Reassessing the Role of QT_c in the Diagnosis of Autonomic Failure Among Patients With Diabetes

A meta-analysis

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OBJECTIVE — A 1992 consensus statement on autonomic testing portrayed Bazett's heart rate–corrected QT interval (QT_c) prolongation as a specific yet insensitive indicator of diabetic autonomic failure. At that time, only a few small studies had evaluated the accuracy of QT_c. To date, even fewer studies have evaluated whether its accuracy is influenced by patient characteristics.

RESEARCH DESIGN AND METHODS — We critically appraised 17 studies reporting the sensitivity and specificity of QT_c for diabetic autonomic failure. The studies represented 4,584 patients with diabetes (mean age 34.9 years, 46% female, 92% with type 1 diabetes, mean duration of diabetes 14.5 years). We summarized the accuracy of QT_c prolongation for diabetic autonomic failure as an odds ratio (OR) (95% CI) and determined whether patient and study design characteristics influenced the accuracy of QT_c prolongation by comparing summary receiver operating characteristic curves.

RESULTS — Autonomic failure, defined as $\geq 1.2 \pm 0.4$ (mean ± SD) abnormal of 2.0 ± 1.6 administered cardiovascular reflex tests, was found in 26% (25–28) of patients. The pooled sensitivity and specificity of $QT_c > 441 \pm 8$ ms for autonomic failure were 28% (26–29) and 86% (85–87), respectively. Autonomic failure was 2.26 times (1.90–2.70) more likely to be present in patients with than in patients without QT_c prolongation. At 86% specificity, the sensitivity of QT_c prolongation was 46 vs. 12% for men versus women ($P = 0.0077$), respectively, and, after adjustment for sex, 66 vs. 17% among patients aged 25 vs. 55 years ($P = 0.1902$) and 61 vs. 27% at thresholds of >420 vs. >460 ms, respectively ($P = 0.2964$).

CONCLUSIONS — QT_c prolongation is a specific albeit insensitive indicator of autonomic failure. Although QT_c prolongation is relatively accurate for men, accuracy may be even greater for young men at low QT_c thresholds.

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Consensus statements released by the American Diabetes Association and the American Academy of Neurology indicate that testing for prolongation of Bazett's heart rate–corrected QT interval (QT_c) (1,2) is easy and specific for diabetic autonomic failure (3,4). The reported validity and reproducibility of QT_c support this practice. Indeed, β-antagonists decrease QT_c, high-dose muscarinic antagonists like atropine increase QT_c (5–11), and the reliability of QT_c is higher than that of several cardiovascular reflex tests more commonly used to evaluate autonomic function (12,13). QT_c, however, is seldom used to evaluate autonomic status in the clinical or experimental setting because of its reported insensitivity for autonomic failure. Inattention to the influence of patient characteristics on test performance may contribute to the reported insensitivity of QT_c (11). We therefore conducted a meta-analysis to determine which characteristics of patients with diabetes are related to the accuracy of QT_c prolongation for autonomic failure. Our goal was to identify a subset of patients with diabetes in whom testing for QT_c prolongation effectively discriminates between presence and absence of autonomic failure as defined by cardiovascular reflex test abnormality.

RESEARCH DESIGN AND METHODS

We searched Medline and Current Contents (1966 through February 1999) by combining free text ("QT," "Q-T," "DIABET," and "AUTONOMIC") with truncation wildcards (*) to identify variant forms of key words. We linked "QT*" and "Q-T*" with the Boolean operator "OR" to maximize search sensitivity and then combined the resultant phrase with the remaining search terms with the Boolean operator "AND" to identify a list of articles for screening.

