in-hospital heart failure, in-hospital mortality, and peak troponin among SSRI users. These preliminary data need to be validated in larger, multicenter registries.

*Andre Dias, MD
Emiliana Franco, MD
Vincent M. Figueredo, MD
*Department of Cardiology
Albert Einstein Medical Center
5501 Old York Road
Philadelphia, Pennsylvania 19141
E-mail: andremacdias@gmail.com

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APPENDIX For a supplemental table, please see the online version of this paper.

REPLY: Catecholamine-Mediated Pathways in Takotsubo Syndrome

Does it Matter If it Is a Serotonin Norepinephrine Reuptake Inhibitor or a Selective Serotonin Reuptake Inhibitor?

Dr. Dias and colleagues presented some interesting observations about serotonin norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) based on their retrospective descriptive study of Takotsubo syndrome (TTS) that was previously reported (1) in addition to their current update. Because of this relatively small registry, we have concerns about representativeness, generalizability to a larger population, and insufficient information to base a causal assessment.

The investigators reported that 22.3% of TTS patients in their registry were SSRI or SNRI users. This percentage is higher than the 12.8% of patients admitted on antidepressants among the 1,750 TTS patients from the International Takotsubo Registry (2). The National Health and Nutrition Examination Survey (NHANES) showed that from 2011 to 2012 antidepressants were prescribed to 13% of the U.S. adult population, consisting of 8.5% SSRIs, 2% SNRIs, and 2.5% other antidepressant classes (3). The registry used by Dr. Dias and colleagues showed a 3:1 ratio of SSRI to SNRI use, which suggests a larger relative presence of SNRI cases in this registry compared with NHANES data; we could not exclude that SNRIs might be over-represented in the series by Dr. Dias and colleagues because of a possible SNRI increase in the risk of TTS.

Additional information from this registry quantifying the amounts of SSRI or SNRI ingested, duration of use, and catecholamine level information for these patients would have been useful to assess causal associations. The investigators previously reported an 80% stressful trigger for their SSRI patients (1), which suggested that SSRI was not likely to be the TTS trigger in these patients.

The registry's investigators possibly misinterpreted the only 2 case reports that they cited. Both the Christoph et al. (4) and Selke et al. (5) references were case reports of TTS associated with SNRI and catecholamine elevations. These patients in these studies did not ingest SSRI medications. Christoph also cites Johnson et al. (6), stating the SSRI fluvoxamine "does not have significant effects on noradrenergic function." Nonetheless, the possibility of SSRI medications having additional neurotransmitter effects is beyond the scope of this brief reply.

The findings by Dr. Dias and colleagues supported the concept that multiple pathways might influence the pathogenesis of TTS. Furthermore, once TTS occurred, several factors might influence subsequent outcome.

We look forward to additional drug safety information from such registries as they continue to accrue data. We used the Food and Drug Administration Adverse Event Reporting System database in addition to a variety of data sources to conduct our post-marketing pharmacological vigilance activities. Although SNRI-associated TTS might be a rare event, practitioners should be aware of this association for SNRI patients who present with TTS. We encourage submission of suspected adverse drug events to MedWatch (www.fda.gov/medwatch).

*Daniel Woronow, MD
Courtney Suggs, PharmD, MPH
Robert Levin, MD
Ida-Lina Diak, PharmD, MS
Cindy Kortepeter, PharmD

*Division of Pharmacovigilance
Office of Surveillance and Epidemiology
Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 3475
Silver Spring, Maryland 20993
E-mail: Daniel.Woronow@fda.hhs.gov

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Time to Diuretic in Acute Heart Failure

We read with great interest the analysis regarding the effect of door-to-diuretic time on clinical outcomes in patients with acute heart failure (AHF) (1). May we ask the authors to provide additional analysis to better support their conclusion?

First, unfortunately several inappropriate statistical tests seem to have been applied when describing the laboratory findings in Table 1 in the article by Park et al. (1). It would be helpful if the authors could provide medians and interquartile ranges for the variables obviously not having a normal distribution including B-type natriuretic peptide, N-terminal prohormone of B-type natriuretic peptide, and troponin I and T. Second, we are concerned that other errors may have been introduced in the binary logistic regression model: for example, ischemic heart disease was more common in the early compared to the delayed treatment group (Table 1: 33.5% vs. 27.6%, respectively), but reported as a predictor of delayed door-to-diuretic time in Table 2. This finding is rather difficult to explain and may have been introduced by substantial confounding in the model. Third, despite a 95% confidence interval clearly passing the 1.00, a highly significant p-value was reported for chronic obstructive pulmonary disease, New York Heart Association functional class, and heart rate. Could the authors explain this in more detail?

Fourth, only patients hospitalized for AHF were included in this analysis. It would be interesting to know how many AHF patients receiving intravenous furosemide in the emergency department were directly discharged and, therefore, excluded. Fifth, to avoid confounding by a delayed or missed diagnosis, in a similar analysis regarding door-to-diuretic time (2), patients were only included if diagnosed with AHF within 3 h of their first evaluation by the attending emergency department physician. Can the authors add a similar analysis restricted to patients diagnosed with AHF within 3 h? Sixth, previous large intercontinental studies have documented differences in outcomes between East Asian and Western populations with AHF, with greater mortality in Western populations (3). Can the authors comment on whether this could increase the importance of door-to-diuretic time on clinical outcomes?

Desiree Wussler, MD
Joan Walter, MD
Jeanne du Fay de Lavallaz, MD
Ivo Strebel, MS
***Christian Mueller, MD**

*Department of Cardiology and
Cardiovascular Research Institute Basel (CRIB)
University Hospital Basel
Petersgraben 4
CH-4031 Basel
Switzerland
E-mail: christian.mueller@usb.ch

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