

# Risk Factors for Clinically Important Adverse Events After Protamine Administration Following Cardiopulmonary Bypass

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**Objectives.** The purpose of this study was to determine risk factors for adverse events following protamine administration after cardiopulmonary bypass.

**Background.** Intravenous protamine administration is associated with a risk of severe systemic reactions. However, risk factors for these events have not been well delineated, thus hampering development of preventive strategies.

**Methods.** A case-control study nested within a cohort of consecutive patients undergoing surgery requiring cardiopulmonary bypass was performed. The primary case definition included those events (pulmonary hypertensive and systemic hypotensive) occurring within 10 min of protamine administration in the absence of other measurable causes of hemodynamic compromise.

**Results.** Comparing the 53 cases to the 223 control subjects, three risk factors were independently associated with events (multivariable odds ratio [95% confidence interval]): neutral protamine Hagedorn insulin use (8.18 [2.08, 32.2]); fish allergy

(24.5 [1.24, 482.3]), and a history of nonprotamine medication allergy (2.97 [1.25, 7.07]). These risk factors demonstrated an increasingly strong association with progressively more specific case definitions. An estimated 39% of cardiopulmonary bypass patients had one or more of these risk factors. Prior intravenous protamine, central venous pressure prior to protamine, preoperative ejection fraction and the need for inotropes when coming off bypass did not exhibit statistically significant associations with events (all  $p > 0.15$ ). Prior protamine allergy was associated specifically with an increased risk of pulmonary hypertension (multivariable odds ratio 189; 95% confidence interval 13, 2,856).

**Conclusions.** Immunologic factors are important in predisposing individuals to protamine reactions, and a substantial proportion of patients are at considerably increased risk. Strategies to reduce the risk of protamine-associated events are needed.

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Protamine, when administered intravenously to neutralize heparin, is associated with occasionally severe systemic reactions (1) that are associated with substantial morbidity and mortality (2–7). Because of its routine use after cardiac surgery requiring cardiopulmonary bypass (CPB) and its use after other procedures that require heparin (8,9), hundreds of thousands of patients are exposed to protamine each year in the U.S. alone (10).

Putative risk factors for protamine reactions have been proposed, mostly based on case reports and the possible

immunologic mechanism of protamine reactions. These possible risk factors include the prior use of protamine-containing insulin preparations (neutral protamine Hagedorn [NPH] and protamine–zinc insulin) (3,7,11–16), prior exposure to intravenous protamine (14), fish allergy (4,17), prior vasectomy (6,18,19), poor left ventricular function (1,20–22), circulatory instability (1,23) and low cardiac filling pressures (1). Prior allergic reactions to other medications may also serve as a marker for increased risk of adverse events to drugs in general (24–27). However, evidence that any of these are truly independent risk factors for protamine reactions is lacking, and results are often inconsistent among studies. These limitations have prevented development of the proper approach to minimizing the risk of these potentially life-threatening reactions.

The purpose of this study therefore was to use a case-control study nested within a retrospective cohort study (28) to identify clinical variables that are independently associated with adverse events following protamine administration in patients undergoing surgery requiring CPB.

## Methods

**Cohort population.** All 2,684 patients who underwent surgery requiring CPB at the Hospital of the University of

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#### Abbreviations and Acronyms

|      |                                              |
|------|----------------------------------------------|
| CI   | = confidence interval                        |
| CPB  | = cardiopulmonary bypass                     |
| CVP  | = central venous pressure                    |
| HUP  | = Hospital of the University of Pennsylvania |
| IABP | = intra-aortic balloon pump                  |
| Ig   | = immunoglobulin                             |
| NPH  | = neutral protamine Hagedorn                 |
| OR   | = odds ratio                                 |

