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The Author's Reply

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We thank Dr. Jin and colleagues(1) for their comments on our manuscript(2) recently published in *Critical Care Medicine*. Our study utilized a large multi-center database to evaluate outcomes associated with full-dose and half-dose alteplase for patients admitted to the ICU with pulmonary embolism (PE).

We agree with Dr. Jin and colleagues that our study does not put the final nail in the coffin for half-dose alteplase. Half-dose alteplase successfully treated approximately 50% of patients without need for further treatment escalation in our study. Mortality rates and other important clinical outcomes were similar between patients receiving half-dose alteplase as their only intervention without any further escalation of care as compared to patients treated with full-dose therapy. However, significant reductions in major bleeding, including intracranial hemorrhage, were not observed.

A notable finding of our study is that alternative thrombolysis strategies for patients with acute PE are being utilized in an attempt to optimize benefits and minimize risk. As noted, differences in treatment escalation between full-dose and half-dose alteplase groups were driven by secondary thrombolysis and thrombosis fragmentation by catheter. In fact, 1 out of every 4 patients treated with half-dose alteplase received an additional dose during hospitalization. We could not determine if treatment escalation was preplanned or a result of decompensation, but only half received the second alteplase dose within 1 hospital day. Therefore, it is possible a sequential strategy, such as suggested by Dr. Jin and colleagues(1), was utilized in some patients. If we conservatively estimate that all patients receiving

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secondary thrombolysis within 1 day was pre-planned, secondary thrombolysis still remains significantly different between treatment groups ($p=0.025$). Thrombus fragmentation by catheter was associated with a trend towards increased length of hospital stay and significantly increased hospital costs without mortality or bleeding benefits.

Evaluation of outcomes based upon PE risk stratification is limited in our study due to the absence of laboratory and radiographic results in the database. We were able to ascertain whether a test (e.g. brain natriuretic peptide) was conducted, but we did not have access to the results. We therefore delineated patients by hemodynamic compromise, utilizing vasopressors as the indicator for shock. Although elevated biomarkers indicating intermediate risk PE have been associated with worse patient outcomes, thrombolysis in these patients has not demonstrated improved mortality or long term outcomes(3); but may increase the risk of intracranial and extracranial bleeding(4).

To address the concern that there were differences in outcomes in the high risk PE subgroup due to loop diuretics, we conducted an additional analysis after removing these patients. No differences in treatment escalation (89.7% vs. 82.7%, $p=0.17$), mortality (41.2% vs. 48.1%, $p=0.36$), major bleeding ($p>0.05$ for all measurements) or fibrinolytic adverse events (0% vs. 3.7%, $p=0.09$) were observed between full-dose and half-dose treatment groups, respectively.

We concur with Dr. Jin and colleagues that future prospective studies are required to optimize thrombolytic therapy in patients with acute PE. Pharmacokinetic and pharmacodynamic studies are lacking and may be prudent to delineate optimal thrombolytic dosing options to test prior to embarking on a large randomized study to evaluate full-dose versus half-dose therapy.

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