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REVIEW

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The potential of electrocardiography for cardiac risk prediction in chronic and end-stage kidney disease

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ABSTRACT

Cardiovascular mortality is very high in chronic and end-stage kidney disease (ESKD). However, risk stratification data are lacking. Sudden cardiac deaths are among the most common cardiovascular causes of death in these populations. As a result, many studies have assessed the prognostic potential of various electrocardiographic parameters in the renal population. Recent data from studies of implantable loop recordings in haemodialysis patients from five different countries have shed light on a pre-eminent bradyarrhythmic risk of mortality. Importantly, heart block addressed by permanent pacing system was detected in a proportion of patients during the prolonged recording periods. Standard electrocardiogram is inexpensive, non-invasive and easily accessible. Hence, risk prediction models using this simple investigation tool could easily translate into clinical practice. We believe that electrocardiographic assessment is currently under-valued in renal populations. For this review, we identified studies from the preceding 10 years that assessed the use of conventional and novel electrocardiographic biomarkers as risk predictors in chronic and ESKD. The review indicates that conventional electrocardiographic markers are not reliable for risk stratification in the renal populations. Novel parameters have shown promising results in smaller studies, but further validation in larger populations is required.

Keywords: cardiovascular, CKD, ECG, ESRD

INTRODUCTION

Non-dialysis chronic kidney disease (CKD) is characterized by much higher cardiovascular mortality and morbidity when compared with the general population. This risk increases exponentially in end-stage kidney disease (ESKD) [1]. US Renal registry data indicate that sudden death and/or fatal arrhythmia is the documented cause of death in ∼26% of ESKD patients [2].

Although atherosclerotic disease is common in CKD and ESKD, evidence indicates that it accounts for only a small proportion of cardiovascular deaths in this population [3]. Furthermore, extrapolating evidence from the general population for cardiac risk modification has proven to be of limited benefit in dialysis patients. Statin therapy for primary prevention does not reduce cardiac risk in dialysis patients [4] and coronary revascularization [3], or use of implantable cardioverter defibrillators [5] based on the current guidelines (i.e. guidelines developed based on studies in cardiac patients), does not reduce arrhythmic mortality in CKD and ESKD patients. In the general population, most fatal arrhythmic events are triggered by underlying myocardial ischaemia, usually in the presence of coronary artery disease [6], and are frequently tachyarrhythmias although bradyarrhythmic sudden deaths also occur. In advanced CKD and ESKD, the mechanism, timeline and specific rhythm of such events are not fully understood. Non-conventional cardiovascular risk factors such as electrolyte imbalances, volume shifts and blood pressure changes have been implicated in extremely high sudden death rates after the long interdialytic interval of the typical three session of haemodialysis (HD) a week [7]. Recent studies of prolonged implantable loop recording in five different HD cohorts have suggested that bradyarrhythmic events may be more common than ventricular arrhythmia in causing sudden cardiac deaths (SCDs) [8]. Although the underlying mechanisms are far from clear, ∼10% of the patients in these cohorts were noted to have heart block or other bradyarrhythmia that could be treated with permanent pacing systems, and this itself should make the case for more frequent use of standard electrocardiogram (ECG) in dialysis populations. In recent years, data from experimental and population-based studies have led to advances in our understanding of the underlying cardiovascular disease mechanisms. This led to focussing on the dynamic interplay between myocardial structural changes, vascular changes, autonomic imbalance, inflammation, and fluid and electrolyte shifts that can lead to arrhythmias [9].

The presumed high burden of arrhythmic deaths in dialysis patients has led to a renewed interest in the evaluation of electrocardiographic parameters as potential risk predictors. The standard 12-lead ECG is an easily accessible and inexpensive bedside test. Moreover, the implementation of advanced software in most modern electrocardiographic machines means that vectorcardiographic indices can be derived with accuracy from standard 12-lead ECGs.

AIMS OF THE REVIEW

This review aims at providing an overview of studies that assessed the use of selected electrocardiographic and vectorcardiographic parameters taken from standard 12-lead and continuous Holter electrocardiography for the purpose of cardiac risk stratification in the CKD and ESKD populations.

REVIEW METHODOLOGY

Data sources and search strategy

MEDLINE through PubMed, Google Scholar and Cochrane Library were searched to identify potentially relevant articles and abstracts. Furthermore, we reviewed the bibliographies of the selected articles for additional relevant studies. The search terms are presented in Table 1.