Pennsylvania (HUP) from 1990 through 1994 were identified for the study cohort by ICD-9-CM procedure code 39.61. The 14 subjects with more than one eligible surgical procedure during the years studied had only one procedure chosen at random for inclusion in the study. Five hundred and twenty-five charts (19.6%) could not be located by the Medical Records Department, and 55 (2.0%) were excluded because they had insufficient data to determine if the patient met the primary case definition (defined below). On the basis of review of our computerized medical records database, there was no difference in the age (mean age 63 versus 64 years;  $p = 0.08$ ) or race ( $p = 0.9$ ) of subjects among those with charts available compared with those without charts available; subjects with charts available were somewhat less likely to be women (29%) than subjects without charts available (36%;  $p < 0.01$ ). Twenty-one patients were excluded because they did not receive protamine after surgery (because the patient either was not put on CPB or died during the operation), and 14 because they had a surgical complication (defined as any intraoperative complication that required surgical repair) at the time of protamine, leaving a total of 2,069 patients.

**Case and control selection.** *Primary definition of cases.* Cases were defined in two stages. First, all adverse events potentially related to protamine were identified from the cohort if they occurred within 30 min of the initiation of protamine, were prolonged (lasting longer than the 5-min period of protamine infusion) and met one or more of the following criteria: 1) a decrease in systemic arterial pressure following protamine of  $\geq 25\%$  of baseline or a decrease of  $\geq 10\%$  requiring inotropic medications, reinstitution of CPB or use of an intra-aortic balloon pump (IABP); 2) an increase in pulmonary artery pressure of at least 25%, resulting in a decrease in systemic arterial pressure as defined in 1) above; 3) noncardiogenic pulmonary edema, defined as any decrease in  $PO_2$  requiring an increase in ventilatory support (increase in percent oxygen delivered or ventilatory rate, or positive end-expiratory pressure) in the absence of evidence of cardiac failure (falling cardiac output or increase in pulmonary capillary wedge pressure), and/or 4) bronchospasm (the use of bronchodilator therapy for either an elevation of peak inspiratory airway pressures of greater than 5 mm Hg or wheezing). These events included those that were preceded by pulmonary hypertension, but clinically insignificant elevations of pulmonary pressures were not considered as events. All patients at

HUP have hemodynamic data recorded every 5 min intraoperatively on standardized data collection forms. Therefore events could be identified in the 98% of procedures with complete hemodynamic data.

Next we excluded from the primary analysis any event that occurred in the setting of other causes of hemodynamic compromise at the time of protamine infusion (use of any vasodilating medications, hypercarbia [ $PCO_2 > 50$ ], hypoxia [a fall in  $PO_2$  of  $>2$  percentage points requiring therapy] or ischemia) and any event occurring more than 10 min after initiation of protamine. Thus, the primary case definition was any event that occurred within 10 min of protamine in the absence of other measurable causes of hemodynamic compromise, and combines some of the strictest criteria from published studies (12,14,29,30). It is important to note that the term “adverse event,” rather than “protamine reaction,” is used explicitly to emphasize that, in any given patient, it is impossible to know if an event is due to protamine alone, some other event, or both.

**Control subjects.** Control subjects were selected at random in a 4:1 ratio to cases from among all subjects in the cohort without an adverse event. Similar to cases, control subjects were excluded from the primary analyses if they were exposed to other potential causes of hemodynamic compromise, thereby avoiding any bias that could occur if the exclusion criteria for control subjects differed from those for cases (31).

**Data collection.** To identify all adverse events, trained abstracters, blinded to the study hypotheses, recorded intraoperative hemodynamic data from the anesthesiologists' data forms for all subjects in the cohort. All records of subjects with adverse events and a 5% sample of control subjects were rereviewed independently by one of the investigators (S.E.K.), and in no case was either an adverse event missed or an adverse event identified when one did not, in fact, occur. All cases and control subjects then had their medical records reviewed in detail by a different group of trained abstracters using a structured data collection instrument to identify all a priori risk factors (listed below), selected prior to the start of the study, and potentially confounding variables. Abstracters collected these data prior to reviewing the subjects' anesthesia records (which would identify adverse events), and used information only if it was recorded in the medical records prior to the administration of protamine. Data were available in more than 98% of records for all variables of interest except central venous pressure (CVP) (93.4% available), prior intravenous protamine (67.8%) and ejection fraction (66.1%). Twenty-seven records were randomly selected for reabstraction by a different abstracter; agreement between abstracters was greater than 90% for most variables.

