Mohammed Faisaluddin, MD<sup>c</sup>

#### Christopher Bianco, DO<sup>a</sup>\*

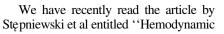
 <sup>a</sup> Division of Cardiology, West Virginia University School of Medicine, Morgantown, West Virgina
<sup>b</sup> Knight Cardiovascular Institute, Oregon Health and Science University, Portland, Oregon
<sup>c</sup> Deccan College of Medical Sciences, Hyderabad, India

<sup>#</sup> Both authors have contributed equally 16 November 2020

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# Systemic Fibrinolytic Therapy Versus Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-High Risk Pulmonary Embolism



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Effects of Ultrasound-Assisted, Catheter-Directed, Very Low-Dose, Short-Time Duration Thrombolysis in Acute Intermediate-High Risk Pulmonary Embolism (From the EKOS-PL Study).<sup>11</sup> We appreciate the authors for their research describing the efficacy and safety of ultrasound-assisted catheter-directed thrombolysis (USAT) in patients with acute intermediate-high risk pulmonary embolism (PE). In contrast, we would like to emphesis some points in the light of the current evidence.

Acute PE is a life-threatening disorder which usually presents as a severe complication of venous thromboembolism.<sup>2</sup> Noninvasive "low-dose" systemic thrombolytic therapy (50 mg t-PA) has been advocated, based on the hypothesis that all venous return and right heart output washes the pulmonary circulation, with lower dosage and avoidance of "invasive" vascular access can maintain increased thrombolytic efficacy with less bleeding. This approach has previously been reported with a limited number of data which dramatically eliminated major bleeding complications while achieving excellent clinical results.<sup>3</sup> Current literature included multiple case reports regarding the use of low-dose t-PA for the treatment of PE. The doses and administration times are inconsistent, and many of these case reports use lowdose t-PA in patients with massive PE when full-dose t-PA was contraindicated or relatively contraindicated.<sup>4</sup> Previously, Sharifi et al<sup>3</sup> reported that low-dose thrombolytic therapy (a 10mg bolus by an intravenous push within 1 minute followed by infusion of the remaining 40 mg within 2 hours) achieved excellent clinical results with a striking absence of bleeding in patients with submassive PE. Based on these promising results, we adopted this low-dose systemic thrombolytic therapy with a 6-hour infusion strategy as an option for "escalation of care" in PE cases that had intermediate-high risk.<sup>2</sup> Recently, we indicated that this regimen was associated with an overall excellent clinical outcome, in contrast to these prior reports which eliminated bleeding complications.<sup>2</sup> The incidence of the total bleeding (n = 2, epistaxis)and hemoptysis) in this was 12.5% with this thrombolytic therapy regimen.

There are some remarkable points about pulmonary circulation. Unlike

deficiency. Iron deficiency was defined as (serum ferritin level,100 ng/ ml, or between 100 and 300 ng/ml if transferrin saturation <20%). We only included RCTs, which enrolled more than 100 patients to avoid the small studies effect. Two authors extracted and analyzed the data using STATA v15.1 software. The outcomes of interest were all-cause mortality, cardiovascular mortality, and heart failure hospitalization. We calculated risk ratios (RRs) and 95% confidence intervals (CIs) using a random-effects model.

We identified 4 RCTs with 2,042 patients, mean duration of follow up  $(31\pm 14 \text{ weeks})$  (age  $69 \pm 3$  years; females 51%). Compared with the standard of care, intravenous iron therapy was associated with a significant reduction of heart failure hospitalization (RR 0.69, 95% CI 0.61 to 0.78, p=0.043; Figure 1). There was no difference between intravenous iron therapy and standard of care in all-cause mortality (RR 0.67, 95% CI 0.36 to 1.23, p=0.37) and cardiovascular mortality (RR 0.90, 95% CI 0.19 to 1.18, p=0.40; Figure 1).

The exact mechanism by which intravenous iron supplementation improves functional status and clinical outcomes in heart failure patients is unclear. Several mechanisms have been proposed, including improving oxygen transport and metabolism through increased hemoglobin, especially in cells with high oxygen requirements, like cardiac and skeletal myocytes. Randomized trials examining the role of oral iron on improving clinical endpoints in heart failure patients have failed to show benefit likely due to poor absorption of oral iron in the setting of chronic inflammatory state associated with heart failure.<sup>1</sup>

In conclusion, in patients with HFrEF and iron deficiency, treatment with intravenous iron therapy has reduced the risk of heart failure hospitalization by almost 30% with no difference in all-cause mortality and cardiovascular mortality compared to standard of care.

