Diuretics and mortality in acute renal failure*

Shigehiko Uchino, MD; Gordon S. Doig, PhD; Rinaldo Bellomo, MD; Hiroshi Morimatsu, MD; Stanislao Morgera, MD; Miet Schetz, MD; Ian Tan, MD; Catherine Bouman, MD; Ettiene Macedo, MD; Noel Gibney, MD; Ashita Tolwani, MD; Claudio Ronco, MD; John A. Kellum, MD; for the Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators

Objective: **According to recent research, diuretics may increase mortality in acute renal failure patients. The administration of diuretics in such patients has been discouraged. Our objective was to determine the impact of diuretics on the mortality rate of critically ill patients with acute renal failure.**

Design: **Prospective, multiple-center, multinational epidemiologic study.**

Setting: **Intensive care units from 54 centers and 23 countries.**

Patients: **Patients were 1,743 consecutive patients who either were treated with renal replacement therapy or fulfilled predefined criteria for acute renal failure.**

Interventions: **Three distinct multivariate models were developed to assess the relationship between diuretic use and subsequent mortality: a) a propensity score adjusted multivariate model containing terms previously identified to be important predictors of outcome; b) a new propensity score adjusted multivariate model; and c) a multivariate model developed using standard methods, compensating for collinearity.**

Measurements and Main Results: **Approximately 70% of patients were treated with diuretics at study inclusion. Mean age was 68 and mean Simplified Acute Physiology Score II was 47. Severe sepsis/septic shock (43.8%), major surgery (39.1), low cardiac output (29.7), and hypovolemia (28.2%) were the most common conditions associated with the development of acute renal failure. Furosemide was the most common diuretic used (98.3%). Combination therapy was used in 98 patients only. In all three models, diuretic use was not associated with a significantly increased risk of mortality.**

Conclusions: **Diuretics are commonly prescribed in critically ill patients with acute renal failure, and their use is not associated with higher mortality. There is full equipoise for a randomized controlled trial of diuretics in critically ill patients with renal dysfunction. (Crit Care Med 2004; 32:1669–1677)**

KEY WORDS: acute kidney failure; critical illness; furosemide; diuretics; epidemiology; renal replacement therapy; logistic regression modeling; multicollinearity; propensity scores

Controversy exists over appropriate fluid management for acute renal failure patients (1–8). In the acute care setting, loop diuretics are often prescribed to maintain or increase urine output.

Furosemide and other loop diuretics reduce oxygen demand in the medullary thick ascending limb and attenuate the severity of acute renal failure (ARF) in animal models (4, 5). They may protect the human kidney from ischemic injury. There have been several small, randomized, controlled trials of diuretics for the treatment or prevention of ARF in various clinical settings (8–20). Some studies showed a reduction in dialysis requirement (15), reduced urinary albumin and N-acetyl glucosaminidase concentration (17), or improved dialysis free survival in oliguric patients (18). Others, however, showed either worsened renal function (10, 12, 14, 16) or no difference in various measured outcomes (8, 9, 11, 13, 19, 20).

Recently, Mehta et al. (21) published an observational study of diuretic use in patients with ARF in the setting of critical illness and showed that, using multivariate analysis and propensity scores, the use of diuretics was associated with an increased risk of death. The methodology used by Mehta et al. (21) was similar to a propensity score adjusted assessment of pulmonary artery catheter use in the critically ill (22). The use of propensity score models, however, has significant potential shortcomings (23, 24), which, together with the limited sample size and the use of only three centers, may have resulted in misleading conclusions.

The statistics used in this study might have also led to incorrect conclusions because of the phenomenon of collinearity: using physiological variables that are often highly correlated (collinear) with each other (e.g., blood urea nitrogen and serum creatinine) can lead to nonsensical results in multivariate analyses (24). When collinearity is detected, there are two main approaches that can be used to ensure that results are reliable: a) Reduce the number of variables considered before undertaking multiple regression; or b) use appropriate statistical techniques

***See also p. 1794.**

From the Department of Intensive Care and Department of Medicine, Austin & Repatriation Medical Centre, Melbourne, Australia (SU, RB, HM); Royal North Shore Hospital and Northern Clinical School, University of Sydney, Sydney, Australia (GSD); Department of Nephrology, University Hospital Charité, Berlin, Germany (SM); Dienst Intensieve Geneeskunde, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium (MS); Intensive Care Unit, Department of Anaesthesia, Pamela Youde Nethersole Eastern Hospital, Hong Kong, China (IT); Adult Intensive Care Unit, Academic Medical Center, Amsterdam, Holland (CB); Nephrology Division, University of São Paulo School of Medicine, São Paulo, Brazil (EM); Division of Critical Care Medicine, University of Alberta, Edmonton, Canada (NG); Department of Medicine, Division of Nephrology, The University of Alabama at Birmingham, Alabama, (AT); Nephrology-Intensive Care, St. Bortolo Hospital, Vicenza, Italy (CR); and Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA (JK).

Supported, in part, by the Austin Hospital Intensive Care Trust Fund.

DOI: 10.1097/01.CCM.0000132892.51063.2F

to investigate and address potential correlations between variables. This was not done in Mehta et al.'s (21) study.

Given the importance of understanding the complex relationship between diuretics and mortality in critically ill patients, we used a comprehensive analytic approach to test the hypothesis that diuretic use affects mortality. Using a large, multinational, multiple-center, prospective database, we investigated the association between diuretic use and outcome using a) a propensity score adjusted multivariate model containing terms previously identified to be important predictors of outcome; b) a new propensity score adjusted multivariate model; and c) a multivariate model developed using standard methods, compensating for collinearity.

MATERIALS AND METHODS

Fifty-four study sites in 23 countries were contacted and invited to participate. A deliberate attempt was made to have a wide variety of countries, continents, and hospital types (academic centers, private hospitals, nonacademic urban hospitals, etc.) participate in the study (see the appendix for complete details). Because of the anonymous and noninterventional fashion of this study, ethical committees in most centers waived the need for informed consent. Where ethics committees or investigational review boards required informed consent, this was obtained.

Study Population. All patients who were admitted to any of the participating intensive care units (ICUs) during the observational period were considered. From this population, only patients who had at least one of the predefined criteria for ARF were included in the study. The criteria for ARF were as follows:

1. Requirement for renal replacement therapy (RRT), and/or
2. Oliguria defined as urine output <200 mL in 12 hrs
3. Anuria defined as urine output <50 mL in 12 hrs
4. Marked acute azotemia defined as a plasma urea >30 mmol/L or blood urea nitrogen >86 mg/dL
5. Hyperkalemia defined as serum potassium >6.5 mmol/L

These criteria were chosen because they are simple, objective, numerically identifiable, and clinically relevant. Patients with any dialysis treatment before admission to the ICU or patients with end-stage renal failure on chronic dialysis were excluded.