**Data analysis.** *Primary analysis of risk factors.* The odds ratio (OR) was used to estimate the relative risk of adverse events for subjects with and without each risk factor. A priori risk factors were: prior or current use of protamine-containing insulin; prior exposure to intravenous protamine; fish allergy; prior vasectomy; a history of protamine allergy; left ventricular function, as measured by preoperative ejection fraction; circu-

**Table 1.** Risk of Events by Definitions

| Event Definition*                                       | Number with Event<br>(Number at Risk = 2,069) | Risk of Event<br>(95% Confidence Interval) |
|---------------------------------------------------------|-----------------------------------------------|--------------------------------------------|
| Primary definition                                      | 53                                            | 2.56% (1.92%, 3.34%)                       |
| Events within 20 min, in absence of<br>other etiologies | 69                                            | 3.33% (2.60%, 4.20%)                       |
| All events within 20 min                                | 190                                           | 9.18% (7.97%, 10.51%)                      |
| All events within 30 min                                | 230                                           | 11.11% (9.79%, 12.55%)                     |

\*Event definitions in text.

latory instability, as measured by the need for inotropes when coming off CPB (but prior to protamine); low cardiac filling pressures, as measured by CVP prior to protamine (because pulmonary capillary wedge pressures were not routinely measured in the operating room), and a history of prior allergic reactions to any medications other than protamine. The chi-square or Fisher's exact statistic and the 95% confidence intervals (CIs) for each OR were determined.

Multivariable logistic regression analysis was performed to estimate the OR for each a priori risk factor after adjusting simultaneously for all other risk factors and potential confounders. Potential confounders were included in the models if their inclusion changed the unadjusted OR for any candidate risk factor by more than 15% (32). Protamine allergy and vasectomy could not be included in the multivariable analyses because there were no exposed cases using the primary definition. Interactions between each putative risk factor and both the other risk factors and the confounders were assessed using the relevant product terms in the multivariable models.

*Analysis by strictness of definition of "protamine reactions."* To assess the specificity of the primary case definition and to better evaluate whether putative risk factors were predicting "protamine reactions" or just hemodynamic events unrelated to protamine, cases were categorized by increasingly liberal definitions of "protamine reactions": 1) the primary definition; 2) events occurring within 20 min of protamine in the absence of other causes of hemodynamic compromise; 3) all events occurring within 20 min regardless of other causes, and 4) all events occurring within 30 min. One would expect that variables that were truly risk factors for protamine-related events would exhibit increasing ORs with increasingly strict definitions of events if these definitions were increasingly specific for protamine reactions, whereas variables that were not directly related to protamine would not exhibit increasing ORs (33).

*Analysis by severity and type of reaction.* Because there are different severities and mechanisms of reactions to protamine, we performed secondary analyses to examine the association between each risk factor and both the severity and type of reactions. "Severe" hypotensive events were defined as a decrease in blood pressure of at least 25% that required treatment with inotropes, IABP or reinstitution of CPB, and "moderately severe" events were all others. The odds of having a "severe" event relative to the odds of having a "moderately severe" event were then determined for each risk factor. Reactions were also divided into those manifest solely as a

decrease in systolic blood pressure versus those manifest initially as an increase in pulmonary pressure. This analysis was limited to those subjects who had pulmonary artery pressures measured during the 30 min after protamine.

All statistical analyses were performed using the SPSS (version 6.1) and Stata (version 5.0) statistical programs, and statistical significance was defined as a two-sided p value <0.05. The study was approved by the University of Pennsylvania Institutional Review Board.

