance agency for up to 21 days in the Gårdlund study, although the mean duration was 8.2 days. However, Gårdlund’s figure shows that the 4-fold difference in fatal PE at 21 days had completely disappeared 2 weeks later. Heparin, thus, may have delayed some events by a few days in the study, but it did not prevent events, and selection of the 21-day time point dramatically distorts the study’s overall findings. Dentali and colleagues never mention their alteration of the original data.

First, Cohen and coworkers report no PEs in the fondaparinux group and 5 “fatal PEs” in the control group at 15 days, but as the authors state: “Two of the five were confirmed by autopsy, the others were assumed to be due to pulmonary emboli, as no other plausible cause was found” (2). Because Dentali and colleagues state that they “only considered objectively documented and independently adjudicated outcomes,” the 3 “assumed” PEs should clearly not have been counted.

Second, for Gårdlund’s study, which had fatal PE at 60 days as its primary outcome, Dentali and colleagues listed 3 fatal PEs in the heparin group and 12 fatal PEs in the control group, numbers that are very different from those reported by Gårdlund (15 and 16, respectively). Dentali and colleagues seem to have taken events at 21 days from Gårdlund’s figure, presumably to consider only events occurring “during anticoagulant prophylaxis.” Prophylaxis was given for up to 21 days in the Gårdlund study, although the mean duration was 8.2 days. However, Gårdlund’s figure shows that the 4-fold difference in fatal PE at 21 days had completely disappeared 2 weeks later. Heparin, thus, may have delayed some events by a few days in the study, but it did not prevent events, and selection of the 21-day time point dramatically distorts the study’s overall findings. Dentali and colleagues include these cases, which favored heparin, as “fatal” PEs, but excluded identical cases from Gårdlund’s study, which favored the control (33 heparin, 12 control).

If the meta-analyses are recalculated with the corrections described here, there are no significant findings in the article by Dentali and colleagues. The value of anticoagulant prophylaxis in hospitalized medical patients remains uncertain.

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Potential Financial Conflicts of Interest: None disclosed.

References


IN RESPONSE: Dr. Lederle and associates question our conclusion that symptomatic VTE in medical patients is reduced during treatment with prophylactic anticoagulants. We acknowledge that a discussion of these matters is important, because our findings could influence the care of many patients.

First, they indicate that Cohen and colleagues’ (1) did not confirm all fatal PEs with autopsy. They propose that this would overestimate the risk for such events. We included these events because, in accordance with our prespecified criteria, they were independently adjudicated as fatal PEs.

Second, they questioned our decision to extract data from only the first 21 days of follow-up in Gårdlund’s study (2). We did this because, in accordance with our analysis plan, we were assessing the effect of prophylaxis during anticoagulant treatment, and prophylaxis was given for up to 21 days in Gårdlund’s study. Nonetheless, we agree with their questioning the efficacy of anticoagulant prophylaxis after treatment is stopped. Indeed, we state that “the risk for VTE in patients after prophylaxis is stopped remains to be clarified and should be evaluated in future studies.”

Third, they criticized our extraction of data because we counted all fatal PE events from Mahé and colleagues’ study (3) but counted only “clinically relevant fatal PE” for Gårdlund’s study. This was not done by choice, as Lederle and associates infer, but was based on our prespecified decision to extract primary outcome data as reported in each study. Although it would be ideal to have a standardized definition of “clinically relevant PE,” this definition does not exist. To account for the differences across studies in their methods of outcome determination, we compared outcomes within each study in an attempt to provide a consistent and nonbiased assessment of the efficacy of anticoagulants to prevent symptomatic VTE.

Although Lederle and associates state that our findings would be rendered null by a more circumspect reporting of outcomes, we disagree. We stand by our conclusion that anticoagulant prophylaxis reduces symptomatic VTE on the basis of the totality of evidence: across-study consistency of risk reduction for PE, risk reduction for symptomatic deep venous thrombosis (odds ratio, 0.47 [95% CI, 0.22 to 1.00]; P = 0.05), and supportive evidence from other studies that anticoagulant prophylaxis reduces asymptomatic deep venous thrombosis in medical patients (4).

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References


CORRECTION

Correction: Counseling about Proper Use of Motor Vehicle Occupant Restraints and Avoidance of Alcohol Use while Driving

In the recent U.S. Preventive Services Task Force guideline on counseling about proper use of motor vehicle occupant restraints and avoidance of alcohol use while driving (1), some errors were found after the article was printed. In the abstract, the second recommendation was omitted: “Current evidence is insufficient to assess the balance of benefits and harms of routine counseling of all patients in the primary care setting to reduce driving while under the influence of alcohol or riding with drivers who are alcohol-impaired. (I state-ment).” The first sentence of the Introduction should have read: “Over the past decade, legislation and enforcement have contributed substantially to the increasing trends in the use of child safety seats and safety belts.” Finally, in the second-to-last paragraph of the Effectiveness of Counseling to Change Behavior section, the third sentence was omitted: “Self-reported seat belt use increased equally in both the control and treatment groups.”

These corrections have been made to the online version of the paper.

Reference