until the end of the T wave where the trace returned to baseline. The QT was measured in at least six leads, including chest and limb leads, and the median QT interval taken. The RR interval was measured from identical points in one complex to the next for at least six complexes in lead II, and the median taken. QT and RR measurements were derived from QTc and HR if these were the only information provided in the report.

Controls were taken from a previous study of ECGs taken in patients following an overdose of a drug regarded as non-cardiotoxic: paracetamol, diazepam, oxazepam or temazepam.9 There were 318 patients, 215 females and 103 males with a median age of 34 years (interquartile range 23–45 years). The full dataset with QT and RR values was available to the authors.

The QT nomogram was developed based on a rearrangement of the Fossa ‘cloud’ diagram (from Figure 1 of reference 7). The Fossa ‘cloud’ diagram was scanned and data relating to the ‘at risk’ line were digitally extracted into a finite range of points and then converted into a QT vs. HR curve. A polynomial was then fitted through the points of the QT–HR data to provide a smoothed line (Figure 1). The polynomial was replaced by a horizontal straight line for HR values <60 bpm, as per the Fossa diagram. For values of HR >105 bpm (RR 570 ms), the equation was used to extrapolate the at-risk line, as the original diagram did not provide an at-risk region above these values.

In this region, the polynomial only minimally diverged from a straight line, with evidence of a weak convex relationship. The extrapolation provided a continuous framework of assessment of risk for HR values between 30 and 160 bpm. A similar nomogram without the extrapolation has been previously published with QT and HR.10 QT–HR pairs corresponding to each case and control were plotted on the QT nomogram. In addition, two curves corresponding to Bazett’s correction factor at QTc values of 440 ms and 500 ms were also plotted. These values have been equated to medium and high risk values, respectively.11

In addition to visual analysis, sensitivity and specificity analyses were performed.12 Analyses were performed by tallying the number of cases above the predictive line and dividing this by the total number of cases (sensitivity) and by tallying the number of controls below the predicted line and dividing this by the total number of controls (specificity). Ninety-five percent confidence intervals (95%CIs) were calculated using a normal approximation.12

Results

The literature review identified 1838 articles. After initial screening, 329 articles were obtained in full. One hundred and thirty cases of drug-induced TdP met the inclusion criteria. Reasons for exclusion included: non-human study, no specific case data, i.e. review article or comment, insufficient evidence that a drug was implicated, insufficient ECG measurement data, i.e. only QTc available so the QT and HR could not be calculated, ECG not recorded within a reasonable time frame, or evidence of abnormal baseline ECG, e.g. presence of long QT syndrome.

Table 2 provides a list of the most common drugs found in the cases of drug-induced TdP. However, this study did not aim to establish causation for particular drugs, because in most cases patients were taking multiple medications. The median age of the patients was 53 years (interquartile range 36–68 years; range 10–95 years).

The QT–HR pairs of the TdP cases were plotted and compared to the QT nomogram based on Fossa, and the at-risk lines defined by Bazett’s formula (Figure 2, a and b). The TdP cases occurred primarily at lower HR values with longer QT intervals, with most cases occurring at HR 30–90 bpm. The controls were more evenly distributed, with HR from 40 to 160 bpm. On visual inspection, it was clear that the QT–HR pairs for TdP...