Validation of the Prognostic Utility of the Electrocardiogram for Acute Drug Overdose

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**Background**—While it is certain that some emergency department patients with acute drug overdose suffer adverse cardiovascular events (ACVE), predicting ACVE is difficult. The prognostic utility of the ECG for heterogeneous drug overdose patients remains to be proven. This study was undertaken to validate previously derived features of the initial ECG associated with ACVE in this population.

**Methods and Results**—We performed a prospective validation cohort study to evaluate adult emergency department patients with acute drug overdose at 2 urban university hospitals over 5 years in whom an emergency department admission ECG was performed. Exclusion criteria were alternate diagnoses, anaphylaxis, chronic drug toxicity, and missing outcome data. ACVE was defined as any of the following: circulatory shock, myocardial injury, ventricular dysrhythmia, or cardiac arrest. Blinded cardiologists interpreted ECGs for previously derived predictors of ACVE (ectopy, QT prolongation, nonsinus rhythm, ischemia/infarction), QT dispersion, and prominent R wave in lead AVR. Of 589 patients who met inclusion criteria (48% male, mean age 42), there were 95 ACVEs (39 shock, 64 myocardial injury, 26 dysrhythmia, 16 cardiac arrest). The most common drug exposures were as follows: benzodiazepines, opioids, and acetaminophen. Previously derived criteria were highly predictive of ACVE, with QT correction >500 ms as the highest risk feature (OR 11.2, CI 4.6–27).

**Conclusions**—This study confirms that early ECG evaluation is essential to assess the cardiovascular prognosis and medical clearance of emergency department patients with acute drug overdose. Furthermore, this study validates previously derived high-risk features of the admission ECG to risk stratify for ACVE in this patient population. *(J Am Heart Assoc. 2017;6:e004320. DOI: 10.1161/JAHA.116.004320.)*

**Key Words:** cardiovascular events • electrocardiogram • overdose • poisoning

With nearly 100 deaths per day since 2007, the United States is currently experiencing its worst drug overdose epidemic of all time.¹ The death rate of 11.8 per 100 000-persons in 2007 was roughly 3 times the rate in 1991.² Ten to 15% of emergency department (ED) patients with acute drug overdose suffer adverse cardiovascular events (ACVE), but prediction is difficult.³ In order to curtail the rise in drug overdose mortality,¹,²,⁴ clinicians must be equipped with valid clinical predictive tools to accurately identify those at risk for morbidity/mortality from the cardiovascular consequences of drug abuse.

In addition to consultation with a regional poison control center or on-site medical toxicologist, routine ED evaluation may include an ECG. We have previously identified characteristics of the initial ECG (ectopy, QT prolongation, nonsinus rhythm, ischemia/infarction) that were associated with ACVE in patients with acute drug overdose.⁵ However, the prognostic utility of the ECG for heterogeneous drug overdose patients has not been definitively established.⁶

Therefore, in this study, we aimed to validate previously derived features of the initial ECG associated with ACVE in this population. Additionally, we aimed to calculate the diagnostic test characteristics of specific ECG factors for prediction of ACVE in ED patients with acute drug overdose. We hypothesized the following: (1) high-risk ECG factors will successfully predict ACVE in ED drug overdose patients; (2) test characteristics of the rule will achieve >90% sensitivity.
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and specificity; and (3) QT correction (QTc) prolongation will afford highest predictive value.

Methods

Study Design and Setting

We performed a secondary data analysis of a prospective cohort study that was previously described.3,7 The study was conducted at 2 urban, tertiary care adult ED over a 4-year period from 2008 to 2012. The EDs have a combined annual visit volume in excess of 150,000 and are staffed 24 hours per day with board-certified emergency physicians. A medical toxicology consulting service was available if deemed necessary in addition to routine clinical care. The study protocol was approved by the institutional program for the protection of human subjects with waiver of informed consent.