## Results

**Adverse events.** Table 1 presents the risks of adverse events under differing case definitions. Overall, 230 procedures were associated with an adverse event. Ninety-eight were excluded from the primary case definition because they occurred more than 10 min after protamine. Of the remaining 132 early events, 78 were excluded because they received concomitant vasodilating medications (six of these subjects also had other exclusion criteria: one had hypercarbia, one had hypoxia and four had ischemia prior to protamine), and one was excluded for isolated ischemia, leaving a total of 53 who met the primary case definition. No events meeting the primary case definition manifest as isolated bronchospasm or pulmonary edema in the absence of systemic hypotension or pulmonary hypertension.

**Risk factors for adverse events.** In unadjusted analysis, higher CVP, a history of nonprotamine drug allergy, fish allergy, need for inotropes and NPH insulin use (no subject had used protamine–zinc insulin) were associated with either a statistically significant increased, or trend toward an increased, risk of adverse events (Table 2). Prior intravenous protamine and ejection fraction were not associated with a significant increase in events (Table 2), and there was no difference in the risk of events among those with known status of these variables versus those with missing data (p = 0.30 for intravenous protamine and p = 0.80 for ejection fraction). The lack of effect of prior intravenous protamine was not explained by the use of potentially prophylactic therapies (intraoperative H1- or H2-receptor blockers or corticosteroids within 24 h of protamine [34–37]); subjects with prior intravenous protamine exposure were no more likely than those without to receive these therapies (OR = 1.38; 95% CI: 0.70, 2.72), nor was prior intravenous protamine associated with events in the subgroup that did not receive prophylactic therapy (OR = 1.02; 95% CI: 0.48, 2.18).

**Table 2.** Distribution of Risk Factors in Cases and Control Subjects and Associations of Risk Factors With Events Using Primary Case Definition

| Risk Factors                                                                | Cases<br>(n = 53) | Controls<br>(n = 223) | Univariate<br>Odds Ratio<br>(95% CI) | Multivariable*<br>Odds Ratio<br>(95% CI) |
|-----------------------------------------------------------------------------|-------------------|-----------------------|--------------------------------------|------------------------------------------|
| Drug allergy other than protamine                                           | 26 (49.1%)        | 63 (28.8%)            | 2.38 (1.29, 4.40)<br>p = 0.005       | 2.97 (1.25, 7.07)<br>p = 0.014           |
| Ejection fraction (mean % ± SD)†                                            | 50.7 ± 17.6       | 49.7 ± 19.0           | 1.03 (0.84, 1.26)‡<br>p = 0.76       | 1.35 (0.89, 2.05)‡<br>p = 0.16           |
| Fish allergy                                                                | 2 (3.8%)          | 1 (0.4%)              | 8.71 (0.77, 97.9)<br>p = 0.09        | 24.5 (1.24, 482.3)<br>p = 0.035          |
| History of protamine allergy                                                | 0 (0%)            | 4 (1.8%)              | 0.00 (0.00, 6.42)<br>p = 1.00        | NC                                       |
| Inotropes needed coming off bypass                                          | 31 (59.6%)        | 99 (45.2%)            | 1.79 (0.97, 3.31)<br>p = 0.06        | 0.85 (0.34, 2.11)<br>p = 0.73            |
| Intraoperative central venous pressure<br>prior to protamine (mean mm ± SD) | 11.5 ± 4.3        | 10.1 ± 3.7            | 1.56 (1.05, 2.33)§<br>p = 0.027      | 0.97 (0.53, 1.77)§<br>p = 0.91           |
| NPH insulin use                                                             | 7 (13.2%)         | 12 (5.4%)             | 2.65 (0.99, 7.10)<br>p = 0.045       | 8.18 (2.08, 32.2)<br>p = 0.003           |
| Prior intravenous protamine†                                                | 19 (50.0%)        | 68 (47.6%)            | 1.10 (0.54, 2.26)<br>p = 0.79        | 1.54 (0.36, 6.57)<br>p = 0.56            |
| Vasectomy                                                                   | 0 (0%)            | 0 (0%)                | NC                                   | NC                                       |