Table 1. Keywords used as Boolean operators or search terms

Renal disease	Outcomes	Parameters
CKD	Survival	LVH
HD	Death	QTc
PD	Mortality	QT
Chronic kidney disease	Cardiovascular outcomes	PR
Renal disease	Cardiac outcomes	QRS–T angle
Haemodialysis		TCRT
Haemodialysis		HRV
Peritoneal dialysis		Left ventricular hypertrophy
Dialysis		Heart rate variability
		ECG
		Electrocardiogram
		Electrocardiographic

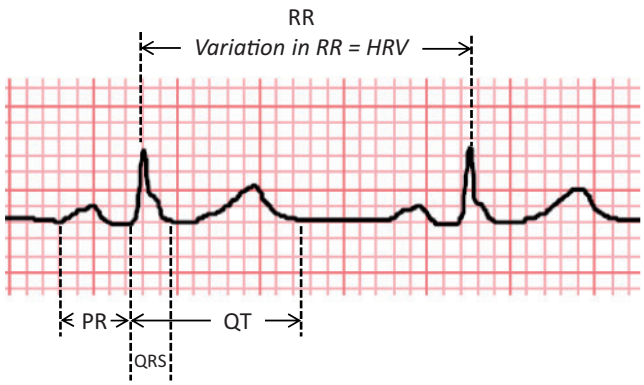

FIGURE 1: Schematic diagram of ECG (sinus rhythm).

Eligibility of studies

Studies in any of the CKD, HD and peritoneal dialysis (PD) populations were considered for inclusion if they met the following criteria: published between January 2007 and December 2016; investigated at least 50 participants in the initial cohort; had a mean follow-up time of at least 1 year; any external, non-invasive ECG methodology (standard 12-lead, Holter, etc.); assessed death and/or cardiac outcomes as an endpoint; studied the association of left ventricular hypertrophy (LVH), QTc interval, QRS complex, PR interval, QRS–T angle and/or heart rate variability (HRV) with these endpoints.

Figure 1 shows a schematic representation of the different components of a standard ECG in sinus rhythm. Figure 2 shows a representation of QRS–T angle from vectorcardiograms.

Cardiac outcomes included coronary events, arrhythmic events, cardiac failure or a combination of these. Death included all-cause mortality and, where available, sudden death as defined by the authors.

Studies are presented in two categories, one for dialysis and the other for CKD. Due to the paucity of studies including PD patients, studies in PD and HD are not listed separately.

ECG PROGNOSTIC INDICES

Electrocardiographic LVH

LVH is a common finding in advanced CKD and ESKD [10]. Up to 75% of patients have LVH upon initiation of maintenance dialysis [10], and increased echocardiographic left ventricular mass index (LVMI) is associated with adverse cardiovascular outcomes and SCD [11]. A summary of studies detailed below is found in Table 2.

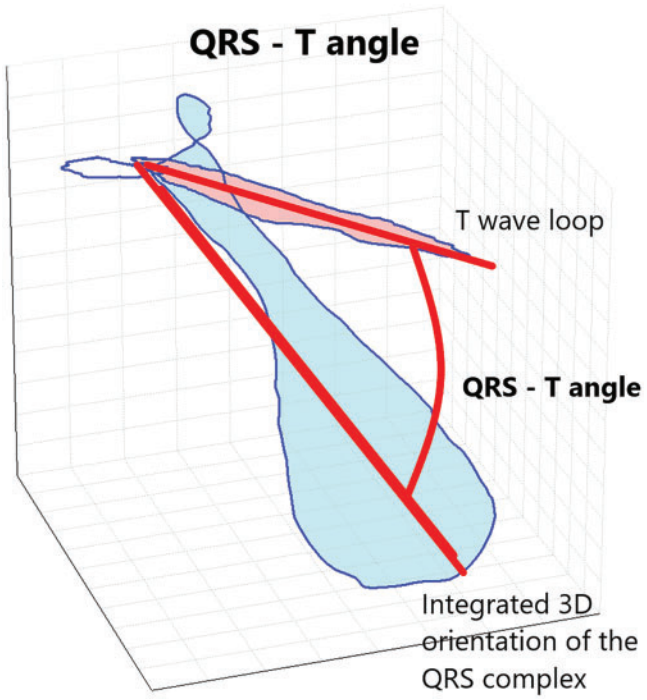

FIGURE 2: A representation of QRS–T angle from vectorcardiograms.