Data Collection. A case report form was developed for the purpose of the study, and relevant demographic, clinical, illness severity related (25), renal function specific (26), biochemical, and therapeutic intervention data were recorded.

Rationale and Methodology of Statistical Analysis. The evaluation of data from observational studies often reveals that physiological variables are highly correlated with each other (e.g., serum sodium with serum chloride levels). When the degree of correlation between variables entered in multiple regression equation exceeds a certain level, regression models can lead to unstable variable estimates, incorrect variance estimates, and difficulties in the numerical calculations involved in fitting the model (24). One of the most widely accepted ways of detecting multicollinearity is to calculate the eigenvalues associated with the predictor variable correlation matrix to determine the condition number (27–30). The condition number is the ratio of the largest eigenvalue to the smallest eigenvalue (30).

When multicollinearity is detected, simple linear transformations of the data that do not result in information loss can often be used to improve model performance (27).

Given the need to address the problems associated with multicollinearity, three distinct multivariate models were used to explore the relationship between diuretic use and mortality: method 1, a propensity score adjusted multivariate model containing the same terms found to be important in Mehta et al.'s study (21); method 2, a propensity score adjusted multivariate model containing terms identified using the same analytic technique as used by Mehta et al. (21); and method 3, a multivariate model considering all available covariates, which involved a formal assessment of multicollinearity using eigenanalysis and linear transformations.

Method 1: Confirmatory Propensity Adjusted Mortality Model. Method 1 involved two distinct logistic regression models. Step 1 required the development of a logistic regression model, predicting diuretic use, to calculate a propensity score for treatment with diuretics. This score represents the probability of treatment with diuretics and was then included in a subsequent logistic regression model predicting mortality. The propensity score logistic regression model developed in step 1 contained the following variables previously identified to be important predictors of diuretic use: patient age, nephrotoxic etiology of ARF, blood urea nitrogen, and presence of acute respiratory failure (21).

In step 2, a model predicting mortality was developed. This second logistic regression model contained the following terms previously identified to be important predictors of mortality: diuretic use, propensity score, patient age, gender and first consultation day values for heart rate, blood urea nitrogen, creatinine, urine output, and respiratory, hematologic, and liver failure (21, 25)

Method 2: New Propensity Adjusted Mortality Model. Method 2 involved the development of a propensity adjusted mortality model using the same methodology, inclusion criteria, and p value thresholds as Mehta et al. (21), which required a two-step process as described in method 1. However, all possible predictors of outcome were screened for inclusion in the maximum models using univariate logistic regression. In step 1, the maximum model contained all univariate predictors of diuretic use with $p < .25$. A backward stepwise elimination process was then used to remove covariates whose multivariate p value was >.25. The final new propensity score model contained all predictors of diuretic use with a multivariate $p < .25$ (21).

In step 2, the new propensity adjusted mortality model contained all eligible univariate predictors of mortality along with terms for diuretic use and the new propensity score developed in step 1. Logistic regression was used to identify predictors of mortality, and a univariate $p < .25$ qualified the variable for consideration in the maximum model. The terms diuretic use and new propensity score were forced to remain in the model, and a backward stepwise elimination process was used to remove any other covariates whose multivariate p value was >.10 (26). The final model contained the terms diuretic use, new propensity score, and all other predictors of mortality with a multivariate $p < .10$.

Method 3: Multicollinearity Adjusted Model. Logistic regression was used to identify all potential confounding variables associated with either diuretic use or mortality. A univariate $p < .25$ qualified the variable for inclusion in the maximum model (28).

The maximum model was formally assessed for the presence of multicollinearity using eigenanalysis, with a condition number ≥30 considered to be indicative of moderate to severe collinearity (29). The presence of moderate to severe collinearity was addressed by standardizing (transforming to the z-scale) all continuous independent variables (31), the success of which was again assessed using eigenanalysis.

After we investigated the presence of, and adjusted for, multicollinearity, the maximum model was entered into a stepwise backward elimination model selection process. All covariates with a multivariate $p > .10$ were removed from the model (31, 28, 29).

Method Comparisons. After generation of the final predictive models, overall performance was assessed using measures of calibration and discrimination. Calibration was assessed with the Hosmer-Lemeshow goodness-of-fit statistic (30), and discrimination was reported using the c-statistic (28), which is numerically equivalent to the area under the receiver operating characteristic curve (32, 33)

Each final model was assessed for the presence of multicollinearity, using eigenanalysis with a condition number ≥30 considered to be indicative of moderate to severe collinearity (29, 33). Final models were also assessed for potential bias arising from the conjoint distribution of missing values.

For propensity score models, the outcome event of diuretic use was modeled as a binary variable, with diuretic use equal to one. For mortality models, the outcome of mortality was modeled as a binary variable with death in hospital equal to one. A marker variable, named count, was set equal to one for all cases. All analysis was conducted in PC SAS (version 6.12, SAS Institute, Cary, NC). Logistic regression analysis was carried out using the events/count model specification in PROC Logist. Eigenanalysis was conducted with Proc Reg, with the collin option specified. We assessed p values for multivariate models using likelihood ratio tests.

RESULTS

We screened 29,269 patients, and 1,758 patients met the eligibility criteria for this study. Among these, 15 patients (0.9%) were excluded because no information about diuretic use was available and 12 patients because of missing hospital outcome information. Diuretics were given to 1,117 (60.8%) patients, with furosemide as the most common choice (1,098 patients, 98.3%). Other diuretics used were various types of loop diuretics in 29 patients, mannitol in 22, metolazone in 19, spironolactone in 18, thiazides in 14, atrial natriuretic peptide in 10, and others in 4. Furosemide and other diuretics were given in combination to 92 patients.

Demographics and admission diagnoses of patients with ARF are shown in Tables 1 and 2. Table 3 contains physiological and laboratory variables at study inclusion, and Table 4 presents patient outcomes. Of note, unadjusted hospital mortality rates were higher for patients receiving diuretics compared with those who did not (62.4% vs. 57.1%; odds ratio [OR], 1.25; $p = .03$; Table 4). However, the difference in hospital mortality rate between groups was no longer significant after we controlled for other variables using all three statistical methods.

Method 1: Confirmatory Propensity Adjusted Mortality Model. After we controlled for propensity score and other variables previously found to be significant predictors of mortality, diuretic use was not found to be significantly related to increased mortality (OR 1.21, $p = 0.10$). Table 5 presents the regression variables, ORs, and p values for all model covariates.

Table 6 presents an in-depth comparison of all cases that could not be included in this model due to missing values. Of all cases with available diuretic use and hospital outcome information, due to missing values in at least one variable required for the logistic regression model, 64 cases could not be included in the final mortality model. The mortality rate in these 64 cases was 48.4% (31 of 64), which was significantly different than the 60.9% (1,016 of 1,667) mortality rate experienced by the cases that could be included in the model ($p = .045$).