\*All odds ratios are adjusted for age, gender, NPH use, fish allergy, nonprotamine drug allergy, need for inotropes coming off bypass (but prior to protamine), central venous pressure, myocardial infarction in prior week, type of surgery, prior cardiac surgery, bypass time, need for intra-aortic balloon pump or left ventricular assist device intraoperatively (but prior to protamine), body mass index, number of prior cardiac catheterizations and hemoglobin level prior to protamine. Models for ejection fraction and prior intravenous protamine include all of the aforementioned variables plus ejection fraction and prior intravenous protamine, respectively. †Analyses in subset of patients with known status of these variables. ‡Odds ratios are for each 10 percentage point increase in ejection fraction. §Odds ratios are for each 5-mm increase in central venous pressure. CI = confidence interval; n = number; NC = not calculable; NPH = neutral protamine Hagedorn; SD = standard deviation.

Under the primary definition, no case had a history of protamine allergy. However, controls with a history of protamine allergy (all noted in the cardiac catheterization laboratory) were significantly more likely than those without to receive potentially prophylactic therapy (OR = 8.53; 95% CI: 2.70, 27.0).

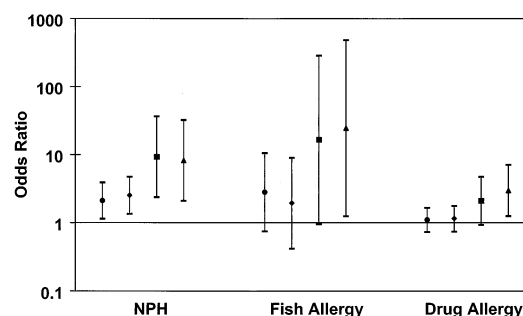
In multivariable analysis, only NPH use, fish allergy and nonprotamine drug allergy were associated with a statistically significant risk of adverse events (Table 2). None of the other a priori risk factors were associated with a significant risk of events. Removing fish allergy from the model, because of the low number of unexposed subjects, did not substantively affect the results for the other predictors. There also was no substantive difference in the results when adjusting for prior intravenous protamine or ejection fraction in the smaller subgroups of subjects with known status of these variables. Among the confounders (those not previously hypothesized as risk factors), only prior heart surgery was associated with events (OR 5.64, 95% CI: 1.16, 22.0). There also were no significant interactions among any of the risk factors and either each other or the confounders.

There were 101 cases (all adverse events, not limited to the primary definition) and 213 (39%) control subjects with one or more of the three a priori identified risk factors. If the proportion of subjects with a risk factor in the rest of the cohort population that were not selected as control subjects is the same as for those selected (as would be expected given the random selection process of control subjects), then the esti-

mated proportion of patients in the entire cohort with one or more risk factor would be 39% ([101 cases + 213 selected control subjects + {39%·1,283 unselected control subjects}] ÷ 2,069).

**Analysis by specificity of case definition.** Figures 1 and 2 illustrate the multivariable ORs for each of the potential risk factors when different definitions of adverse events were used. As the possibility that adverse events were due to causes other

**Figure 1.** Association between risk factors and adverse events using progressively more specific case definitions. Multivariable odds ratios and 95% confidence intervals (bars) are plotted on a logarithmic scale for risk factors that showed significant associations with the outcome when using the primary definition of adverse events. All odds ratios are adjusted for variables stated in footnote to Table 2. NPH = neutral protamine Hagedorn. Circles = all events; diamonds = all events within 20 min; squares = events within 20 min without other causes; triangles = events within 10 min without other causes (primary definition).