Dialysis. Covic *et al.* [12] evaluated the prognostic value of estimating LVH by 12 different sets of commonly used electrocardiographic criteria in a retrospective, observational, single-centre study, which included both prevalent HD and PD patients [12]. Novacode, a method that does not use voltage criteria but incorporates repolarization indices into an algorithm, was found to be predictive of cardiovascular mortality, while 11 other methods, including the widely used Sokolow–Lyon and Cornell criteria, were not.

A Korean prospective observational study of incident HD patients [13] compared the prognostic value for cardiovascular mortality of commonly used ECG criteria for LVH, namely Sokolow–Lyon and Cornell, with the voltage duration product method that encompasses the QRS duration. The diagnosis of LVH using voltage duration product methods was an independent risk factor for cardiovascular outcomes, but LVH defined by fixed voltage Sokolow–Lyon and Cornell was not. Approximately half of the individuals with an echocardiographic diagnosis of LVH did not have a matching electrocardiographic one.

Krane *et al.* [14], in a study of 1253 maintenance HD patients with diabetes, identified that ECG LVH with Sokolow–Lyon criteria was predictive of sudden death and stroke [hazard ratio (HR) = 1.60, 95% confidence interval (CI) 1.05–2.44; P = 0.027], but not of all-cause mortality, cardiac deaths and myocardial infarction, although a trend towards statistical significance for cardiovascular endpoints was observed.

Cice *et al.* [15], in a prospective study of normotensive maintenance HD patients without coronary artery disease, found that the strain pattern on the ECG was associated with cardiovascular and sudden death.

CKD. There is a paucity of studies assessing the association between ECG diagnosis of LVH and mortality or cardiovascular outcomes. Agarwal and Light, in a cross-sectional study of 387 patients that included 243 patients with various degrees of CKD,

Table 2. Studies evaluating the association of electrocardiographic LVH with clinical outcomes in chronic renal disease

References	Population	Sample size	Follow-up	Results	Comments
Covic *et al.* [12]	Prevalent HD and PD	418	67 months (mean)	LVH by Novacode predictive of cardiovascular mortality (HR = 3.04, 95% CI 1.11–8.28; P < 0.05)	11 other methods not predictive
Kim *et al.* [13]	Incident HD	317	27.4 months (mean)	LVH by Sokolow–Lyon voltage duration product (HR = 3.43, 95% CI 1.32–892; P = 0.011) and Cornell voltage duration product (HR = 3.07, 95% CI 1.16–8.11; P = 0.024) predictive of cardiovascular mortality	50% discordance between ECG and echocardiographic diagnosis of LVH
Cice *et al.* [15]	Prevalent HD	407	46 months (mean)	LVH with strain predictive of cardiovascular deaths (P < 0.05) and sudden deaths (P < 0.01)	Univariate analysis
Krane *et al.* [14]	HD with diabetes	1253	48 months (mean)	LVH with Sokolow–Lyon criteria was predictive of sudden death (HR = 1.60, 95% CI 1.05–2.44; P = 0.027)	A trend towards higher risk for cardiovascular endpoints was detected
Agarwal and Light [16]	CKD, excluding ESRD	387	90 months (median)	LVH with Sokolow–Lyon criteria prognostic for all-cause mortality (HR = 2.84, 95% CI 1.50–5.37; P < 0.001)	Multivariate analysis including adjustment for blood pressure

found a statistically significant association between diagnosis of LVH with Sokolow–Lyon criteria and all-cause mortality. The LVH group had perhaps unsurprisingly higher baseline blood pressure readings, but the association between LVH and mortality still persisted even after adjustment for blood pressure [16].

Comment. The electrocardiographic detection of LVH in CKD patients correlates poorly with LVH diagnosis using echocardiography. This observation is in line with the findings in the general population [17], suggesting that changes in electrical remodelling depicted by ECG LVH do not reflect anatomical structural changes established by echocardiogram and that they carry additional independent prognostic information. On the other hand, the predictive value of ECG LVH with fixed voltage criteria is variable in dialysis patients and this may be the result of a variable and fluctuant impact of fluid and electrolyte status on the ECG waveform. Timing of the ECG is important as fluid removal immediately after dialysis leads to an increase in ECG voltage due to impedance changes, which is gradually attenuated as fluid accumulates until the next dialysis session [18]. As a result, an inter-dialytic ECG may obfuscate the presence of LVH in a patient with large inter-dialytic fluid gains, which itself is in turn an independent mortality risk factor [19].

