vide information regarding efficacy, because it was underpowered for a mortality effect; morbidity also was not reported. Furthermore, since our studies in the medical and the surgical ICU have shown that survival curves separated only after 30 days or more, studies aiming for an early mortality benefit would predictably fail.

Sustained blood-glucose control in patients with diabetes[2] or critical illness prevents the cellular damage inflicted by hyperglycemia, a benefit that outweighs the risk of hypoglycemia. Continuous glucose-monitoring systems are awaited, which could further reduce episodes of hypoglycemia and hyperglycemia. Current data support careful maintenance of normoglycemia in all patients in the ICU, from admission on.

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THE EDITORIALIST REPLIES: Tamler et al. suggest that we should overlook the excess mortality potentially associated with short-term intensive insulin therapy in the study by Van den Berghe et al. The excess early deaths in the intensive-treatment group could have a substantial effect on both the subgroup analyses of patients with long stays in the medical ICU and on morbidity. The assignment to subgroups after randomization is problematic, since patients were considered to have a long stay in the ICU on the basis not just of randomization but also of survival during the first three days in the ICU. Thus, the results for those with long stays may reflect true benefits of intensive insulin therapy or survivor effects before these patients were included in the subgroup (i.e., the sickest patients died before being included). The morbidity data in the intention-to-treat analysis are exciting but difficult to interpret because of the differential time to death — early deaths in the intensive insulin group could effectively protect against the development of renal failure and prolonged use of mechanical ventilation. My opinion regarding target therapeutic values of glucose is based on published international consensus,[1] since the data available from randomized trials are equivocal (one positive phase 2 study, one negative phase 2 study, and the reportedly negative multicenter Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis [VISEP] study[2]).

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Long-Term Outcome of Renal Transplantation from Older Donors

TO THE EDITOR: We have used an approach similar to that of Remuzzi et al. (Jan. 26 issue)[1] in the assessment of kidneys from donors older than 60 years of age and the implantation of organs with minimal renal changes as assessed on biopsy before transplantation. During a three-year period, we performed 150 renal biopsies (with a mean of 80 glomeruli obtained per biopsy) of kidneys from 75 cadaveric donors 61 through 84 years of age. A pathologist evaluated the biopsy specimens using strict, objective, blinded criteria (as discussed by Karpinski et al.[2]).

Kidneys of cadaveric donors in their 60s were adequate for single transplantation 44.1 percent of the time (total score, 0 to 3, according to the scoring system used by Karpinski et al.) and for dual transplantation 35.2 percent of the time (total score, 4 to 6). Kidneys from cadaveric donors 70 through 80 years of age were adequate for single and dual transplantation in 40.5 percent and 35.1

percent of cases, respectively. Our data confirm that preimplantation biopsy of kidneys from older cadaveric donors may be useful for increasing the number of kidneys available for transplantation.

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TO THE EDITOR: The methods of Remuzzi et al. do not justify the conclusions the authors reached. A major limitation of their study is that the majority of the patients were recipients of dual allografts, whereas only eight patients received single allografts. An appropriate control group would have been recipients of dual kidneys from older donors without preimplantation biopsy. In the Cox regression model the authors used, preimplantation biopsy was included as an independent factor, but not whether the transplant was dual as compared with single. The appropriate conclusions seem to be that the rate of graft survival for dual allografts from older donors matches that for single allografts from donors 60 years old or younger and is better than that for single allografts from older donors. These conclusions are not new, since it has already been demonstrated that recipients of dual kidneys from donors selected with the use of expanded criteria for donation do as well as recipients of single kidneys from donors selected with standard criteria.[1]

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TO THE EDITOR: In the study by Remuzzi et al., graft survival for kidneys from older cadaveric donors that are allocated on the basis of histologic evaluation approached the rate for kidneys from younger donors. However, all methods of histologic evaluation of donor kidneys are not equivalent. Remuzzi et al. examined specimens obtained by core needle biopsy, as opposed to wedge biopsy, which is used in many centers with more variable results.[1-4] Core biopsy samples the full cortical thickness, including arteries near the corticomedullary junction. In contrast, wedge-biopsy specimens often lack these vessels and frequently overrepresent the superficial cortex, with the greatest degree of glomerular and tubulointerstitial scarring in older people.

Remuzzi et al. report no graft losses resulting from biopsies performed with 16-gauge needles; they also report equivalent median cold-ischemia times for kidneys that were biopsied and those that were not biopsied. Thus, the use of histologic evaluation (if it is performed on core-biopsy specimens) in the assessment of kidneys from donors selected with the use of extended criteria should markedly reduce variability in the prediction of outcome.

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TO THE EDITOR: Remuzzi et al. suggest that a strategy based on histologic evaluation of kidneys from older donors improves outcome while expanding the donor pool. However, the data are inconclusive.

First, it appears that patients in the positive-reference group (who received single kidney transplants from donors 60 years of age or younger) were recruited from various transplantation centers without matching for retransplantation, panel-reactive antibodies, and immunosuppressive ther-

apy. Moreover, the shorter waiting time of the patients in the study group, which is explained by their preferential position on the waiting list, might have biased the results.[1]

Second, there is no evidence supporting expansion of the donor pool. The numbers of discarded kidneys in the study and reference groups are not provided, and in their presentation of data, the authors do not take into account that more patients remain on dialysis if dual transplantation is performed. If such potential patients are included in the analysis, the proposed strategy results in more patients who remain on dialysis (Table 1). Such patients would be harmed, since the life expectancy of patients receiving dialysis is worse than that of graft recipients, even when the kidney comes from a donor selected with the use of expanded criteria for donation.[2]

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Table 1. Effects of Histologic Evaluation of Donor Kidneys.*

Variable	Donor Age >60 Yr	
	Histologic Evaluation	No Histologic Evaluation
	number	
Donors	58	58
Kidneys available for transplantation	116	116
Patients receiving dialysis on waiting list	116	116
Results after transplantation		
Patients receiving grafts	62	116
Patients remaining on dialysis	54	0
Patients who died	3 (plus 4)†	9
Patients back on dialysis	4	27
End of observation		
Patients alive with functioning graft	55	80
Patients on dialysis	54	27

* Calculations are based on the number of patients in Table 2 of the study by Remuzzi et al.
† It is assumed that the death rate of patients receiving dialysis was at least the same as that of graft recipients in the control group.