An expert in the diagnosis of diabetic autonomic failure screened the list for possible omissions. Members of the Departments of Medicine, Oral Surgery, and Slavic Languages and Literature at the University of Washington (Seattle, WA) and the University of Cluj (Cluj, Romania) translated non–English language articles identified in the search. One unblinded reader then determined which articles met four prospectively defined criteria for critical appraisal: *1*) a focus on human subjects with diabetes, *2*) the use of QT_c as a diagnostic test, *3*) the use of a cardiovascular reflex test as a "gold standard," and *4*) the presence of sufficient data for estimation of sensitivity and specificity.

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Abbreviations: OR, odds ratio; QT_c, Bazett's heart rate–corrected QT interval; SROC, summary receiver operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of study design and patients*

First author (ref.)	Year	*n*	Study design	Mean age (years)	Female (*n* [%])	Type 1 diabetes (*n* [%])	Mean duration of diabetes (years)
Kahn (21)	1987	30	*†‡§‖	33.0	20 (67)	30 (100)	17.0
Gonin (22)	1990	73	‡§‖	41.9	38 (52)	46 (63)	15.1
Jermendy (23)	1990	41	‡§‖	57.3	13 (32)	0 (0)	11.4
Ewing (24)	1990	75	†	43.9	0 (0)	—	—
Chambers (25)	1990	34	†‡§	51.1	22 (65)	34 (100)	36.3
Wierusz-Wysocka (26)	1992	58	—	41.6	30 (52)	27 (47)	12.7
Erbas (27)	1992	20	‡§	30.0	5 (25)	15 (75)	8.7
Lo (28)	1993	44	*‡§‖	26.0	20 (45)	44 (100)	14.0
Sivieri (29)	1993	374	*†	32.1	183 (49)	374 (100)	15.5
Yokoyama (30)	1993	58	*†‡‖	50.0	0 (0)	—	4.0
Veglio (31)	1995	168	*†‡§‖	54.9	57 (34)	38 (29)	9.0
Schnell (32)	1996	97	*‡§‖	35.0	58 (60)	97 (100)	18.0
Vardhan (33)	1996	50	*‡§‖	—	—	0 (0)	—
Grossmann (34)	1997	80	‡§‖	34.0	39 (49)	80 (100)	13.7
Tentolouris (35)	1997	105	*†‡§‖	43.3	39 (37)	53 (50)	10.1
Kempler (36)	1998	27	—	23.0	10 (37)	27 (100)	—
Veglio (37)	1999	3,250	*†	32.7	1,582 (49)	3,250 (100)	14.7
All studies¶	1987–1999	4,584	—	34.9	2,116 (46)	4,115 (92)	14.5

*Patient selection consecutive or random; †measurement of QT_c blinded to results of the gold standard; ‡no heart disease; §not using cardiovascular medications; ‖normal electrolytes; ¶mean (weighted for study size), *n*, and % exclude studies with unreported data.

We abstracted the publication year, sample size, patient selection strategy, patient inclusion criteria, number of abnormal and administered cardiovascular reflex tests used in establishing the diagnosis of autonomic failure, QT_c threshold (in milliseconds), basis for QT_c threshold selection, blinding of QT_c measurement, and the sensitivity and specificity of QT_c for autonomic failure from the articles that met all inclusion criteria. We also abstracted mean age, percentage of females, percentage with type 1 diabetes, and mean duration of disease when studies reported overall population characteristics. We calculated weighted means when studies only reported stratum-specific estimates of age and duration of diabetes.

Based on guidelines for meta-analyses evaluating diagnostic tests (14), we plotted sensitivity against 100 – specificity and then used SAS software (SAS Institute, Cary, NC) and a weighted summary receiver operating characteristic (SROC) model to fit a curve to the scatterplot (15–17). We determined whether differences in test accuracy were related to characteristics of patients and study design by adding pertinent variables to the SROC