Study Population

Consecutive, adult ED patients with suspected acute drug overdose were screened 24 hours per day by trained research assistants. Excluded were patients with alternate diagnoses (eg, trauma, sepsis, anaphylaxis), age <18 years, chronic presentations, nondrug toxicity (eg, plants), duplicate ED visits, do-not-resuscitate orders, exposure limited to topical or inhalation, prisoners, and missing/incomplete data (ie, left against medical advice, transferred to an outside institution, or otherwise eloped from the hospital). Eligible patients were included in this analysis if there was performance of an initial ECG within the first hour of ED arrival.

Data Collection

Data collection from the medical chart occurred in accordance with accepted guidelines for valid medical chart abstraction, including training of abstractors and 95% agreement of a random sampling of 10 test charts prior to mass data abstraction.8 Medical record data were relied upon for all data measurements, including study outcomes. These data included demographics (sex, age, race), exposure information (timing of exposure, number of exposures, intent, suicidality), toxin identification (detail from history of present illness, serum drug concentrations if available), prior cardiovascular medical history (hypertension, diabetes, coronary artery disease or congestive heart failure), and toxicology screens (urine ELISA panel and serum concentration, if any). Blood and urine toxicology screen results sent as routine part of clinical care (ie, no confirmatory gas chromatography/mass spectrometry) were recorded in order to confirm exposure. Data were abstracted to a de-identified electronic database with password protection.

Study Outcomes

We used the previously derived definition of ACVE as the primary study outcome, which is outlined in Table 1. For myocardial injury assessment, subjects without a laboratory evaluation of troponin I were assumed to be negative. For ventricular dysrhythmia assessment, rhythm strips in the charts of inpatients receiving telemetry monitoring were reviewed to evaluate any alarmed segments. As an exploratory analysis, we evaluated ECG evidence of ischemia/infarction using myocardial injury alone as a secondary outcome.

ECG Interpretation

ECGs were performed as clinically indicated according to the standard of care, as previously described.5 ECGs were interpreted by 2 blinded cardiologists (who were unaware of the diagnosis or whether an ACVE occurred) using de-identified copies of the initial ECG, and using a standard ECG interpretation form, were evaluated for the initial rhythm, intervals, QRS duration, evidence of ischemia/infarction, and QT dispersion (QTD). ECG evidence of ischemia was defined as either T wave inversion or ST depression. ECG evidence of infarction was defined as either ST elevation or Q waves. In addition, the presence of any R wave ≥3 mm in lead AVR (RavR) was documented, as previously described.9

QT Correction

Based on prior experience,5 the computer-generated corrected QT interval (Bazett’s corrected QTc, QT/RR1/2) was used because it was exceedingly rare that manual measurements ever substantially changed the QTc value. “QTc prolongation” was defined using standard criteria as QTc ≥470 ms regardless of sex.10 Additionally, a “severe QTc” cutoff of ≥500 ms regardless of sex was evaluated based on prior data suggesting utility of this cut point to predict adverse cardiovascular outcomes.

Table 1. Definition of the Primary Study Outcome, ACVE

| Outcome                  | Definition                                      | N*   |
|--------------------------|-------------------------------------------------|------|
| Myocardial injury        | Elevation in cardiac troponin I (≥0.09 ng/mL)   | 64   |
| Shock                    | Hypotension or hypoperfusion requiring use of a vasopressor | 39   |
| Ventricular dysrhythmia  | Ventricular tachycardia/fibrillation or torsade de pointes | 26   |
| Cardiac arrest           | Loss of pulses requiring CPR                    | 16   |

ACVE indicates adverse cardiovascular events; CPR, cardiopulmonary resuscitation; N, number of patients with individual outcome occurrence in this study.

*Some patients had more than 1 single outcome.
QT Dispersion

For the purposes of QTD calculation, QT interval was measured from the beginning of the QRS complex to the end of the T wave (defined as the return to T-P baseline using the threshold method). When U waves were present, the QT interval was measured as the nadir of the curve between T and U waves. QTD was defined as the difference between the longest and the shortest manual raw QT measurement on a 12-lead ECG according to the optimal technique described by Malik and colleagues. To ensure validity of QTD measurements, a random sampling of a subset of ECGs underwent independent interpretation by a second cardiologist; interrater reliability for the QTD cut point (QTD ≥ 35 ms) was assessed on 10 randomly chosen ECGs by 2 independent cardiologists with perfect agreement (k=1.0).