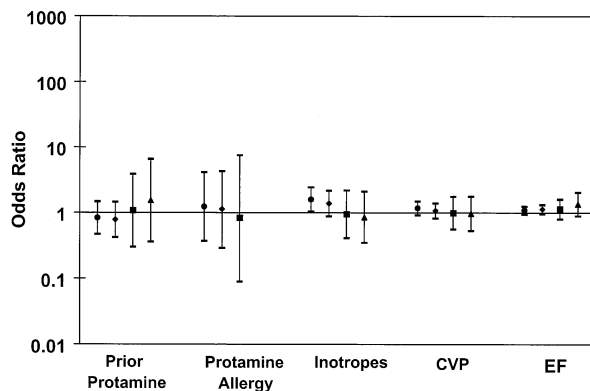


**Figure 2.** Association between risk factors and adverse events using progressively more specific case definitions. Multivariable odds ratios and 95% confidence intervals (bars) are plotted on a logarithmic scale for risk factors that did not show a significant association with the outcome when using the primary definition of adverse events. All odds ratios are adjusted for variables stated in footnote to Table 2, except for the odds ratios for protamine allergy, which are unadjusted. The odds ratios for protamine allergy for events defined as those occurring within 10 min of protamine in the absence of other causes of hemodynamic compromise are undefinable. The odds ratios for central venous pressure are for each 5-mm increase, and the odds ratios for ejection fraction are for each 10 percentage point increase. CVP = central venous pressure; EF = ejection fraction. Symbols as in Figure 1.

than protamine decreased, the association between adverse events and associated risk factors increased (Fig. 1). There was no clear trend toward increasing ORs among risk factors that were not associated with the primary definition of events (Fig. 2). Although the ORs did increase for prior intravenous protamine and ejection fraction, none of these ORs was statistically distinguishable from one.

**Analysis by severity and type of event.** The risk of severe events (11 cases) was not statistically significantly different from the risk of moderately severe events (42 cases) for any of the risk factors studied using the primary definition of adverse events (all  $p$  values  $\geq 0.15$ ). That is, none of the risk factors were more strongly associated with severe than with moderately severe events.

Among those with known pulmonary artery pressures, the risk of "systemic hypotensive" events (80 events) was not statistically different from the risk of "pulmonary hypertensive" events (14 events) within 30 min of protamine for any of the risk factors (all  $p$  values  $> 0.15$ ) except prior protamine allergy. Subjects with a history of protamine allergy had a 15-fold increased risk of having a pulmonary hypertensive event relative to a systemic hypotensive event ( $p = 0.047$ ). For those with a history of a protamine allergy, the univariate OR for pulmonary hypertensive events relative to no events was 12.3 (95% CI: 2.34, 64.9), and the multivariable OR was 189 (95% CI: 12.6, 2,856).

## Discussion

**Study findings.** This study demonstrates that NPH insulin use, fish allergy and a history of nonprotamine medication

allergy are all independent risk factors for clinically important adverse events following protamine administration. These risk factors did not differ in their association with adverse events based on their severity, nor did they differ with respect to the type of event. The other a priori risk factors were not associated with an increased risk of events. However, definitive conclusions cannot be drawn about the risk associated with prior vasectomy and protamine allergy because of inadequate numbers of exposed subjects when using our primary definition. In addition, control subjects with a history of protamine allergy were more likely to receive potentially prophylactic therapies prior to protamine, and the documentation of prior protamine reactions is likely to be poor (38), thus possibly masking an overall association. However, a history of protamine allergy did increase the risk of pulmonary hypertensive events, although this isolated finding from a subgroup analysis must be interpreted cautiously.

Definitive evidence proving or disproving an association between the risk factors examined in this study and protamine reactions has previously been lacking because of limited power in some studies (12,16,39), the absence of control groups in case reports and case series (4,6,17,19,29), the possibility that some reports of adverse events were biased by knowledge of putative risk factors and a lack of multivariable analyses in all studies.

The analyses by specificity of the definition of adverse events also strongly support the hypothesis that the risk factors identified are associated specifically with protamine reactions. If the study had used any of the less strict definitions, the significant finding among subjects with fish allergy and non-protamine drug allergy would have been missed, despite the greater number of subjects included in the analyses using these more liberal definitions. Although it is impossible to know for sure if an event truly is related to protamine, our data suggest that the definition of adverse events used in this study is specific enough to identify previously postulated risk factors, without being insensitive enough to miss potential factors.

