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14. Validation of a Prediction Rule for Adverse Cardiovascular Events from Drug Overdose

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Study Objectives: Adverse cardiovascular events (ACVE) complicate > 16% of hospitalizations for acute drug overdose. Previously a risk prediction rule was derived for risk assessment of in-hospital ACVE in acute drug overdose patients, with > 97% negative predictive value (NPV). Our aim was to externally validate the ACVE rule.

Methods: This prospective cohort study was conducted over three years (2017- 2019) using the Toxicology Investigators Consortium (ToxIC) at over 65 U.S. hospitals in 35 major cities nationwide. Adult (>18y) emergency department (ED) patients at participating institutions receiving bedside medical toxicology consultation for suspected acute drug overdose were screened for inclusion, and excluded for the following: non-drug overdose (eg, caustic), chronic toxicity, international sites, alternate diagnosis (according to the attending medical toxicologist), and missing data. The composite study outcome, ACVE, has previously been defined as any of the following: myocardial injury (elevated cardiac troponin I), shock (requiring vasopressors), ventricular dysrhythmia (VT/VF/TdP), or cardiac arrest (pulselessness requiring CPR). The risk prediction rule included any of these 3 factors: (1) any prior cardiac disease (CAD or CHF); (2) initial QTc **≥** 500ms; (3) initial serum bicarbonate ≤ 20 mmol/L. Sample size was predetermined in order to calculate NPV with 95% confidence interval (CI) widths < 2%; we calculated the need to analyze 5,000 patients.

Results: There were 21,793 patients screened, of whom 13,874 were excluded (6499 pediatrics, 4658 non-drug overdose, 1976 chronic, 574 international, 118 alternate diagnosis, 46 non-ED, 3 missing data), leaving 7919 for analysis (mean age, 39.1 years; female, 50.3%; suicidal, 27.7%). ACVE occurred in 845 (10.7%, CI 10.0- 11.4) patients (myocardial injury, 348; shock, 529; dysrhythmia, 81; cardiac arrests, 183), 14.0% of hospitalizations/admissions (622/4441, CI 13.0-15.1), and there were 131 deaths (1.7%, CI 1.4-2.0). The multivariable model adjusting for the previously derived risk factors, controlling for age, confirmed the following independent predictors of ACVE: QTc **≥** 500 msec (OR 2.6, $p < 0.001$), bicarbonate ≤ 20 mmol/L (OR 3.3, $p < 0.001$) and prior cardiac disease (OR 2.3, $p < 0.001$). Prediction rule performance in 5500 patients with documentation of all 3 factors was the following: 61.4% sensitivity (CI 57.5-65.3), 78.8% specificity (CI 77.7-79.8), and 95.4% negative predictive value (CI 95.0-95.9). Prediction rule receiver operating curve performance is illustrated in the Figure. The presence of 2+ risk factors was 96.4% specific with an LR+ of 4.33 (CI 3.5-5.4) and 5.8-fold increased odds of ACVE ($p<0.001$).

Conclusion: We have externally validated the previously-derived risk prediction rule for ACVE, with all components of the rule remaining independently predictive of ACVE. The validation cohort had comparable ACVE incidence to previous reports. The rule performed with similar sensitivity and NPV to the derivation cohort. Clinical application of the rule to ED patients may aid intensive care unit triage and medical clearance. Implementation science studies are warranted for incorporation into clinical practice.