Method 2: New Propensity Adjusted Mortality Model. Variables that demonstrated a univariate p value associated with diuretic use $<.25$ and thus qualified for entry into the new propensity score maximum model are listed in Tables 1 and 3. However, the final propensity score model contained the following variables: patient age, Simplified Acute Physiology Score II score, creatinine at ICU admission, requirement of renal replacement therapy, time from ICU admission to study inclusion, and the following variables measured at study inclusion; central venous pressure, Glasgow Coma Scale score, vasopressor use, urine volume for the 6 hrs preceding inclusion, platelet count, creatinine, arterial pH, septic etiology, low cardiac output etiology, and other etiology.

Variables that demonstrated a univariate p value associated with mortality $<.25$ and thus qualified for entry into the final model are listed in Tables 1 and 3.

After we controlled for propensity score and other variables found to be significant predictors of mortality, diuretic use was not found to be significantly related to increased mortality rate (OR 1.21, $p = .18$). Regression variables, ORs, and p values for the final model are presented in Table 7.

Table 8 presents an in-depth comparison of all cases that could not be included in this model due to missing values. Of all cases with available diuretic use and hospital outcome information, due to missing values in at least one variable required for the final logistic regression model, 346 cases could not be included in the mortality model. The mortality rate in these 346 cases was 51.1% (177 of 346), which was significantly different than the 62.8% (870 of 1,385) mortality rate experienced by the cases that could be included in the model ($p = .001$).

Method 3: Multicollinearity Adjusted Model. Variables that demonstrated a univariate p value associated with mortality and/or diuretic $\leq.25$ and thus qual-

Table 1. Baseline patient characteristics at the time of study inclusion

	Total	No Diuretics	Diuretics
No. of patients	1,743	626	1,117
Patient age, yrs[a,b]	67 (53–75)	64 (50–74)	68 (55–75)
Male gender, %	63.9	65.2	63.1
Body weight, kg	74 (63–85)	74 (60–85)	74 (64–84)
Premorbid renal function, %			
Normal	55.9	51.6	58.4
Chronic impairment[b]	29.7	28.8	30.3
Unknown	14.3	19.6	11.4
Premorbid Cr, μmol/L	97 (79–150)	99 (78–167)	97 (79–147)
Hospital to ICU, days[b]	1 (0–6)	1 (0–4)	2 (0–7)
ICU to study inclusion, days[a,b]	1.1 (0.3–3.8)	0.7 (0.1–2.6)	1.7 (0.5–4.6)
SAPS II[a,b]	48 (38–61)	50 (40–63)	47 (37–60)
Cr at ICU admission, μmol/L[a,b]	180 (110–310)	211 (117–383)	163 (106–283)
Urea at ICU admission, mmol/L[a,b]	14.9 (8.8–27.0)	16.5 (9.2–31.1)	14 (8.6–24.6)
Estimated Cr clearance, mL/min	35 (20–59)	31 (17–57)	37 (21–60)
Contributing factors to ARF, %			
Sepsis/septic shock[a,b]	46.8	52.0	43.8
Major surgery[a,b]	34.5	26.4	39.1
Low cardiac output[a,b]	26.7	21.3	29.7
Hypovolemia[a]	26.3	25.1	28.2
Drug induced[a,b]	19.0	18.2	19.4
Hepatorenal syndrome[a]	5.7	8.0	4.4
Obstructive uropathy[a,b]	2.8	3.5	2.3

Cr, creatinine; hospital to ICU, duration between hospital admission and intensive care unit admission; ICU to study inclusion, duration between ICU admission and study inclusion; SAPS, Simplified Acute Physiology Score; ARF, acute renal failure.

[a]Variable was associated with diuretic use and qualified for consideration in new propensity score (univariate logistic regression $p \leq .25$); [b]variable was associated with mortality (univariate logistic regression $p \leq .25$). Data are presented as median (interquartile range) or percentage.

Table 2. Diagnostic group at intensive care unit admission for patients with acute renal failure

	Total, %	No Diuretics, %	Diuretics, %
Medical admission			
Cardiovascular	11.1	10.5	11.5
Respiratory	13.3	13.6	13.1
Gastrointestinal	9.9	14.2	7.5
Neurologic	2.0	2.2	1.9
Sepsis	10.0	13.4	8.1
Trauma	2.0	3.2	1.3
Metabolic	3.7	5.3	2.8
Hematologic	4.6	5.1	4.4
Renal	2.2	3.0	1.7
Surgical admission			
Cardiovascular	23.2	9.4	30.9
Respiratory	1.8	2.6	1.4
Gastrointestinal	11.4	12.1	10.9
Neurologic	0.6	0.6	0.6
Trauma	2.3	2.1	2.4
Renal	0.9	1.0	0.9
Gynecologic	0.3	0.3	0.4
Orthopedic	0.6	1.3	0.3

Table 3. Physiologic and laboratory variables for patients with acute renal failure

	Total		No Diuretics		Diuretics	
Heart rate, beats/min[a]	98	(84–112)	99	(84–115)	98	(84–112)
Respiratory rate, breaths/min[b]	18	(15–24)	20	(15–24)	18	(15–23)
Systolic AP, mm Hg[a,b]	112	(100–130)	111	(97–130)	114	(100–130)
Diastolic AP, mm Hg[a]	57	(50–66)	56	(49–66)	59	(50–66)
Mean AP, mm Hg[a,b]	75	(66–86)	75	(65–85)	75	(67–87)
SBP <100 mm Hg, %[a,b]	37.7		39.9		36.5	
CVP, mm Hg[a,b]	13	(10–18)	13	(9–17)	14	(10–18)
PAC usage[b]	24.9%		23.0%		26.0%	
PAOP, mm Hg	18	(15–22)	17	(14–21)	18	(15–22)
Glasgow Coma Scale score[a,b]	14	(10–15)	13	(8–15)	14	(11–15)
Mechanical ventilation, %[a,b]	75.4		72.4		77.1	
Vasopressors/inotropes, %[a,b]	68.8		63.4		71.9	
Urine output						
mL/6 hrs[a,b]	120	(40–379)	100	(25–350)	140	(50–400)
mL/24 hrs	675	(250–1509)	475	(189–1343)	756	(290–1638)
Furosemide						
mg/6 hrs		—		—	80	(20–200)
mg/24 hrs		—		—	240	(80–500)
RRT requirement, %[b]	71.5		66.8		74.2	
WCC, $\times 10^3/\mu L$[b]	13.2	(8.9–19.3)	13.5	(8.2–20.3)	13.0	(9.1–19.0)
Platelet count, $\times 10^3/\mu L$[a,b]	127	(69–204)	136	(66–214)	126	(71–200)
Creatinine, μmol/L[a,b]	283	(187–407)	277	(172–432)	285	(194–399)
Urea, mmol/L[a,b]	27.5	(16.0–33.6)	28.3	(14.3–34.6)	27.0	(16.9–33.0)
Bilirubin, mmol/L[a,b]	19	(11–51)	20	(10–61)	18	(11–45)
Sodium, mmol/L[a]	139	(134–143)	139	(134–143)	139	(135–143)
Potassium, mmol/L[a]	4.5	(4.0–5.2)	4.5	(4.0–5.3)	4.5	(4.0–5.2)
Pa_{O_2}/F_{IO_2} ratio[a,b]	211	(141–301)	208	(141–305)	214	(141–300)
pH[a,b]	7.33	(7.25–7.40)	7.33	(7.23–7.40)	7.34	(7.26–7.41)