**Support for an immunologic mechanism of protamine reactions.** The etiology of protamine reactions may include true allergic reactions (immunoglobulin [Ig]E-mediated or IgG-mediated), anaphylactoid events (complement-mediated) or direct toxicity (1,5,11,40,41). That serum IgE and IgG antibodies are strong predictors for adverse events following protamine (30) suggests that immune mechanisms are responsible for a large proportion of protamine reactions. Although not designed specifically to examine the mechanism of protamine reactions, our study supports this hypothesis. Risk factors for induction of a drug-specific immune response (i.e., prior sensitization to protamine and fish proteins or an allergic history) were associated with protamine-related events, but nonimmunologic factors (e.g., cardiac function and filling pressures) were not associated with events. In addition, there appeared to be no difference in the effects of the immunologic risk factors (i.e., no interactions) based on the presence or absence of nonimmunologic factors that may contribute to the elicitation of a clinically overt reaction in previously sensitized

subjects. This is not to suggest that nonimmunologic factors could not increase the risk of adverse events following protamine (14,22,30,42), only that immunologic ones appear to be the strongest predictors.

**Risk of protamine reactions.** The overall incidence of clinically significant adverse events is difficult to assess because this was an observational study. Because protamine reactions are diverse, mimic other complications and vary over a spectrum of severity, only randomized trials of protamine alternatives or prophylactic therapies will be able to determine the true incidence of events attributable to protamine. Nonetheless, the range of risk, 2.6% to 11%, is consistent with most prior prospective and retrospective studies. Although our primary definition certainly may include some non-protamine-related events (i.e., the risk could be less than 2.6%), the analysis by specificity of definitions suggests that a substantial proportion of these events are related to protamine and that, in fact, some events occurring at later times after protamine are probably protamine reactions. In addition excluding patients with ischemia (which may be due to protamine [43]) or receiving concomitant vasodilators may have excluded protamine reactions. Thus, our primary definition may underestimate the absolute risk.

**Potential limitations.** This study must be interpreted with the usual cautions inherent in observational research. It is possible that true associations between risk factors and adverse events were not detected due to chance (type II error). However, the 95% confidence intervals make it unlikely that relative risks greater than two were not detected for most risk factors, except for prior intravenous protamine. We also could not assess the effects of rate of infusion of protamine because this was not routinely recorded in the medical records; however, we routinely administer protamine slowly (over at least 5 min), making rate of infusion an unlikely risk factor in our population. Type I error (identifying an association by chance) is unlikely in this study because we purposely focused on a limited number of biologically plausible risk factors that was determined prior to the start of the study. Differential misclassification of exposures could have biased our results, but this is extremely unlikely given the methods used to ensure unbiased collection of data on risk factors. Also, there was no difference in the risk of events for subjects with, versus those without, missing information for specific risk factors, suggesting a lack of bias from this missing information. Our study also used methods to minimize the possibility of misclassification of outcomes, a major concern in all prior studies of protamine reactions, and also demonstrated the specificity of our case definition. Although nondifferential misclassification is still possible, this would only underestimate the effects of the risk factors identified. Selection bias is unlikely given that the reason for missing charts should not in any way be related to either the outcome or the exposures of interest in this study. Finally, the generalizability of our findings is limited by the use of a single tertiary-care hospital.

**Conclusions.** In summary, this study demonstrates that NPH insulin use, fish allergy and nonprotamine drug allergies

are independent risk factors for clinically important adverse events following protamine administration in patients undergoing surgery requiring CPB. Prior protamine allergy may be a risk factor specifically for pulmonary hypertensive events, but further study is needed to validate this finding. The study also derives a definition of protamine-related events that should be useful in future studies exploring strategies to reduce the risk of these events. Based on our results, a substantial proportion of patients undergoing CPB are at considerably increased risk of events that have been associated with important morbidity and mortality. Because there are no clearly proven, effective approaches to preventing protamine reactions, further progress must be made in developing prophylactic strategies (41,44,45) and protamine substitutes (46,47), targeting the large number of patients at increased risk for adverse events following intravenous protamine.

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