Statistical Analysis

Diagnostic test characteristics (ie, sensitivity, specificity) were calculated for previously derived ECG factors (ectopy, QT prolongation, nonsinus rhythm, and ischemia/infarction). ECG factors were evaluated for prediction of ACVE with χ², t test, odds ratios (OR), and 95% CI. OR of ACVE for dichotomized ECG measures were estimated as measures of effect, and adjusted OR for ECG variables were calculated using multivariable logistic regression adjusting for hypertension, diabetes, and prior coronary disease.

Receiver operating characteristics curves were plotted for QTc and QTD measurements, with optimal cut points chosen that maximized the sum of sensitivity plus specificity. In addition, because ECG evidence of ischemia/infarction may be felt to have a different interpretation in the setting of drug overdose (ie, different clinical picture than patients with chest pain), we assessed whether ECG evidence of ischemia/infarction could predict overdose-related adverse events (ACVE, as well as myocardial injury alone, as defined in Table 1).

In order to determine the number of ECGs needed for cardiologist analysis, the study sample size was calculated a priori. We assumed 10% prevalence of ECG predictor variables, as well as baseline 8% ACVE rate in the population based on prior literature. A clinically meaningful increase in risk was deemed to be a 3-fold increase in odds of ACVE for a given ECG factor. Using these assumptions, we calculated the need to enroll 552 patients with 80% power and 5% alpha.

Results

Patient Characteristics

Out of 2378 patients screened during the study period, 1796 were eligible and 589 were included for analysis; complete study enrollment with inclusion/exclusion criteria are summarized in Figure 1. Compared to those missing an ECG (N=1207), included patients were of similar age (mean age difference 2.6 years), similar sex (48% versus 54% males), and had similar prevalence of coronary artery disease (9% versus 4%), congestive heart failure (5% versus 2%), diabetes (15% versus 13%), and hypertension (28% versus 24%). Of all patients who met inclusion criteria, 48% were male, and the mean age was 42 years. All patients had confirmation of drug exposure either by self-report or serum/urine toxicology. Baseline clinical characteristics of included patients are summarized in Table 2. The most common drug exposures were the following drug classes: benzodiazepines, opioids, and acetaminophen.

ECG Characteristics of Entire Cohort

Mean heart rate was 87 beats/minute, mean QRS was 90.6 ms, and mean QTc was 439.9 ms. Sinus rhythm was observed in 557 patients (including 117 sinus tachycardia, and 31 sinus bradycardia), 18 atrial fibrillation/flutter, 4 atrioventricular block, 1 supraventricular tachycardia, 1 junctional, and 8 other/unknown. There were 23 patients with ectopy visible on the ECG, and 82 patients with positive Ravr. Interpretation of ischemia/infarction identified 72 patients with evidence of ischemia (55 T-wave inversion, 23 ST depression), and 60 with evidence of infarction (18 ST elevation, 43 Q waves). Regional distributions of ischemia/infarction were as follows: 30 anterior, 41 inferior, 49 lateral, 2378 Screened
582 Excluded
236 age <18 years
186 lacked outcome data
99 had an alternate diagnosis
27 topical/inhaled exposure
23 prisoners
7 duplicate ED visits
2 non-drug overdose
1 chronic poisoning
1 do not resuscitate
1796 Eligible
1207 lacked an ECG within 1 hour of ED arrival
589 Included

Figure 1. Study enrollment table. ED indicates emergency department.
Table 2. Baseline Clinical Characteristics

| Clinical Characteristic         | ACVE (N=95) | No Events (N=494) |
|--------------------------------|-------------|------------------|
| Age, y*                        | 53.1        | 40.4             |
| Female                         | 45          | 49               |
| Past cardiovascular history    |             |                  |
| Hypertension†                  | 57          | 27               |
| Diabetes                       | 27          | 17               |
| Coronary artery disease†       | 27          | 6                |
| Congestive heart failure†      | 18          | 1.5              |
| ECG intervals                  |             |                  |
| Heart rate, bpm†               | 109         | 86               |
| QRS, ms†                       | 111         | 90               |
| QTc, ms*                       | 457         | 437              |

ACVE indicates adverse cardiovascular events; bpm, beats per minute; N, number of patients; QTc, corrected QT interval.