### Disclosures

The authors have no conflicts of interest to report.

Mohammed Osman, MD<sup>a#</sup> Moinuddin Syed, MD<sup>a#</sup> Sudarshan Balla, MD<sup>a</sup> Babikir Kheiri, MD<sup>b</sup>



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other organs that take part of the cardiac output (CO), the lungs take the integrity of the CO (in the absence of a shunt). From the existing guidelines, the "standard practice" uses the same or similar t-PA dose for PE that is used for thrombolysis in the systemic arterial circulation.<sup>5</sup> For instance, in acute myocardial infarction, 100 mg of t-PA is given within 1.5 hours for a thrombus in the coronary circulation, which receives only 5% of the CO.<sup>6</sup> These doses have the potency to withstand "route attrition": t-PA is given into the venous circulation, it traverses the lung capillaries, enters the arterial circulation, reaches a steady-state, and is still capable of dissolving arterial clots. However, the crucial point, is whether it is necessary to use the same dose designed for thrombolysis in the systemic circulation for the lungs or not? Furthermore, another essential point is that it does not matter from which venous access site the t-PA is given as all t-PA molecules converge in the lungs. The corollary of this perspective might be applied to USAT except for isolated segmental or subsegmental PE. In contrast to almost every other vascular bed with thrombosis, which would benefit from catheterdirected thrombolysis, in the lungs it would probably not be necessary if the PE is massive and diffuse because the lungs are the center of convergence of all venous flow, and, ultimately, all administered molecules of t-PA would reach the pulmonary circulation. We do not dispute the established efficacy of USAT in the treatment of PE but only suggest that a similar result might be obtained by thrombolytic therapy through the peripheral venous circulation using similar low doses.

### Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

> Ahmet Güner, MD<sup>a</sup>\* Ezgi Gültekin Güner, MD<sup>a</sup>

Macit Kalçık, MD<sup>b</sup>

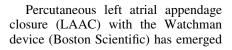
 <sup>a</sup> Department of Cardiology, University of Health Sciences, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey
<sup>b</sup> Department of Cardiology, Faculty of Medicine, Hitit University, Corum, Turkey

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# Procedural and Short-Term Outcomes of Percutaneous Left Atrial Appendage Closure in Patients With Cancer



Ethical approval: This study was exempted from the approval of the institutional review board because it used anonymized and de-identified data from a publicly available database. as an alternative to anticoagulation in patients with atrial fibrillation (AF). Cancer is a common comorbidity in patients with AF.<sup>1,2</sup> Also, AF patients with cancer reportedly have a higher bleeding risk with a similar or higher stroke risk than those without cancer.<sup>3</sup> Thus, AF patients with cancer unsuitable for anticoagulation can be indicated for LAAC to prevent AF-related thromboembolism.<sup>2</sup> However, scarce data are available on the procedural complication risk and outcomes of LAAC among cancer patients. Therefore, we aimed to investigate them using a population-based database in the United States.

We conducted a retrospective analysis using the Nationwide Readmissions Database (NRD) 2016 to 2017, an administrative claims database managed by the Healthcare Cost and Utilization Project.<sup>4</sup> The International Classification of Diseases, tenth revision codes were used to identify patients  $\geq 18$  years of age with a primary diagnosis of AF (I48.0/I48.1/ I48.2/I48.91) who underwent percutaneous LAAC (02L73DK). Eligible patients were divided into 3 groups based on cancer status: those with no cancer, those with active cancer (C00. x-C97.x), and those with prior history of cancer (Z85.xx). The outcomes of interest were in-hospital adverse events and 30-day/180-day readmission outcomes. The composite outcome was defined as in-hospital death, ischemic stroke/transient ischemic attack (TIA), systemic embolism, bleeding requiring blood transfusion, pericardial effusion/ cardiac tamponade treated with pericardiocentesis or surgically, and removal of embolized device. We presented data on the national estimates based on the discharge weights provided by the NRD. We also examined the association between cancer status and outcomes in multivariable logistic regression models adjusted for patient characteristics in Table 1 except for organ/diagnosis and progression of cancer.

Of 15,399 eligible patients, 12,712 (82.6%) had no cancer history, 364 (2.4%) had active cancer, and 2,323 (15.1%) had a prior history of cancer. Active-cancer patients, compared with those with no or prior history of cancer, were more often male, had a higher prevalence of mitral regurgitation, pulmonary hypertension, carotid artery