Table 2—*Sensitivity and specificity of QT_c for autonomic failure*

First author (ref.)	Gold standard		Autonomic failure‡	QT_c threshold (ms)§	Sensitivity (%)	Specificity (%)
	Threshold*	Total†				
Kahn (21)	≥2	5	57	>440	71	100
Gonin (22)	≥2	4	47	>433	53	82
Jermendy (23)	≥1	3	66	>440	70	71
Ewing (24)	≥2	5	45	>453	15	88
Chambers (25)	≥2	5	79	>440	48	57
Wierusz-Wysocka (26)	≥2	3	47	>402	96	90
Erbas (27)	≥1	5	35	>427	29	85
Lo (28)	≥2	5	7	>441	33	93
Sivieri (29)	≥2	3	25	>460	18	90
Yokoyama (30)	1	1	67	>440	72	74
Veglio (31)	≥1	5	64	>440	15	89
Schnell (32)	≥2	5	30	>440	38	76
Vardhan (33)	≥0.5	4	62	>430	29	100
Grossmann (34)						
Men	≥2	6	24	>427	50	97
Women	≥2	6	26	>434	70	93
Tentolouris (35)	≥2	5	62	>440	6	95
Kempler (36)	≥1	5	26	>440	43	100
Veglio (37)						
Men	1	1	19	>440	21‖	91‖
Women	1	1	18	>440	22‖	80‖
All studies¶	≥1.2 ± 0.4	2.0 ± 1.6	26 (25–28)	>441 ± 8	28 (26–29)	86 (85–87)

*Number of abnormal and †number of administered cardiovascular reflex tests used to establish the diagnosis of autonomic failure; ‡prevalence; §based on convention (>440 ms), an observed upper limit of normal (>mean ± 1 or 2 SD), or a referenced QT_c cut point (>430 ms) (38); ‖adjusted for age and HbA_{1c}; ¶weighted mean ± SD or pooled percentage (95% CI).

model. For individual studies, we summarized test accuracy as the odds of autonomic failure in patients with versus patients without a prolonged QT_c expressed as odds ratios (ORs) (95% CIs) (18). We summarized test accuracy for the combination of studies as the Mantel-Haenszel OR (95% CI) after testing for homogeneity of ORs across studies (19,20).

RESULTS — The electronic search identified a list of 71 English language and 7 non–English language articles for screening. The complete list can be reviewed online at http://faculty.washington.edu/ewhitsel/qtc_meta_analysis.html. Seventeen (22%) of the 78 articles met criteria for critical appraisal and were abstracted (Table 1) (21–37). The abstracted articles were published between 1987 and 1999. With four notable exceptions, the studies were small in size ($n \leq 100$). Together, however, the abstracted articles represented 4,584 relatively young men and women predominantly diagnosed with type 1 diabetes of modest duration.

Of the 17 abstracted articles, 9 (53%) reported using consecutive or random selection of patients (Table 1). Patients had normal electrolytes, did not use cardiovascular medication, and had no heart disease in 10 (59%), 11 (65%), and 12 (71%) of the studies, respectively. Eight (47%) of the studies reported blinding measurement of QT_c to autonomic status. One (6%) of the abstracted studies selected a QT_c threshold based on a referenced QT_c cut point (>430 ms) (38), 7 (44%) selected a QT_c threshold based on an observed upper limit of normal (>mean ± 1 or 2 SD), and 9 (53%) selected a QT_c threshold based on convention (>440 ms).

Approximately one-fourth of the study population had autonomic failure, which was defined on average as ≥1.2 ± 0.4 (mean ± SD) abnormal out of 2.0 ± 1.6 administered cardiovascular reflex tests (Table 2). When examined separately, the pooled sensitivity of a QT_c >441 ± 8 ms for autonomic failure was low, and the pooled specificity was relatively high. Although the diagnostic accuracy of QT_c varied across studies (Fig. 1), a test of homogeneity was not significant (P = 0.2385). Combining ORs with the Mantel-Haenszel estimator demonstrated that autonomic failure was 2.26 times (1.90–2.70) more likely to be present in diabetic patients with than in patients without an abnormal QT_c.