QT interval

The electrocardiographic QT interval represents the time from the onset of ventricular depolarization to the completion of repolarization. QTc is the value of QT after correction for heart rate. The Bazett formula is the most commonly used method for QT correction in clinical studies [20]. Other formulae (Fridericia, Framingham, Hodges, etc.) tend to provide similar estimates when resting heart rates are close to 60 b.p.m. [21]. Clinically meaningful prolongation of QTc is often defined as QTc >460 ms in women and QTc >450 ms in men [22].

Electrocardiographic QT duration reflects both cardiac conduction and repolarization and is influenced by electrolyte shifts, myocardial ischaemia and structural heart disease. QTc prolongation increases the risk of ventricular tachyarrhythmia. A summary of studies detailed below is found in Table 3.

Dialysis. Hage *et al.* [23] found that QT prolongation was an independent predictor of all-cause mortality in a prospective cohort of both HD and PD patients evaluated for renal transplantation (HR = 1.008, 95% CI 1.001–1.014; P = 0.016). This study did not show any difference in the proportion of patients with QT prolongation between HD and PD.

In another prospective study of both incident and prevalent dialysis patients evaluated for renal transplantation, Flueckiger *et al.* [24] showed similar associations between the prolongation of the QT interval and all-cause mortality in 930 patients (HR = 1.71, 95% CI 1.11–2.63; P = 0.0158).

Genovesi *et al.* [25] used 24-h Holter electrocardiography in a cohort of 122 prevalent HD patients. The mean QTc was estimated in three periods: during dialysis treatment for 4 h, 4 h after dialysis treatment and the remaining 16 h after dialysis treatment [25]. After a median follow-up of 3.9 years, QTc prolongation was found to be independently associated with SCD (HR = 8.33, 95% CI 1.71–40.48; P = 0.009). Interestingly, the mean QTc interval did not change significantly during or after dialysis.

In contrast to the previous observational studies, a large multicentre randomized controlled trial of statin therapy in diabetic HD patients, the German Diabetes and Dialysis study (4D, Die Deutsche Diabetes Dialyse Studie), did not find any association between the duration of the QTc interval and cardiovascular outcomes [14].

CKD. In the CKD population, several observational studies have identified a link between QTc duration and cardiovascular outcomes [24, 26, 27]. Deo *et al.*, in a prospective study of almost 4000 CKD patients, found that prolongation of the QTc interval was associated with all-cause and cardiovascular mortality. This association, however, ceased to exist in sub-group analysis adjusted for LVMI and left ventricular ejection fraction (LVEF) [27].

Similarly, Dobre *et al.* [26] in a study of mainly CKD 3 patients demonstrated that QTc was associated with cardiovascular events.

In the National Health and Nutrition Examination Survey III, the addition of QTc in the adjusted model that included traditional risk factors for cardiovascular mortality improved risk prediction for all-cause and cardiovascular mortality. The main strengths of this study were the large sample size (6565 individuals) and the long follow-up period (median follow-up 13.3 years).

Comment. Fluid and electrolyte shifts may affect QT interval; fluid and potassium removal both contribute to QTc prolongation at the end of the dialysis, whereas calcium changes are less consistent and can have a variable effect on the QTc [18]. Genovesi *et al.* [28] have previously reported that low potassium and calcium dialysate are associated with prolongation of QTc interval towards the end of HD. Also, Bazett's correction, which has been used in many of the studies, is known to lead to artificially prolonged QTc values in the presence of increased heart rate. Although this is of little concern when dealing with singular QTc measurements in any given patient, it might represent a potential source of bias in statistical studies linking outcomes to QTc duration.

QRS complex—amplitude and duration

The electrocardiographic QRS complex represents the electrical activation of the ventricular myocardium, spreading from septal activation to the depolarization of the base of the ventricular free walls.

A broad QRS complex (>120 ms) has been used as a marker of cardiac dyssynchrony in studies evaluating the incidence of SCD in patients with heart failure [29], and is one of the criteria for resynchronization therapy in congestive heart failure [30].

Dialysis. A Spanish prospective study of 285 incident HD and PD patients with generally well-preserved left ventricular function did not show any independent association between QRS duration and SCD incidence [31].