AP, arterial pressure; SBP, systolic blood pressure; CVP, central venous pressure; PAC, pulmonary artery catheter; PAOP, pulmonary artery occlusion pressure; RRT, renal replacement therapy; WCC, white cell count.

[a]Variable was associated with mortality (univariate logistic regression $p \leq 0.25$); [b]variable was associated with diuretic use and qualified for consideration in new propensity score (univariate logistic regression $p \leq 0.25$). Data are presented as median (interquartile range) or percentage.

ified for entry into the maximum model are listed in Tables 1 and 3. Before commencing the backward elimination model selection process, we assessed the maximum model for the presence of multicollinearity. Eigenanalysis revealed a condition number of 460.5, demonstrating the presence of severe multicollinearity. To address the presence of severe multicollinearity, all continuous variables were standardized (z-transformed). The condition number for the standardized maximum model was 13.62, indicating that standardization adequately addressed the problem of multicollinearity. The stepwise backward elimination selection process was undertaken on the standardized maximum model.

After we controlled for all possible confounding variables, diuretic use was not found to be significantly related to increased mortality (OR 1.22, $p = .15$). Regression variables, ORs, and p values for the final model are presented in Table 9.

Table 10 presents an in-depth comparison of all cases that could not be included in this model due to missing values. Of all cases with available diuretic use and hospital outcome information, due to missing values in at least one variable required for the final logistic regression model, 327 cases could not be included in the model-building process. The mortality rate in these 327 cases was 60.9% (199 of 327), which was not significantly different than the 60.4% (848 of 1,404) mortality rate experienced by the cases that could be included in the model ($p = .879$).

Final Model Comparison: Goodness of Fit and Multicollinearity. As measured by the Hosmer-Lemeshow goodness-of-fit statistic and area under the receiver operating characteristic curve, all final models demonstrated good fit and good discrimination (Table 11).

Eigenanalysis conducted on the final model developed in method 1 revealed a condition number of 54.24, which indicates the presence of severe multicollinearity and may make any measures of association (i.e., regression variables and odds ratios) unreliable. Eigenanalysis conducted on the final model developed in method 2 revealed a condition number of 329.96, which indicates the presence of severe multicollinearity, again making measures of association unreliable. Eigenanalysis of the final model developed in method 3 revealed a condition number of 8.6, suggesting that there was no multicollinearity present in this model.

DISCUSSION

Using a comprehensive statistical approach and a large international prospective database of patients with acute renal failure, we tested the hypothesis that an association existed between the use of diuretics and mortality. We found that, after appropriate statistical adjustment and using three separate methodologies, there was no statistically significant association between the use of diuretics and

Table 4. Outcomes of patients with acute renal failure

	Total	No Diuretics	Diuretics
Length of ICU stay, days	10 (5–22)	9 (4–20)	11 (5–22)
Length of hospital stay, days	22 (11–44)	21 (9–44)	23 (12–45)
ICU mortality, %	51.6	48.2	53.4
Hospital mortality, %	60.5	57.1	62.4
Hospital discharge without RRT, %	34.7	38.2	32.7
Hospital discharge with RRT, %	4.8	4.6	4.9

ICU, intensive care unit; RRT, renal replacement therapy.
Data are presented as median (interquartile range) or percentage.

Table 5. Method 1: Confirmatory propensity adjusted mortality model

	Regression Variable ± SE	*p* Value	Odds Ratio (95% CI)
Intercept	−2.108 ± 0.702	.002	
Diuretic use	0.191 ± 0.116	.100	1.210 (0.96–1.5)
Propensity score	−1.424 ± 1.195	.233	0.241 (0.02–2.5)
Patient age, yrs	0.028 ± 0.005	.0001	1.028 (1.02–10.4)
Gender	0.015 ± 0.115	.891	1.016 (0.81–1.3)
Heart rate	0.010 ± 0.002	.000	1.010 (1.01–1.02)
Urea at INCL	0.010 ± 0.006	.098	1.010 (0.99–1.02)
Creatinine at INCL	−0.0018 ± 0.0001	.0001	0.998 (0.99–1.0)
Urine volume 6 hrs before INCL	−0.001 ± 0.0001	.0001	0.999 (0.99–1.0)
Respiratory failure at INCL	1.235 ± 0.175	.0001	3.441 (2.4–4.8)
Hematologic failure at INCL	1.936 ± 1.06	.067	6.937 (0.86–55.4)
Liver failure at INCL	0.563 ± 0.128	.0001	1.757 (1.3–2.2)

CI, confidence interval; INCL, time of study inclusion.

Table 6. Method 1: Comparison of missing cases to included cases

	Missing Cases ± SD (No.)	*p* Value	Included Cases ± SD (No.)
Diuretic use, %[a]	50 (76)	.01	64% (1,667)
Patient age, yrs	63 ± 17 (67)	.65	62 ± 16 (1,667)
Gender, male	65% (76)	.80	64% (1,667)
Heart rate, beats/min	96 ± 21 (74)	.45	99 ± 21 (1,667)
Urea at INCL, mmol/L	31 ± 15 (75)	.005	26 ± 13 (1,667)
Creatinine at INCL, μmol/L	476 ± 373 (73)	.0001	323 ± 204 (1,667)
Urine volume 6 hrs before INCL, mL	158 ± 156 (28)	.0001	275 ± 368 (1,667)
Respiratory failure at INCL	63% (76)	.0001	79% (1,667)
Hematologic failure at INCL	1.3% (72)	.49	0.9% (1,667)
Liver failure at INCL	22% (75)	.29	28% (1,667)

INCL, time of study inclusion.
[a]Key variable (known prognostic importance or relevant to main question of study).

mortality. Our findings differ from those of a recently published and editorialized investigation (21). As the issue of diuretic use is important to clinical practice and as complex statistical analyses were used, a discussion of the methodology is necessary.