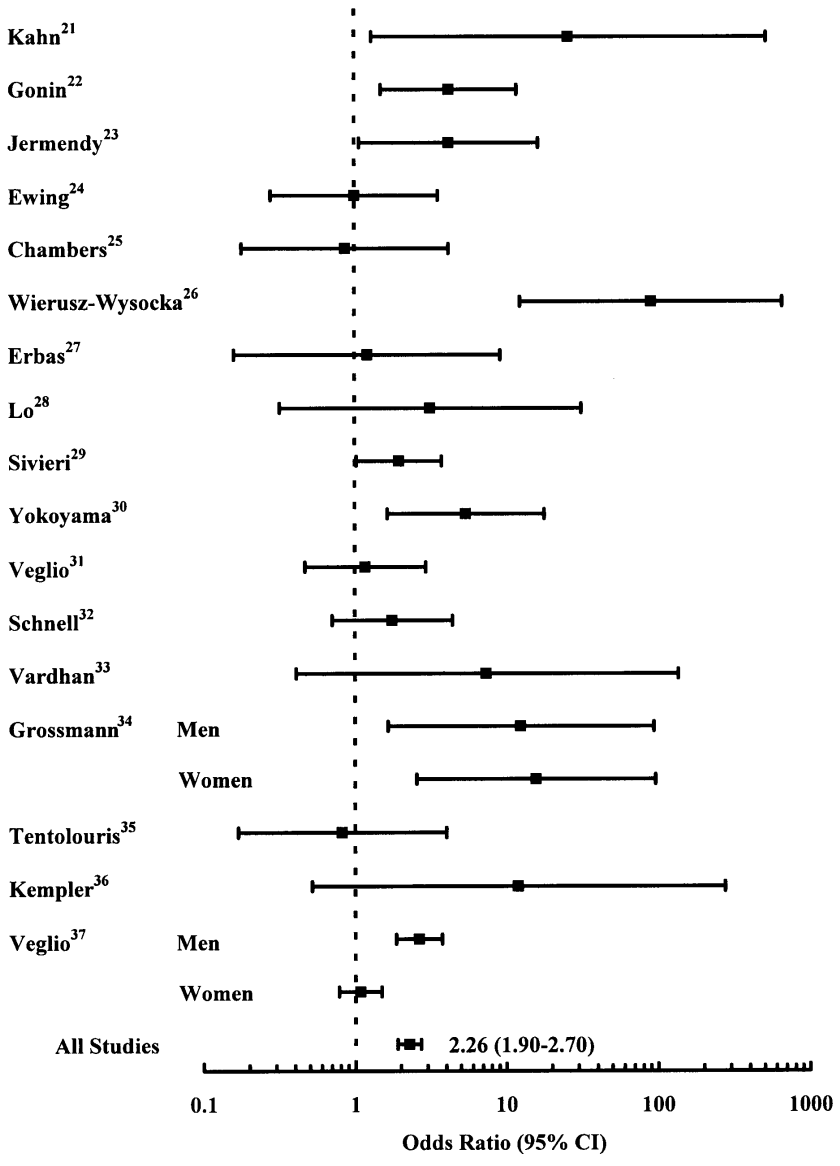

Figure 1—*Accuracy of QT_c for diabetic autonomic failure. Primary studies are referenced according to first author. Test accuracy is summarized as an OR (95% CI).* P = *0.2385 for the test of homogeneity across studies.*