*P<0.001.
†P<0.05.

There were 95 patients who suffered the primary study outcome (ie, ACVE), with numbers of occurrences of each individual outcome (shock, myocardial injury, ventricular dysrhythmia, and cardiac arrest) listed in Table 1. Some patients had more than 1 individual outcome.

Main Results

ECG variables and associations with ACVE are summarized in Table 3. All previously derived criteria (ectopy, QTc ≥470 ms, nonsinus rhythm, any ischemia/infarction) were highly predictive of ACVE. Test characteristics of 2 rules were calculated: (1) those of the previously derived version (ectopy, QTc ≥470 ms, nonsinus rhythm, and any ischemia/infarction); and (2) new revised criteria utilizing the 4 highest risk factors from this validation study (ectopy, QTc ≥500 ms, nonsinus rhythm, and any ischemia). The revised criteria substantially improve upon specificity (up by 18.2%) and positive predictive value (up by 16.2%), without sacrificing sensitivity or negative predictive value. The comparison of diagnostic characteristics for the derivation cohort as well as the validation cohort, with original/revised criteria, is summarized in Table 4.

Results of the QT interval analysis are illustrated in Figure 2. Mean QTc was significantly higher in the ACVE group compared with those without events (mean difference +20.0 ms, P=0.0004). The optimal QTc cut point based on receiver operating characteristics analysis was QTc ≥500 ms, which conferred over 11-fold higher odds of ACVE (OR 11.2, CI 4.6–27). Mean QTD was significantly higher in the ACVE group compared with those without events (mean difference +13.8 ms, P=0.00018). The optimal QTD cut point based on receiver operating characteristics analysis was QTD ≥35 ms, which conferred over 3-fold higher odds of ACVE (OR 3.1, CI 2.0–5.0).

Finally, we assessed whether ECG evidence of ischemia/infarction was associated with drug overdose–induced myocardial injury. The results of this analysis are summarized in Table 5. ST elevation had the highest specificity (97.7%), followed by ST depression (97.3%). Any nonsinus rhythm was highly predictive of myocardial injury (OR 11.0, P<0.01). Severe QTc prolongation (>500 ms, OR 5.3, P<0.001) as well as severe QTD prolongation (>50 ms, OR 2.5, P<0.01) were both highly associated with myocardial injury.

Discussion

This study validates the utility of the ECG for the initial approach to ED patients with acute drug overdose. We found
that previously derived ECG factors, including QT prolongation, rhythm, and presence of ischemia/infarction, were highly predictive of in-hospital ACVE. The test characteristics (eg, sensitivity) of the ECG factors alone were not sufficient enough to exclude the likelihood of ACVE; however, the ECG was highly specific for both myocardial injury and ACVE, with many factors reaching specificity >90%. Therefore, future study should evaluate combining highly sensitive methods (eg, clinical risk scores)\(^7\) with the highly specific tools described within this study.

Many recommendations for the emergency cardiovascular care of poisoned patients are based on expert consensus, rather than scientific evidence.\(^{14}\) Additionally, because standard guidelines for emergency cardiovascular care may not be optimal for the management of acute poisoning and overdose, urgent consultation with a medical toxicologist or regional poison control center is recommended for patients with cardiovascular toxicity by the American Heart Association, the American Academy of Clinical Toxicology, and the American College of Emergency Physicians.\(^{15}\) Previously, we defined