Table 3. Studies evaluating the association of QTc with clinical outcomes in chronic renal disease

References	Population	Sample size	Follow up	Results	Comments
Hage *et al.* [23]	HD and PD evaluated for transplantation	280	40 months (mean)	QTc independent predictor of survival (HR = 1.008, 95% CI 1.001–1.014; P = 0.016)	
Flueckiger *et al.* [24]	CKD 5 and ESRD evaluated for renal transplantation	930	37.2 months (median)	QTc >450 ms associated with risk of death in adjusted analysis (HR = 1.71, 95% CI 1.11–2.63; P = 0.0158)	
Deo *et al.* [27]	CKD	3939	90 months (median)	Prolonged QTc associated with all cause (HR = 1.46, 95% CI 1.16–1.84) and cardiovascular mortality (HR = 1.72, 95% CI 1.19–2.49)	Association with cardiovascular death ceased to exist in subgroup adjusted analysis that included LVMI and LVEF
Dobre *et al.* [26]	CKD 3–5	1165	123.6 months (mean)	Prolonged QT was associated with 61% higher risk for cardiovascular events (HR = 1.61, 95% CI 1.16–2.23)	Predominantly CKD 3 (95.6% of study population)
Genovesi *et al.* [25]	HD	122	46.8 months (median)	Prolonged QTc independently associated with all cause mortality (HR = 2.16, 95% CI 1.20–3.91; P = 0.011) and sudden death (HR = 8.33, 95% CI 1.71–40.48; P = 0.009)	
Krane *et al.* [14]	HD with diabetes	1253	48 months (mean)	QT interval not associated with outcomes	
Malik *et al.* [71]	CKD	6565	159.6 months	QTc improved the risk prediction of traditional models (P < 0.00001 for all-cause mortality and P < 0.00001 for cardiovascular mortality)	

CKD. The use of the QRS complex for cardiovascular risk prediction is poorly investigated and appears to be unreliable as an independent marker based on the currently available evidence. Research suggests that the QRS interval duration increases with the progression of CKD [32].

In a prospective study of 3587 individuals with mainly early to moderate CKD [mean estimated glomerular filtration rate (eGFR) 50–60 mL/min/1.73 m^2, median follow-up 7.5 years), Deo *et al.* identified prolongation of the QRS interval as an independent risk predictor for cardiovascular death, even after adjustment for LVMI and ejection fraction. For QRS duration of 100–119 ms, the HR was 1.64 (95% CI 1.20–2.25) and for QRS >120 ms, the HR was 1.75 (95% CI 1.17–2.62) [27].

Comment. The amplitude of the QRS complex increases after HD [33, 34]. The latter is thought to be a result of the changes in body fluid volume. Fluid removal also leads to a decrease in tissue conductivity which, as a result, affects the surface voltage of the electrocardiographic complexes [35]. Therefore, the change of the QRS amplitude with different fluid status is a result of different thorax impedance and not of electrophysiological cardiac changes.

LBBB versus RBBB QRS morphology

There are few data available in comparing left bundle branch block (LBBB) versus right bundle branch block (RBBB). In the study of diabetic patients on HD by Krane *et al.* [14], neither RBBB nor LBBB showed any association with mortality or cardiovascular outcomes in multivariate analysis adjusting for comorbidities and demographics. The presence of LBBB may obscure the electrocardiographic diagnosis of LVH as they both cause conduction delays and as a result the inclusion of LBBB as a separate variable in a model that includes electrocardiographic LVH is not without problems [36]. Covic *et al.* [12], in a study of HD patients that compared different electrocardiographic methods of LVH estimation and their association with outcomes, also noted that LBBB was associated with all-cause mortality in univariate analysis. However, they suggested caution while using LBBB and ECG LVH in the same model.

PR interval

The electrocardiographic PR interval represents the propagation of the myocardial electrical impulse between atrial depolarization and the onset of ventricular depolarization, and is normally between 120 and 200 ms. The PR interval is also affected by fluid and electrolyte shifts. In the general population, prolongation of the PR interval has been associated with increased risk of developing atrial fibrillation, of requiring pacemaker implantation and of overall mortality [37]. A summary of the studies detailed below is found in Table 4.

Dialysis. Flueckiger *et al.* [24], in their study of 930 transplant candidates undergoing HD, demonstrated that prolonged PR interval was associated with all-cause mortality in multivariate analysis (HR = 1.97, 95% CI 1.18–3.29; P = 0.090).

Green *et al.* [11] undertook a prospective observational study of 211 HD and 112 PD patients and identified a significant association between prolongation of the PR interval and cardiovascular outcomes in univariate, but not in multivariate, analysis (mean follow-up 3.6 years).