The purpose of using three different methods for assessing the impact of diuretic use on mortality was not motivated by the desire to determine which method was most appropriate. On the contrary, since allocation to a treatment in an observational study is beyond the control of the investigators, the methodological literature recommends that a propensity score analysis should be conducted in addition to a more traditional analysis (34). Indeed, in this specific exercise, all three methods resulted in similar findings. Methods 1, 2, and 3 all failed to demonstrate a significant ($p_{m1} = .10, p_{m2} = .18, p_{m3} = .15$, respectively) relationship between treatment with diuretics and subsequent mortality. It is also interesting to note that the magnitude and direction of the odds ratio between diuretic use and outcome was similar between all three methods (OR_{m1} 1.21, OR_{m2} 1.21, and OR_{m3} 1.22, respectively).

Thus, after we controlled for known differences between groups, an apparent association between diuretics and mortality could not be confirmed. Indeed, the ORs from our models were not very different from the crude mortality data (OR 1.25). Therefore, although our data do not permit us to draw the same conclusion as Mehta et al. (21), that the "use of diuretics in critically ill patients with acute renal failure should be discouraged," our data do suggest that a clinical trial to evaluate the use of diuretics in acute renal failure is warranted. Using our findings and assuming a baseline mortality rate of 60%, a sufficiently powered randomized controlled trial would need to enroll 4,734 patients to detect a difference in outcome associated with an OR of 1.21 (4% absolute reduction).

Our study differs from the Mehta et al. (21) study in several important ways. First, in our study, approximately 70% of patients were recruited at the time of RRT commencement and we used a higher blood urea nitrogen concentration for the definition ARF (86 mg/dL compared with 40 mg/dL in the previous study). This difference in criteria could have caused a delay in the inclusion of study patients. However, the serum creatinine concentration was lower (e.g., 3.3 vs. 3.6 mg/dL in patients with diuretics), and our patients were included in the study at a median of only 1 day after ICU admission. Therefore, the timing of inclusion is unlikely to have affected our findings.

The choice of diuretics was also different. Most of our patients received furosemide (98%), and other diuretics were rarely used. Thus, we had a more uniform sample in terms of intervention. On the other hand, only 62% of patients in Mehta et al.'s (21) study received furosemide, and other diuretics were also commonly used (bumetanide 58%, metolazone 33%, hydrodiuril 4%). It is possible that the results observed in the Mehta et al. study are attributable to differences in practice patterns not observed in our study. Compared with the previous study, our study was larger, was conducted prospectively, and was multinational in design (54 centers in 23 countries vs. four centers in one country), and the findings are thus more likely to be widely applicable and generalizable. It was also conducted more recently (2000–2001 vs. 1989–1995) and with fewer patient exclusions.

Table 7. Method 2: New propensity adjusted mortality model

	Regression Variable ± SE	*p* Value	Odds Ratio (95% CI)
Intercept	6.782 ± 4.187	.105	
Diuretic use	0.196 ± 0.147	.181	1.217 (0.91–1.6)
Propensity score	1.079 ± 0.605	.074	2.942 (0.98–9.6)
Patient age, yrs	0.026 ± 0.004	.0001	1.027 (1.02–1.04)
Hospital to ICU admit time, days	0.036 ± 0.008	.0001	1.037 (1.0–1.1)
SAPS II	0.015 ± 0.004	.001	1.015 (1.00–1.02)
Renal replacement therapy	0.432 ± 0.173	.012	1.541 (1.1–2.1)
Heart rate at INCL	0.008 ± 0.003	.010	1.008 (1.00–1.01)
Mean blood pressure at INCL	−0.011 ± 0.004	.005	0.988 (0.98–0.99)
Glasgow Coma Scale at INCL	−0.084 ± 0.021	.0001	0.919 (0.88–0.96)
Urine volume 6 hrs before INCL	−0.0005 ± 0.0001	.002	0.999 (0.99–1.00)
Platelet count at INCL	−0.001 ± 0.0001	.013	0.998 (0.99–1.00)
Creatinine at INCL	−0.002 ± 0.0001	.000	0.998 (0.99–1.00)
Urea at INCL	0.019 ± 0.006	.002	1.019 (1.00–1.03)
Arterial pH at INCL	−1.218 ± 0.568	.032	0.296 (0.09–0.90)
Respiratory failure at INCL	0.552 ± 0.177	.001	1.738 (1.2–2.4)
Liver failure at INCL	0.364 ± 0.150	.015	1.439 (1.1–1.9)
Septic etiology	0.360 ± 0.147	.014	1.434 (1.1–1.9)
Surgical etiology	−0.286 ± 0.142	.044	0.751 (0.56–0.99)

CI, confidence interval; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; INCL, measured at time of study inclusion.

Table 8. Method 2: Comparison of missing cases to included cases

	Missing Cases ± SD (No.)	*p* Value	Included Cases ± SD (No.)
Diuretic use, %[a]	49 (358)	.001	67 (1,385)
Patient age, yrs	61 ± 17 (349)	.13	63 ± 16 (1,385)
Hospital to ICU admit time, days	5.5 ± 16 (358)	.58	6.0 ± 13 (1,385)
SAPS II[a]	50 ± 18 (356)	.57	50 ± 17 (1,385)
Renal replacement therapy, %[a]	61 (358)	.0001	74 (1,385)
Heart rate at INCL, beats/min	94 ± 23 (356)	.0003	99 ± 21 (1,385)
Mean blood pressure at INCL, mm Hg	79 ± 21 (356)	.001	76 ± 16 (1,385)
Glasgow Coma Scale at INCL[a]	12 ± 3.7 (344)	.23	12 ± 3.9 (1,385)
Urine volume 6 hrs before INCL, mL	255 ± 332 (310)	.35	277 ± 374 (1,385)
Platelet count at INCL, $\times 10^3/\mu L$	178 ± 131 (338)	.0001	149 ± 112 (1,385)
Creatinine at INCL, μmol/L	428 ± 305 (355)	.0001	303 ± 178 (1,385)
Urea at INCL, mmol/L	31 ± 14 (357)	.0001	25 ± 13 (1,385)
Arterial pH at INCL	7.3 ± 0.1 (309)	.08	7.3 ± 0.1 (1,385)
Respiratory failure at INCL, %	58 (358)	.0001	83 (1,385)
Liver failure at INCL, %	24 (357)	.075	29 (1,385)
Septic etiology, %	39 (356)	.0001	48 (1,385)
Surgical etiology, %	13 (356)	.0001	40 (1,385)

ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; INCL, time of study inclusion.
[a]Key variables (known prognostic importance or relevant to main question of study).

It should be pointed out that we treated urine output differently. In Mehta et al.'s model, the logarithm of urine output was included as a covariate, whereas we elected not to calculate the log of urine output. Since the logarithm of a zero value is undefined, because many of the patients in our database had no (zero) urine output recorded over the time interval leading to consultation, it is likely that a log transformation of urine output would lead to unnecessary missing values. Mehta et al. (21) did not report what was done with patients who had a zero urine output and thus an undefined (missing) log-urine output.