THE AUTHORS REPLY: We observed that a strategy based on histologic evaluation of kidneys from older donors improves outcome while expanding the donor pool. Hilbrands and Wetzels suggest that our data might be confounded by positive-reference recipients recruited from various centers. We addressed this concern with an additional analysis of the outcome of recipients of grafts from older donors that had undergone histologic evaluation and of age-matched and sex-matched recipients in the positive-reference group, with both groups of patients coming from two centers of the Double Kidney Group network. Graft survival in the two cohorts was similar.

The shorter waiting time in the study group is explained not by the preferential position on the waiting list but, rather, by the expansion of the donor pool, which enhanced the chance of retransplantation and was an additional advantage of our proposed strategy. Twenty-four percent of donors of kidneys that were biopsied were more than 74 years old. Kidneys from donors older than 74 years of age were never used for transplantation without preimplantation biopsy. Thus, our strategy actually translates into an expansion of the donor pool. This is a major advantage for patients on waiting lists, and this issue is not considered in the table provided by Hilbrands and Wetzels. They are correct in saying that more patients remain on dialysis if dual transplantations are performed. However, they do not mention that patients who return to dialysis after undergoing transplantation have a higher death rate than do patients receiving dialysis who have not undergone transplantation, a fact that should be considered in their calculations.[1]

Our mathematical modeling indicates that for 100 patients on a waiting list, at 10 years there will be 3 deaths among recipients of grafts that have undergone histologic evaluation and 11 deaths among recipients of grafts that have not undergone histologic evaluation (Fig. 1). At the same time, the numbers of patients who are predicted to be alive with a functioning kidney are similar in the two groups (45 and 43, respectively).

In the series by Tan and colleagues[2] cited by Panesar et al., the two-year rate of graft survival (82.1 percent) was less than that in our series (94

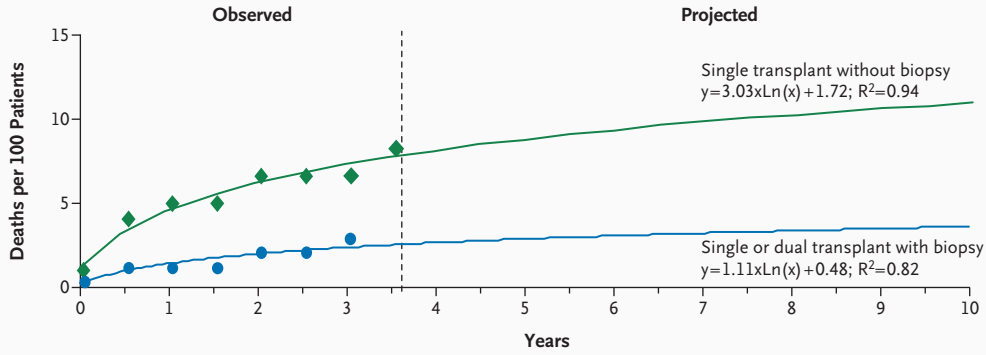

Figure 1. Projected Deaths during a 10-Year Follow-up Period for 100 Patients on a Waiting List for Kidney Transplants.
Projections are made according to the use of kidneys from donors older than 60 years for single or dual transplantation on the basis of the histologic-evaluation score and for single transplantation without histologic evaluation. Data have been adjusted to include a projected 24 percent increase in the number of available donors (resulting from the use of biopsy-based histologic evaluation) and similar death rates among patients who receive a transplant, who remain on dialysis, or who return to dialysis after their transplant has failed. In the equation, x denotes time, y number, and Ln(x) the natural logarithm of time.

percent), despite a younger mean age of donors (61±1 vs. 69±8, respectively). Other series of dual transplantations without histologic evaluation report even lower rates of survival.[3] Moreover, the systematic use of kidneys from older donors for dual transplantation would unnecessarily reduce the number of transplantations. Raspollini et al. correctly report that some 40 percent of kidneys that are harvested from donors older than 60 years of age appear to be adequate for single transplantation on the basis of histologic evaluation. We agree with Haas et al. that core biopsy markedly reduces variability in the prediction of outcome for recipients of renal transplants.

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Tumor Necrosis Factor α in Refractory Asthma

TO THE EDITOR: In our opinion, the randomized clinical trial by Berry et al. (Feb. 16 issue)[1] appears to mitigate the excitement that has been generated in recent years concerning the use of tumor necrosis factor α (TNF-α) inhibitors in the management of refractory asthma.[2] In an open-label study,[3] 12 weeks of treatment with etanercept resulted in a substantial improvement in symptoms; all but one of the patients were able to discontinue the use of bronchodilators. By contrast, the observed statistically significant improvement in quality-of-life and symptom scores in the trial by Berry et al. is probably not of clinical relevance, and none of the patients could discontinue or reduce the use of nebulized or oral treatment.

Examination of the individual quality-of-life scores and comparison of the data obtained in the placebo and etanercept treatment periods suggest that only two patients would unambiguously benefit from this expensive treatment. It is unfortunate that it was not possible to dissect out from the data presented any specific characteristics that would clearly identify those who would have a response to etanercept. In our opin-