Another prospective study of 116 HD patients by Badarau *et al.* evaluated that the PR interval derived from standard ECGs were acquired 5 min before and 30 min after a HD session. In this study, for the majority of patients, the PR interval decreased after dialysis and in multivariate Cox regression analysis, the difference between the pre- and post-dialysis PR interval duration was identified as an independent predictor of cardiovascular outcomes with longer PR having a lower risk (HR for log of

Table 4. Studies evaluating the association of PR interval with clinical outcomes in CKD

References	Population	Sample size	Follow-up	Results	Comments
Flueckiger *et al.* [24]	CKD 5 and ESRD evaluated for renal transplantation	930	37.2 months (median)	PR interval was associated with all-cause mortality (HR = 1.97, 95% CI 1.18–3.29; P = 0.090)	
Deo *et al.* [27]	CKD	3939	90 months (median)	PR >200 ms is associated with cardiovascular mortality (HR = 1.62, 95% CI 1.19–2.19)	
Green *et al.* [11]	HD and PD	323	43.2 months (mean)	No independent association between PR interval and cardiovascular outcomes in multivariate analysis	
Kestenbaum *et al.* [40]	CKD	600	110.4 months (median)	No independent association between PR prolongation and incident cardiovascular events	
Badarau *et al.* [38]	HD	116	17.5 months (median)	Log pre- and post-dialysis difference in PR interval predicts cardiovascular events (HR = 0.387, 95% CI 0.251–0.597; P < 0.001)	
Silva *et al.* [39]	HD	100	14 months (mean)	The duration of the PR interval was independently associated with bradyarrhythmias (odds ratio = 1.05, 95% CI 1.02–1.08; P < 0.001)	Candidates for renal transplantation

change in PR = 0.387, 95% CI 0.251–0.597; P < 0.001), but not of all-cause mortality [38].

A Brazilian prospective observational study aimed to evaluate the incidence of arrhythmias and their associations with ECG findings in a cohort of 100 HD patients using implantable loop recorders. During a follow-up period of 424 ± 124 days, prolongation of the PR interval was found to be independently associated with the development of bradyarrhythmias [39].

CKD. In a prospective study of 3587 patients with different stages of pre-dialysis CKD, a prolonged PR interval was identified as an independent predictor of cardiovascular mortality (HR = 1.62, 95% CI 1.19–2.19) [27].

In contrast, Kestenbaum *et al.* [40] prospectively studied 600 individuals with a moderate degree of CKD (median eGFR 53 mL/min/1.73 m^2) and did not observe any independent association between PR prolongation and incident cardiovascular events [40].

Comment. In conclusion, the PR interval demonstrates variable associations with mortality in CKD and ESKD that may be explained by fluid and electrolyte influences on PR interval. The link between prolonged PR interval and mortality is unclear, but it may be related to mortality associated with bradyarrhythmias or atrial fibrillation.

QRS–T angle

In the last decade, there has been increasing interest in the spatial QRS–T angle that is defined as the angular difference between the orientation of the three-dimensional (3D) QRS and T vectorcardiographic loops that are either directly captured or calculated from the standard 12-lead recordings. This is because the angle has emerged as a novel marker for cardiac risk stratification [41]. A number of studies in different populations have demonstrated an association between a wide spatial QRS–T angle and cardiovascular and all-cause mortality [42].

The spatial QRS–T angle can easily be measured either on vectorcardiograms recorded using the Frank electrode positions [43] or by following orthogonal transformation from a digital 12-lead ECG using conversion systems such as Kors or inverse Dower matrices [44, 45]. In these methods, the spatial orientation of the orthogonal XYZ leads is defined anatomically and is subject independent. A novel descriptor uses singular value decomposition to construct a mathematically derived subject-dependent 3D space optimizing the orthogonal leads in order to capture most of the ECG energy in each individual, and calculates the difference between the global direction of depolarization and repolarization expressed as an average cosine of the angles between the QRS and T vectors [total cosine R-to-T (TCRT)] [46]. Figure 2 depicts the TCRT.

The definition and range of normal and abnormal QRS–T angles in healthy individuals depend on the method of estimation as well as on gender, age and underlying heart rate [47–50]. The spatial QRS–T angle may be calculated by several methods including using the peak angular difference between the QRS and T-vectors, their mean angular difference [51], the angle between the spatial mean QRS vector and spatial peak T-vector [52] and by using the average cosine of the angles between the QRS and T-vectors [53]. Therefore, 'absolute' values of the QRS–T angle should only be referenced in relation to the individual studies and methods they derive from. A summary of the studies detailed below is found in Table 5.