With regard to other missing values, we have explicitly reported the number of patients with missing values that could not be included in each method, along with the patient outcomes and characteristics (Tables 6, 8, and 10). These patients tended to be less severely ill and have a better outcome than those that could be included.

The fact that ICU patients who generate missing values in observational studies are more likely to be less severely ill and have better outcomes is well established (35). Although the potential direction of bias due to missing values was not explicitly addressed, Mehta et al. (21) reported missing values in 35% of all cases. Our overall missing value rate ranged from 5% in method 1 to approximately 20% in method 2 and method 3. Although it is possible that the difference in results between our study and Mehta et al.'s is due to fewer missing values in the current study, it is likely that missing values were generated for similar reasons in both studies. The remarkable similarity of the estimate of the odds ratio (OR_{m1} 1.21, OR_{m2} 1.21, and OR_{m3} 1.22) obtained from all three methods would suggest that missing cases, which differed between all three approaches, likely had little impact.

Diuretics are commonly prescribed in critically ill patients with acute renal failure, and their use is not associated with higher mortality.

Although the use of a propensity score can address problems that arise due to multicollinearity, it is interesting to note that the final models obtained by method 1 and method 2 both demonstrated the presence of moderate to severe multicollinearity (condition number >30). Because we found that propensity scores may not always adequately address problems associated with multicollinearity, we strongly support the recommendation that a propensity score method should not replace more traditional approaches but rather that they "should be thought of as an additional tool available" to investigators and compared directly with the results obtained with more traditional methods (34). Furthermore, we recommend that formal methods for detecting problems associated with multicollinearity should be employed.

Finally, it is interesting to note that method 3 included a variable representing the presence of a pulmonary artery catheter at study inclusion and, to our surprise, this variable was independently associated with a reduction in mortality rate (OR 0.59, $p < .001$). Given these

Table 9. Method 3: Multicollinearity adjusted model

	Regression Variable ± SE	*p* Value	Odds Ratio (95% CI)
Intercept	−0.790 ± 0.211	.0002	
Diuretic use	0.200 ± 0.140	.153	1.222 (0.92–1.6)
Patient age, yrs[a]	0.527 ± 0.072	.000	1.694 (1.4–1.9)
Hospital to ICU admit time, days[a]	0.474 ± 0.114	.0001	1.607 (1.2–2.0)
SAPS II[a]	0.265 ± 0.078	.001	1.304 (1.1–1.5)
Urea at ICU admission[a]	0.191 ± 0.081	.019	1.211 (1.0–1.4)
Renal replacement therapy	0.503 ± 0.152	.001	1.655 (1.2–2.2)
Heart rate at INCL[a]	0.135 ± 0.068	.049	1.145 (1.0–1.3)
Systolic blood pressure at INCL[a]	−0.142 ± 0.069	.041	0.868 (0.75–0.99)
Glasgow Coma Scale at INCL[a]	−0.256 ± 0.074	.001	0.774 (0.66–0.89)
Urine volume 6 hrs before INCL[a]	−0.148 ± 0.065	.023	0.862 (0.75–0.98)
Platelet count at INCL[a]	−0.242 ± 0.067	.0003	0.784 (0.68–0.89)
Creatinine at INCL[a]	−0.455 ± 0.090	.0001	0.634 (0.53–0.75)
Bilirubin at INCL[a]	0.165 ± 0.089	.065	1.180 (0.99–1.4)
Potassium at INCL[a]	0.135 ± 0.071	.055	1.145 (0.99–1.3)
Arterial pH at INCL[a]	−0.145 ± 0.063	.021	0.864 (0.76–0.97)
Pulmonary artery catheter at INCL	−0.524 ± 0.147	.0004	0.592 (0.44–0.79)
Respiratory failure at INCL	0.687 ± 0.169	.0001	1.988 (1.4–2.7)
Liver failure at INCL	0.363 ± 0.176	.039	1.439 (1.0–2.0)
Septic etiology	0.397 ± 0.137	.003	1.488 (1.1–1.9)
Low cardiac output etiology	0.316 ± 0.153	.038	1.373 (1.0–1.8)

CI, confidence interval; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; INCL, time of study inclusion.

[a]Variable was standardized to address issues of multicollinearity.

Table 10. Method 3: Comparison of missing cases to included cases

	Missing Cases ± SD (No.)	*p* Value	Included Cases ± SD (No.)
Diuretic use, %[a]	63 (339)	.80	64 (1,404)
Patient age, yrs	64 ± 16 (330)	.09	62 ± 16 (1,404)
Hospital to ICU admit time, days	6.2 ± 16 (339)	.65	5.8 ± 13 (1,404)
SAPS II[a]	47 ± 16 (337)	.001	51 ± 18 (1,404)
Urea at ICU admission, mmol/L	21 ± 16 (335)	.06	19 ± 14 (1,404)
Renal replacement therapy, %[a]	65 (339)	.01	72 (1,404)
Heart rate at INCL, beats/min	96 ± 21 (337)	.03	99 ± 21 (1,404)
Systolic blood pressure at INCL, mm Hg	118 ± 26 (331)	.14	115 ± 26 (1,404)
Glasgow Coma Scale at INCL[a]	12 ± 3.6 (325)	.20	12 ± 3.9 (1,404)
Urine volume 6 hrs before INCL, mL	254 ± 319 (291)	.33	277 ± 376 (1,404)
Platelet count at INCL, $\times 10^3/\mu L$	173 ± 122 (319)	.002	150 ± 115 (1,404)
Creatinine at INCL, μmol/L	381 ± 264 (336)	.0001	317 ± 201 (1,404)
Bilirubin at INCL, mmol/L	58 ± 138 (102)	.87	57 ± 102 (1,404)
Potassium at INCL, mmol/L	4.8 ± 1.2 (337)	.02	4.6 ± 1.0 (1,404)
Arterial pH at INCL	7.3 ± 0.1 (290)	.93	7.3 ± 0.1 (1,404)
Pulmonary-artery catheter at INCL, %	18 (339)	.001	26 (1,404)
Respiratory failure at INCL, %	71 (339)	.001	80 (1,404)
Liver failure at INCL, %	10 (338)	.001	32 (1,404)
Septic etiology, %	38 (337)	.001	48 (1,404)
Low cardiac output etiology, %	27 (337)	.58	26 (1,404)

ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; INCL, time of study inclusion.

[a]Key variables (known prognostic importance or relevant to main question of study).