Sensitivity and 100 – specificity (Table 2) were plotted, and SROC curves were fitted to the scatterplot (Fig. 2*A*). At the pooled specificity of 86%, the sensitivity estimated by a weighted SROC model was similar to that estimated by pooling. Addition of patient and study design characteristics to the weighted model demonstrated a strong association between sex and diagnostic accuracy (Fig. 2*B*). In fact, the sensitivity of QT_c for autonomic failure was 3.8 times greater in men than in women (P = 0.0077). After adjustment for sex, none of the remaining patient or study design characteristics was significantly associated with diagnostic accuracy (Table 3). However, diagnostic accuracy tended to be higher in young patients, particularly at lower unconventional QT_c thresholds. Conversely, accuracy tended to be lower among studies that consecutively sampled patients and blinded measurement of QT_c to the results of the gold standard. Although accuracy was inversely related to the prevalence of autonomic failure, it decreased only slightly with a concomitant increase in prevalence of 60%. Larger multivariate models could not estimate diagnostic accuracy with validity because of the limited number of primary studies identified by our literature review.

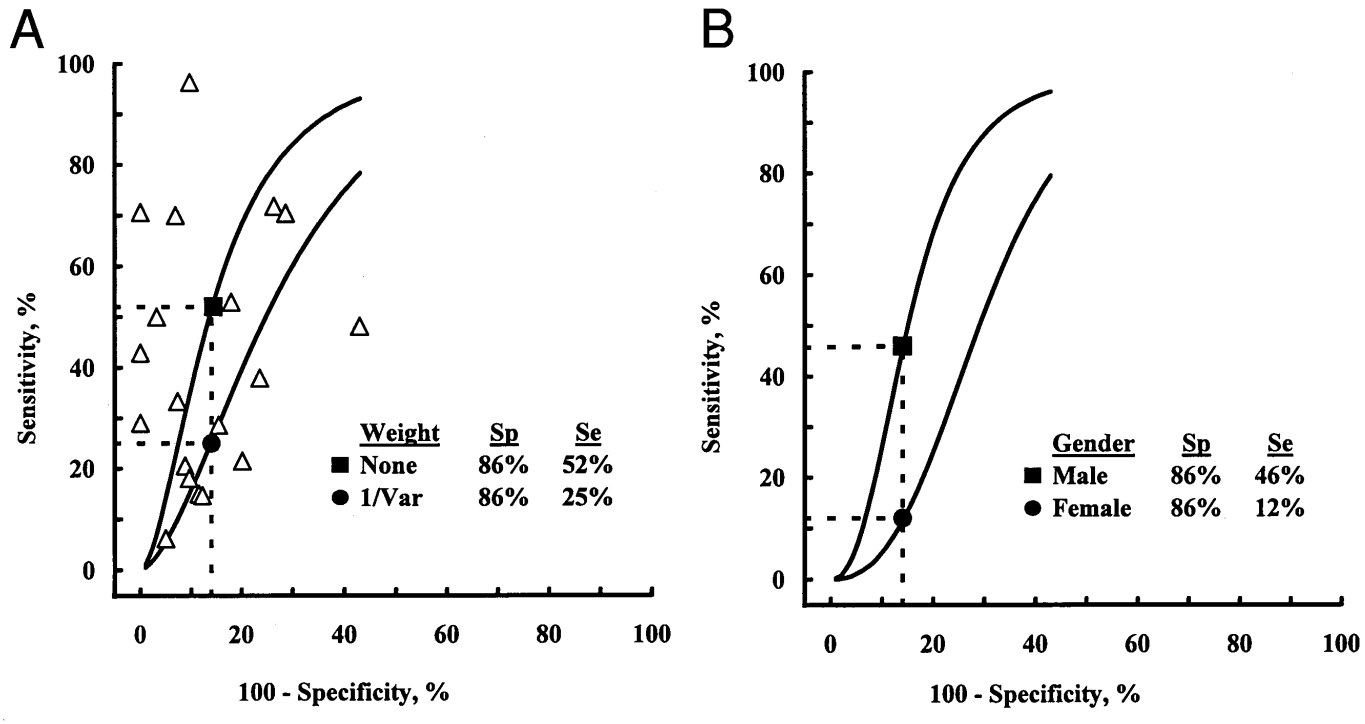

Figure 2—*Scatterplot of sensitivity versus 100 – specificity of QT_c for diabetic autonomic failure and the effects of study weight (*A*) and sex (*B*)on fitted SROC curves. Sensitivity was back-calculated within the observed range of specificity by using the intercept and regression coefficients derived from SROC models. Models were weighted except where indicated for the reciprocal of study-specific variance (1/Var). Sensitivity (Se) at the pooled specificity (Sp = 86%) was tabulated to facilitate group comparison. Sex was significantly associated (*P = 0.0077) with diagnostic accuracy, which is highest for curves in the upper left corners of the graphs. △, Data points; ——, fitted SROC curves.*

CONCLUSIONS — Based on guidelines for meta-analyses evaluating diagnostic tests (14), we attempted to determine which characteristics of patients with diabetes are related to the accuracy of QT_c prolongation for autonomic failure. We found that, in general, QT_c was a specific albeit insensitive marker for autonomic failure at a threshold for abnormality of >441 ± 8 ms. Despite its relative insensitivity, we also found that autonomic failure was 2.3 times more likely to be present in diabetic patients with than in those without a prolonged QT_c. More importantly, however, we found that the accuracy of QT_c for autonomic failure was related to several patient characteristics, including sex and age.