Dialysis. Several studies evaluated the prognostic value of spatial QRS–T angle for all-cause and cardiovascular mortality in dialysis patients. In a retrospective study of 277 incident HD and PD patients, de Bie *et al.* [54] identified abnormal spatial QRS–T angle as an independent predictor of all-cause mortality (HR = 2.33, 95% CI: 1.46–3.70; P < 0.01) and SCD (HR = 2.99, 95% CI 1.04–8.60; P < 0.05) after multivariate analysis [54]. An abnormal spatial QRS–T angle was defined as >130° in men and >116° in women in that study, and the length of follow-up was 2.1 ± 1.7 years.

In a pilot study of 81 prevalent HD patients, which used continuous Holter electrocardiographic recordings, Poulikakos *et al.* [55] reported higher TCRT values (expressed in degrees) in individuals who suffered major arrhythmic events (TCRT) [56].

Couderc *et al.* calculated the QRS–T angle from ECG Holter recordings in a study of 50 prevalent HD patients. They

Table 5. Studies evaluating the association of spatial QRS–T angle and outcomes in ESRD

References	Population	Sample size	Follow-up	Results	Comments
de Bie *et al* [54]	HD and PD	277	25.2 months (mean)	QRS–T angle independent predictor of all cause mortality (HR = 2.33, 95% CI 1.46–3.70; P < 0.01) and SCD (HR = 2.99, 95% CI 1.04–8.60; P < 0.05)	Single surface ECG
Poulikakos *et al.* 2014 [55]	HD	81	18 months	Extremely high TCRTs in patients who experienced arrhythmic events	Holter
Couderc *et al.* [57]	HD patients above the age of 40 with history of diabetes or hypertension	50	13 months	Statistically significant increase of the QRS–T angle after the dialysis session in the non-survivor group (P < 0.05)	Holter
Tereshchenko *et al.* [52]	Incident HD	358	864.6 person years	Spatial QRS–T angle >75° was independently associated with all-cause (HR = 2.38, 95% CI 1.41–4.04; P = 0.001) and cardiovascular mortality (HR = 2.99, 95% CI 1.31–6.82; P = 0.01)	5 min SA ECG

demonstrated a statistically significant greater average QRS–T angle in the first 6 h after initiation of the dialysis session compared with pre-dialysis that correlated with all-cause mortality [57].

A large prospective study of incident HD patients by Tereshchenko *et al.* evaluated the spatial QRS–T angle for risk stratification in a cohort of patients of predominantly African origin with overall normal LVEFs. The authors calculated the QRS–T angle as the angle between spatial mean QRS vector and spatial peak T-vector in averaged XYZ ECG from 5 min signal-averaged ECGs. In multivariate adjusted analysis, a spatial QRS–T angle >75° was independently associated with all-cause (HR = 2.38, 95% CI 1.41–4.04; P = 0.001) and cardiovascular mortality (HR = 2.99, 95% CI 1.31–6.82; P = 0.01) [52].

CKD. There were no suitable studies at the time of this review.

Comment. The QRS–T angle has showed promising results for risk prediction in dialysis patients. However, there is a need for standardization of the measurement [53] so that normal limits and clinically relevant risk stratification dichotomies can be established.

HRV

HRV gained popularity, among other ECG parameters, because of its importance for cardiovascular risk prediction [58, 59]. HRV measurement is based on different assessments of the oscillations of the intervals between consecutive cardiac beats. It has been used as a surrogate method of assessing the sympathetic and parasympathetic cardiac autonomic modulation [60]. Reduced HRV has been associated with increased mortality in different populations including healthy individuals and patients post-myocardial infarction [61, 62]. HRV can be measured using time- and frequency domain methods as well as employing nonlinear dynamics analyses. Standards of HRV assessment are available [63, 64] and are followed in most of the risk assessment studies. A summary of studies detailed below is found in Table 6.

Dialysis. In a study of 383 incident and prevalent HD patients, Oikawa *et al.* [65] reported an independent association between reduced overall HRV and all-cause (HR = 2.181, 95% CI 1.530–3.108; P < 0.001) and cardiovascular mortality (HR = 2.114, 95% CI 1.200–3.725; P = 0.01) [65].

A study of 81 PD patients also reported on the prognostic value of spectral HRV assessment for all-cause mortality during 4 years of follow-up [66]. In a prospective study of 281 prevalent HD patients, Suzuki *et al.* evaluated different HRV measures. Time and spectral assessment of short-term HRV indices predicted mortality but after adjusting for age, LVEF, serum albumin, C-reactive protein and calcium × phosphate product, only one of the nonlinear dynamics parameters was an independent mortality predictor (HR = 1.46, 95% CI 1.16–1.85; P = 0.001) [67].