### Table 4. Test Characteristics of the ECG Factors as a Prediction Rule for ACVE

|                      | Sensitivity (CI) | Specificity (CI) | PPV (CI) | NPV (CI) | OR (CI) |
|----------------------|------------------|------------------|----------|----------|---------|
| Derivation cohort*   | 94.1% (80–99)    | 49.5% (39–60)    | 96.2% (87–100) | 38.6% (28–50) | 1.6 (1.3–1.9) |
| Validation cohort    | 68.4% (58–78)    | 68.6% (64–73)    | 91.9% (87–94) | 29.6% (24–36) | 4.7 (2.9–7.6) |
| Original criteria*   | 68.4% (58–78)    | 68.6% (64–73)    | 91.9% (87–94) | 29.6% (24–36) | 4.7 (2.9–7.6) |
| Revised criteria†    | 57.9% (47–68)    | 86.8% (84–90)    | 91.5% (89–94) | 45.8% (37–55) | 4.4 (3.3–5.9) |

ACVE indicates adverse cardiovascular events; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; QTc, corrected QT interval.

*Presence of at least 1 of the following: (1) ectopy; (2) QTc ≥470 ms; (3) nonsinus rhythm; (4) ischemia/infarction.
†Presence of at least 1 of the following: (1) ectopy; (2) QTc ≥500 ms; (3) nonsinus rhythm; (4) ischemia.

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**Figure 2.** ROC analysis of QT interval methods for prediction of ACVE. Boxplots for QTD (A) and QTc (B) demonstrate the median (central line), IQR (boxes), range (upper/lower lines), and outliers (circles/asterisks). ROC curves for QTD (C, blue line) and QTc (D, red line) demonstrate the optimal cut points and c statistic (area under the curve). ACVE indicates adverse cardiovascular events; c, area under the curve; QTc, corrected QT interval; QTD, QT dispersion; ROC, receiver operating characteristics.
Table 5. Prediction of Myocardial Injury Using ECG Evidence of Ischemia/Infarction

| ECG Finding                | OR (CI)   | Sensitivity | Specificity |
|----------------------------|-----------|-------------|-------------|
| Ischemia findings          |           |             |             |
| ST depression *            | 6.0 (2.5–14.4) | 14.1         | 97.3        |
| T wave inversion *         | 4.6 (2.4–8.8)   | 26.6         | 92.8        |
| Any Ischemia *             | 6.0 (3.3–10.7)  | 37.5         | 90.9        |
| Infarction findings        |           |             |             |
| ST elevation †             | 4.4 (1.6–12.2)  | 9.4          | 97.7 ‡      |
| Q waves †                  | 2.8 (1.3–5.9)   | 15.6         | 93.7        |
| Any infarction *           | 3.3 (1.7–6.3)   | 23.4         | 91.4        |
| Combined findings          |           |             |             |
| Any ischemia/infarct *     | 5.1 (3.0–8.8)   | 51.4 §       | 82.8        |

Myocardial injury is defined in Table 1. OR indicates odds ratios.
*P<0.001.
†P<0.01.
‡Highest specificity.
§Highest sensitivity.

in-hospital ACVE as a complication of drug overdose consisting of any of the following: myocardial injury, shock, dysrhythmias, and cardiac arrest. We also previously identified characteristics of the initial ECG (ectopy, QTc ≥470 ms, nonsinus rhythm, ischemia/infarction) that were associated with ACVE in patients with acute drug overdose. This study adds to this body of literature by confirming and revising these criteria to include the presence of at least 1 of the following: ectopy; QTc ≥500 ms, nonsinus rhythm, or ischemia.

Drug toxicity may cause myocardial injury through a variety of mechanisms. Myocardial injury is the most common ACVE that occurs because of drug overdose. Serum cardiac troponin I is a useful biomarker for drug toxicity. According to guidelines from the American Heart Association, the approach to patients with symptoms of drug-induced myocardial injury should differ in both diagnostic and therapeutic management. However, such guidelines currently rely upon expert consensus on the role of the ECG and cardiac biomarkers because of a previous lack of evidence-based tools to risk-stratify and guide management. This study therefore verifies and improves upon these guidelines to optimize the prediction of adverse events in this patient population.