Correlates of QT prolongation like sex and age are well established (39). Among older adults, for example, women are three times more likely to have a prolonged QT interval after adjustment for other factors associated with QT prolongation. The sex difference, however, depends on age and is explained by a 20-ms fall in the QT_c in males after puberty (40). Because effects of sex and age on the ability of QT_c prolongation to identify autonomic dysfunction are comparatively obscure, we explored how sex, age, and other patient characteristics influenced the accuracy of QT_c for autonomic failure. We found that, at 86% specificity, the sensitivity of QT_c for autonomic failure was 3.8 times greater in men than in women and, after adjustment for sex, 3.9 times greater in individuals aged 25 years versus individuals aged 55 years. The findings suggest that measurement of QT_c is a more accurate test for autonomic failure in young men with diabetes. Although sensitivity and specificity of QT_c for autonomic failure may be relatively high in this demographic subset, our examination of the relationships between the remaining patient characteristics and the accuracy of QT_c suggests that accuracy may be even higher among young men at lower unconventional QT_c thresholds.

Estimates of diagnostic accuracy can be influenced by the validity of study design. For example, estimates may be biased if the diagnostic test requires judgment and that judgment is made by an investigator who has knowledge of the results of the gold standard. Estimates also may be biased when a cumbersome gold standard reduces the likelihood of gold standard evaluation in patients with a negative diagnostic test (41). Because manual measurement of QT_c requires judgment, blinding individuals involved in its measurement to results of cardiovascular reflex testing ensures the independence of observations. Moreover, consecutively or randomly sampling patients avoids the potential for biased verification of QT_c testing. Incomplete reporting of QT_c measurement and patient selection strategies prevented us from excluding studies based on failure to blind measurement of QT_c or failure to sample patients consecutively. Alternatively, we explored how the reported presence of these design features influenced the accuracy of QT_c for autonomic failure. We found that the sensitivity of QT_c for autonomic failure at 86% specificity was 1.8 times lower when measurement of QT_c was blinded to the results of cardiovascular reflex testing and 1.5 times lower in studies reporting consecutive or random patient selection. Our findings suggest that the diagnostic accuracy of QT_c for autonomic failure varies inversely with study validity.

In theory, sensitivity and specificity are independent of prevalence (pretest probability of disease), but in practice, they may not be (42). Because sensitivity varies with prevalence when the gold standard is imperfect (43), we explored how the prevalence of autonomic failure and other characteristics of the gold standard influenced the accuracy of QT_c for autonomic failure. We found that, at 86% specificity, sex-adjusted sensitivity varied slightly with prevalence of autonomic failure and noted that it decreased only 20% with a large increase in prevalence from 10 to 70%. Our finding suggests that the cardiovascular reflex tests used in the primary studies were an admittedly imperfect but nonetheless adequate gold standard assessment of autonomic function.