Table 11. Final model comparisons

	H-L GoF Statistic	*p* Value	aROC
Method 1. Confirmatory propensity model	8.72	.36	0.72
Method 2. New propensity model	9.25	.32	0.77
Method 3. Multicollinearity adjusted model	11.29	.19	0.78

H-L GoF Statistic, Hosmer-Lemeshow goodness-of-fit statistic; *p* value, obtained from H-L GoF statistic with 8 degrees of freedom; aROC, area under the receiver operating characteristic curve. Obtained from c-statistic.

findings, we suggest that perhaps the role of diuretics must be taken into a larger context of fluid and hemodynamic management. We note that in the recently published trial of routine pulmonary artery catheter use (36), acute renal failure was a rare event, but a trend toward a decrease in incidence was seen in the patients receiving a pulmonary artery catheter.

CONCLUSIONS

When causal inferences are addressed, even the use of a propensity score cannot overcome the primary limitation of an observational study: Analytic methods can only adjust for observed confounding variables and not for unobserved ones (23). Similar to the decision to use a pulmonary artery catheter, the decision to use a diuretic in a critically ill patient could be driven by many factors that may not be adequately captured in an observational database. It is possible that these unquantifiable factors, in and of themselves, are more important in determining an individual patient's outcome than the use of diuretics.

In a large, prospective, multinational cohort, despite rigorous statistical analysis, we could not confirm the findings of Mehta et al. (21) that diuretics are associated with a higher mortality rate in critically ill patients with ARF. Thus, we would not discourage the use of diuretics in such patients. However, we would encourage a clinical trial, which our findings and those of Mehta et al. suggest is both desirable and logistically possible.

REFERENCES

1. Kellum JA: Use of diuretics in the acute care setting. *Kidney Int Suppl* 1998; 66:S67–S70
2. Gambaro G, Bertaglia G, Puma G, et al: Diuretics and dopamine for the prevention and treatment of acute renal failure: A critical reappraisal. *J Nephrol* 2002; 15:213–219
3. Majumdar S, Kjellstrand CM: Why do we use diuretics in acute renal failure. *Semin Dial* 1996; 9:454–459
4. De Torrente A, Miller PD, Cronin RE, et al: Effects of furosemide and acetylcholine in norepinephrine-induced acute renal failure. *Am J Physiol* 1978; 235:F131–F136
5. Kramer HJ, Schuurman J, Wasserman C, et al: Prostaglandin-independent protection by furosemide from oliguric ischemic renal failure in conscious rats. *Kidney Int* 1980; 17: 455–464
6. Better OS, Rubinstein I, Winaver JM, et al: Mannitol therapy revisited (1940–1997). *Kidney Int* 1997; 52:886–894

7. Denton MD, Chertow GM, Brady HR: "Renal-dose" dopamine for the treatment of acute renal failure: Scientific rationale, experimental studies and clinical trials. *Kidney Int* 1996; 50:4–14
8. Kleinknecht D, Ganeval D, Gonzalez-Duque LA, et al: Furosemide in acute oliguric renal failure. A controlled trial. *Nephron* 1976; 17: 51–58
9. Brown CB, Ogg CS, Cameron JS: High dose furosemide in acute renal failure: A controlled trial. *Clin Nephrol* 1981; 15:90–96
10. Solomon R, Werner C, Mann D, et al: Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994; 331:1416–1420
11. Shilliday IR, Quinn KJ, Allison ME: Loop diuretics in the management of acute renal failure: A prospective, double-blind, placebo-controlled, randomized study. *Nephrol Dial Transplant* 1997; 12:2592–2596
12. Cotter G, Weissgarten J, Metzkor E, et al: Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. *Clin Pharmacol Ther* 1997; 62:187–193
13. Stevens MA, McCullough PA, Tobin KJ, et al: A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: Results of the P.R.I.N.C.E. Study Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. *J Am Coll Cardiol* 1999; 33:403–411
14. Lassnigg A, Donner E, Grubhofer G, et al: Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. *J Am Soc Nephrol* 2000; 11:97–104
15. Sirivella S, Gielchinsky I, Parsonnet V: Mannitol, furosemide, and dopamine infusion in postoperative renal failure complicating cardiac surgery. *Ann Thorac Surg* 2000; 69: 501–506
16. Gubern JM, Sancho JJ, Simo J, et al: A randomized trial on the effect of mannitol on postoperative renal function in patients with obstructive jaundice. *Surgery* 1988; 103: 39–44
17. Nicholson ML, Baker DM, Hopkinson BR, et al: Randomized controlled trial of the effect of mannitol on renal reperfusion injury during aortic aneurysm surgery. *Br J Surg* 1996; 83:1230–1233
18. Allgren RL, Marbury TC, Rahman SN, et al: Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. *N Engl J Med* 1997; 336:828–834
19. Lewis J, Salem MM, Chertow GM, et al: Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. *Am J Kidney Dis* 2000; 36:767–774
20. Bellomo R, Chapman M, Finfer S, et al: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 2000; 356:2139–2143
21. Mehta RL, Pascual MT, Soroko S, et al: Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA* 2002; 288:2547–2553
22. Connors AF Jr, Speroff T, Dawson NV, et al: The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996; 276:889–897
23. Rubin D: Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997; 127(8 Suppl):757–763
24. Van Steen K, Curran D, Kramer J, et al: Multicollinearity in prognostic factor analyses using the EORTC QLQ-C30: Identification and impact on model selection. *Stat Med* 2002; 21:3865–3884
25. Le Gall JR, Lemeshow S, Saulnier F: A new simplified acute physiology score (SAPS-II) based on a European/North American multicenter study. *JAMA* 1993; 270:2957–2963
26. Cockroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 15:31–36
27. Marcus M, Minc H: Introduction to Linear Algebra. New York, Dover, 1988
28. Hosmer DW, Lemeshow S: Applied Logistic Regression. New York, Wiley, 1989
29. Belsley DA, Kuh E, Welsch RE: Regression Diagnostics: Identifying Influential Data and Sources of Collinearity. New York, Wiley, 1980
30. Hosmer DW, Lemeshow S: A goodness-of-fit test for the multiple logistic regression model. *Commun Stat* 1980; A10:1043–1069
31. Kleinbaum DG, Kupper LL, Muller KE, et al: Applied Regression Analysis and Other Multivariable Methods. Third Edition. Pacific Grove, CA, Duxbury Press, 1998
32. Harrell FE, Lee KL, Califf RM, et al: Regression modeling strategies for improved prognostic prediction. *Stat Med* 1984; 3:143–152
33. Iezzoni LI: Risk Adjustment for Measuring Health Care Outcomes. Ann Arbor, MI, Health Administration Press, 1994
34. D'Agostino RB: Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; 17:2265–2281
35. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818–829
36. Sandham JD, Hull RD, Brant RF, et al: A randomised controlled trail of the use of pulmonary artery catheters in high-risk surgical patients. *N Engl J Med* 2003; 348:5–14