ECG evidence of ischemia or infarction was highly specific for drug-induced myocardial injury. An implication of this study is that early drug cardiotoxicity can be detected by screening for ischemia and infarction, in addition to rhythm and intervals. The strongest predictor of cardiac arrest was ST depression, which conferred over 6-fold increased odds. Unfortunately, the sample size of the present study did not allow for subgroup analysis of ECG findings for individual or specific drugs; therefore, external validation of these findings is warranted. The combination of the ECG findings coupled with real-time clinical judgment may provide the basis for future implementation studies of these findings. On the basis of these results, we believe that detection of high-risk ECG factors (eg, QTc prolongation, ischemia/infarction) should mandate evaluation of a serum cardiac troponin as part of the initial ED evaluation of acute drug overdose.

Previously, use of QRS prolongation and Ravl had been utilized to risk-stratify for seizures and dysrhythmia limited only to patients with tricyclic antidepressant poisoning. Because the present study utilized a patient population with a low (<5%) rate of tricyclic antidepressant use, and different composite study outcome (ie, ACVE), it is not surprising that QRS parameters performed differently in this study. Similar to our prior derivation study, Ravl was not associated with ACVE in our population. However, this validation study was able to detect an association between the QRS interval and ACVE (Table 2). It should be noted that QTc vastly outperformed QRS for prediction of the study outcome. Therefore, QTc should be used preferentially over QRS for the ACVE risk stratification of acute overdose patients. However, these data should in no way dissuade practitioners from the traditional application of QRS cut points and Ravl to risk-stratify patients with known tricyclic toxicity.

In patients with cardiac disease, QTD predicts myocardial injury, sudden cardiac death, and adverse cardiac events in patients with Long QT Syndrome. Malik and colleagues previously defined normal QTD values between 10 and 70 ms, with abnormal QTD >100 ms. However, QTD was previously evaluated in the drug overdose literature, finding a strong association with ACVE using a cutoff >50 ms. The current study therefore used the latter definition of severely prolonged QTD, and these results confirm those of the prior derivation study. However, we found that QTc outperformed QTD for ACVE prediction, both using receiver operating characteristics analysis as well as diagnostic test characteristics (eg, sensitivity, specificity). Therefore, given the superiority and ease of use of the QTc, we do not recommend routine calculation of the QTD for patients with acute drug overdose. Further studies evaluating QTD for acute drug poisoning do not appear to be warranted.

In order to calculate the QTD, we measured the raw QT using the threshold method (ie, the intersection point of the descending T-wave and the isoelectric line), as opposed to the tangent method (ie, the intersection of the isoelectric line and a tangent line, fitted by least squares, over the descending slope of the T-wave). Some data exist indicating there is higher reproducibility of the threshold method over the tangent method. To the best of our knowledge, there is no universally accepted standard for QT measurement in the
context of calculating QTd; we have therefore used the threshold method based on prior work from our group, and from others.26,27

Limitations
Because of regional differences in drugs of abuse, the ACVE rates in other settings may not be similar to those found in this study. Real-time cardiologist interpretation of ischemia or infarction in clinical practice may not be possible in the majority of settings; however, emergency physicians are generally proficient at interpreting ECGs for ischemia/infarction,18 and furthermore the best predictor (i.e., QTc ≥500 ms) was computer generated. This study used computer-generated Bazett’s formula for QT correction, rather than more accurate manual measurement with linear correction formulae24,25,28,29 to enhance this study’s generalizability given that Bazett’s is still the most widely used QTc formula. We acknowledge that this may have slightly limited the accuracy of the QTc data; however, we anticipate that this may have improved the real-world applicability of our results. It is difficult to assign causality for ACVE to a single drug, especially in multidrug exposures; therefore, this underscores the utility of objective ECG findings, rather than reliance on drug concentrations, as part of the initial risk stratification to predict ACVE in patients with acute drug overdose. In addition, the estimates of effect, such as the OR, were not very precise with 95% CIs ranging from 4 to 27.

Conclusions
This study confirms that the ECG is an essential tool for evaluation of the cardiovascular prognosis and medical clearance of all ED patients with acute drug overdose. Furthermore, this study validates previously derived high-risk features of the admission ECG (ectopy, QTc prolongation, nonsinus rhythm, and ischemia/infarction) to risk stratify for ACVE in this patient population.

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Disclosures
None.
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