Because our findings are based on meta-analytic methods, they are prone to selection biases that may limit their generalizability. For example, this meta-analysis represented 4,584 patients with diabetes, but 71% of the patients originated in a single large study. Excluding this study nevertheless demonstrated that it had only a slight influence on our estimates. This meta-analysis also included smaller nonrandomized studies, two of which were published in non–English language journals, and one of which described a particularly strong relationship between QT_c and autonomic failure. Although small studies reporting strong relationships between QT_c and autonomic failure may have been more likely to be published, little empirical evidence has been accumulated to determine the practical importance of publication bias for meta-analyses of diagnostic tests (14). Moreover, use of an English language restriction increases the potential for selection bias (44,45). Accordingly, we did not assume that research quality varies by language of publication or that language restriction cannot alter the results of meta-analysis.

Despite their limitations, we believe that our findings have important implications for diagnosis of autonomic failure in experimental and clinical settings. Traditional teaching suggests that diagnostic tests with high specificity are best used for confirming illness among patients with a high pretest probability of disease (42). However, exclusive focus on the specificity of QT_c for autonomic failure may lead to incorrect conclusions about its diagnostic utility (46). For example, when specificity is held constant across sex and age, we recognize that QT_c rules out autonomic failure

Table 3—*Sensitivity* of QT_c for autonomic failure, by characteristics of patients and study design*

	Sensitivity (%)	*P*
Patient characteristic		
Age (years)†		
25	66	
35	48	
45	31	
55	17	0.1902
Diabetes type		
1	55	
2	48	0.8508
Diabetes duration (years)		
5	55	
20	41	
35	30	0.6431
Autonomic failure (%)‡		
10	56	
40	46	
70	36	0.5217
Heart disease		
No	46	
Unknown	45	0.9379
Electrolytes		
Normal	50	
Unknown	41	0.6217
Using medications§		
No	48	
Unknown	44	0.7803
Consecutively selected‖		
Yes	38	
Unknown	57	0.3322
Study design characteristic		
Publication year		
1987	51	
1993	47	
1999	42	0.7391
Sample size (*n*)		
100	49	
1,000	42	0.4620
QT_c threshold (ms)		
>420	61	
>440	43	
>460	27	0.2964
QT_c threshold type¶		
Conventional	40	
Other	63	0.1209
QT_c measurement		
Blinded#	35	
Unknown	62	0.1006
Gold standard threshold**		
≥1	40	
≥2	56	0.2545
Gold standard total††		
2	44	
4	49	
6	55	0.4504

*Adjusted for sex at 86% specificity; †age-adjusted estimates of sensitivity and specificity were excluded from the model; ‡prevalence; §cardiovascular medications; ‖randomly selected; ¶based on convention (>440 ms), an observed upper limit of normal (>mean ± 1 or 2 SD), or a referenced QT_c cut point (>430 ms) (38); #to results of the gold standard; **number of abnormal; ††number of administered cardiovascular reflex tests used to establish the diagnosis of autonomic failure.

best among diabetic patients in whom it is most sensitive (i.e., men and young people). Although tests with SROCs like those of QT_c are used in populationwide screening programs (47), we also recognize that the cautious use of QT_c in the diagnosis of autonomic failure is appropriate until well-controlled population-based studies confirm that testing for QT_c prolongation effectively discriminates between presence and absence of autonomic dysfunction. If and when they do, QT_c could be used with legitimacy to help diagnose subclinical autonomic dysfunction, stratify risk, and conceivably direct therapy. Therapies designed to prevent the adverse consequences of autonomic failure (48), including exercise training, β-antagonists, muscarinic agonists, and (paradoxically) low-dose muscarinic antagonists, are currently under evaluation.

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