APPENDIX

Participating Centers and Investigators

Australia: Intensive Care Unit, Austin and Repatriation Medical Center (Hiroshi Morimatsu, Rinaldo Bellomo), Department of Intensive Care, Western Hospital (Craig French), Intensive Care Unit, Epworth Foundation (John Mulder), Department of Intensive Care, Sir Charles Gairdner Hospital (Mary Pinder, Brigit Roberts), Intensive Care, Frankston Hospital (John Botha, Pradeen Mudholkar), Critical Care Unit, Flinders Medical Centre (Andrew Holt, Tamara Hunt). **Belgium:** Service de Soins Intensifs, Clinique Saint-Pierre (Patrick Maurice Honoré, Gaetan Clerbaux), Dienst Intensieve Geneeskunde, Universitair Ziekenhuis Gasthuisberg (Miet Maria Schetz, Alexander Wilmer). **Czech Republic:** ICU, Department of Internal Medicine I, Charles University Hospital Plzen (Richard Rokyta, Ales Krouzecky). **Germany:** Department of Nephrology, University Hospital Charité, CCM (Stanislao Morgera, Hans-Hellmut Neumayer), Klinik für Anaesthesiologie, Universitätsklinikum Duesseldorf (Kindgen-Milles Detlef, Eckhard Mueller). **Greece:** Intensive Care Unit, General Regional Hospital, "G. Papanikolau" (Vicky Tsiora, Kostas Sombolos). **Holland:** Intensive Care Unit, Onze Lieve Vrouwe Gasthuis (Helena Maria Oudemans-Van Straaten), Adult Intensive Care Unit, Academic Medical Center (Catherine S.C. Bouman, Anne-Cornelie J.M. de Pont). **Israel:** Intermediate Intensive Care Unit, Rambam Medical Center (Yaron Bar-Lavie, Farid Nakhoul). **Italy:** Anesthesia and Intensive Care Unit, Cliniche Humanitas-Gavazzeni (Roberto Ceriani, Franco Bortone), Nephrology-Intensive Care, St. Bortolo Hospital (Claudio Ronco, Nereo Zamperetti), Istituto di Anestesia e Rianimazione Servizio di Anestesia e Rianimazione per la Cardiochirurgia, Ospedale San Raffaele IRCCS Università Vita e Salute (Federico Pappalardo, Giovanni Marino), Unità Operativa di Rianimazione, Ospedale Vittorio Emanuele (Prospero Calabrese, Francesco Monaco), Anestesia e Rianimazione, City Hospital of Sesto San Giovanni (Chiara Liverani, Stefano Clementi), Intensive Care Unit, Surgical and Medical Emergencies Institute (Rosanna Coltrinari, Benedetto Marini). **Norway:** Department of Anesthesia, Rikshospitalet (Jan Frederik Bugge, Fridtjov Riddervold), Department of Anaestesiology, University and regional hospital in tromsø (Paul Åge Nilsen, Joar Julsrud). **Portugal:** Unidade de Cuidados Intensivos (ICU), Hospital de Curry Cabral (Fernando Teixeira e Costa, Paulo Marcelino), Unidade De Cuidados Intensivos Polivalente, Hospital Fernando Fonseca (Isabel Maria Serra). **Russia:** Unit for Extracorporeal Blood Purification, Ba-

koulev Scientific Center for Cardiovascular Surgery (Mike Yaroustovsky, Rachik Grigoriyanc). **Spain:** Anaesthesiology and Critical Care Department, Hospital Comarcal De Viaros (Ferran Barrachina, Julio Llorens), Department of Intensive Care Medicine, Section of Severe Trauma, Hospital Universitario "12 de Octubre" (Jose Angel Sanchez-Izquierdo-Riera, Darío Toral-Vazquez). **Sweden:** Dep. of Anesthesia and Intensive Care, Sunderby Hospital (Ivar Wizelius, Dan Hermansson). **Switzerland:** Department of Surgery, Surgery Intensive Care Unit and Department of Medicine, Medical Intensive Care Unit, University Hospital Zürich (Tomislav Gaspert, Marco Maggiorini), **UK:** Center for Nephrology, Royal Free Hospital (Andrew Davenport). **Canada:** Intensive Care, Maisonneuve-Rosemont Hospital (Martine Leblanc, Lynne Senécal), Division of Critical Care Medicine, University of Alberta, Edmonton (R.T. Noel Gibney, Curtis Johnston, Peter Brindley). **USA:** Department of Critical Care Medicine, University of Pittsburgh Medical Center (Ramesh Venkataraman, John Kellum), Department of Medicine, Section of Nephrology, The University of Chicago (Patrick Murray, Sharon Trevino), Surgical Intensive Care Unit, Mount Sinai Medical Center (Ernest Benjamin, Jerry Hufanda), Nephrology and Hypertension , The Cleveland Clinic Foundation (Emil Paganini), Department of Medicine, Division of Nephrology, The University of Alabama at Birmingham (Ashita Tolwani, David Warnock), Internal Medicine/Nephrology, University of Nebraska Medical Center (Nabil Guirguis, Gerald Groggel). **Brazil:** Nephrology Division, University of São Paulo School of Medicine (Luis Yu, Ettiene V. Macedo), Nephrology Division, do Hospital Servidor Público Estadual de São Paulo (Sandra Maria Rodriques Laranja, Cassio José Rodrigues), Nephrology Unit, Casa de Saúde São José/CDR Serviços Hospitalares (José Hermógenes Rocco Suassuna, Frederico Ruzany), Lutheran University of Brasil (Bruno Campos, Jayme Burmeister). **Uruguay:** Department of Critical Care Medicine, Impasa (Raúl Lombardi, Teresita Llopart). **China:** Intensive Care Unit, Department of Anesthesia, Pamela Youde Nethersole Eastern Hospital (Ian K.S. Tan), Surgical Intensive Care Unit, Beijing Chao Yang Hospital (Hui De Chen, Li Wan). **Indonesia:** ICU, National Cardiovascular Center and Mitra Keluarga Hospital (Iqbal Mustafa, Iwayan Suranadi). **Japan:** Intensive Care Center, Teikyo University School of Medicine Ichihara Hospital (Nobuo Fuke, Masaaki Miyazawa), Intensive Care Unit, Okayama University Hospital (Hiroshi Katayama, Toshiaki Kurasako), Department of Emergency and Critical Care Medicine, Graduate School of Medicine, Chiba University (Hiroyuki Hirasawa, Shigeto Oda), Emergency and Critical Care Medicine, Fukuoka University Hospital (Koichi Tanigawa, Keiichi Tanaka). **Singapore:** Medicine Department, National University of Singapore (Kang Hoe Lee), Surgical Intensive Care Unit, Tan Tock Seng Hospital (Shi Loo, Kulgit Singh).