Badarau *et al.* [38] reported an association between very low frequency HRV and all-cause mortality in a study of 116 HD patients (HR = 1.741, 95% CI 1.047–2.895; P = 0.033), but did not find such an association with the other spectral HRV components.

In the latter two studies, the 24-h Holter ECG was recorded during interdialytic interval, whereas in other studies, it took place on a dialysis day that included the dialysis session.

CKD. A multicentre prospective study of 305 patients with CKD stages 3–5 demonstrated a strong association between decreased spectral HRV parameters and the cumulative probability of adverse cardiovascular events [68].

Comment. The variable results of studies using out-of-hospital 24-h Holter ECGs can be explained by the difficulty in standardizing the environmental factors that influence HRV assessment, including HD [69], during the recording. Indeed, total 24-h R–R interval variability analysis of recordings in truly ambulating out-of-hospital patients is of little prognostic value because of the differences in the environmental challenges to which the autonomic system responds, and is no longer recommended as a favoured approach for autonomic nervous system assessment [70, 71].

It has also been reported that high phosphate and parathyroid hormone levels [72] and fluid overload [73] are associated with reduced HRV in HD patients, whereas daily HD [74] and haemofiltration [75] are associated with less pronounced reductions in HRV compared with standard HD.

Table 6. Studies evaluating the association of HRV and outcomes in CKD

References	Population	Sample size	Follow-up	Results	Comments
Oikawa *et al.* [65]	HD	383	2110 ± 903 days	Independent association between reduced SDNN and all-cause (HR = 2.181, 95% CI 1.530–3.108; P < 0.001) and cardiovascular mortality (HR = 2.114, 95% CI 1.200–3.725; P = 0.01)	
Chandra *et al.* [68]	CKD 3–5	305	2.7 years (median)	A LF/HF ratio below the median was associated with a significantly increased risk of cardiac events (HR = 2.52; P = 0.002)	
Pei *et al.* [66]	PD	81	43.78 ± 14.77 months	LF/HF below the median significantly associated with all-cause mortality (P = 0.012)	
Suzuki *et al.* [67]	HD	281	87 months (median)	The scaling component α_1 was independently associated with all-cause mortality (HR = 1.46, 95% CI 1.16–1.85; P = 0.001)	None of the traditional HRV parameters was associated with mortality
Badarau *et al.* [38]	HD	116	17.5 months (mean)	Association between VLF component and all-cause mortality (log VLF, HR = 1.741, 95% CI 1.047–2.895; P = 0.033)	

SDNN = standard deviation of normal to normal R–R intervals; VLF = very low frequency; LF = low frequency; HF = high frequency.

CONCLUSION

A number of electrocardiographic parameters have been used as potential risk predictors in advanced renal disease and dialysis with variable results. The use of conventional ECG parameters is severely limited by the influence of fluid and electrolyte shifts on their measurements. Inconsistency and lack of reproducibility make them unreliable as independent biomarkers.

In the case of the PR interval prolongation, in particular the link between abnormal PR and mortality might reflect the mortality risk associated with bradyarrhythmias or atrial fibrillation. In the determination of electrocardiographic LVH, the use of Novacode has shown promising results. Novacode has the advantage of not relying on voltage criteria, but requires computer processing of EGC waveform. Hence, unlike conventional methods such as Sokolow–Lyon, LVH cannot be determined by manual observation.

We elected to omit QTc dispersion from the review in order to keep the presented results more relevant. Previous research has indicated that QT dispersion as a metric is problematic as it has very poor reproducibility and cannot be used consistently for risk stratification. There is also some controversy regarding the meaning of QT dispersion as some previous research has questioned whether it truly represents repolarization heterogeneity [76, 77].

Novel markers, such as the QRS–T angle, have shown promising results in HD cohorts. However, the definitions of abnormal QRS–T angle vary significantly depending on the method of calculation used. Further standardization is therefore required. Moreover, the prognostic value of the QRS–T angle needs to be evaluated in larger prospective studies. In general, there is a paucity of studies assessing electrocardiographic markers as risk prediction tools in PD when compared with HD.

In summary, larger and more comprehensive studies are required, including those assessing the evolution of electrocardiographic changes from CKD to HD and PD and the relation of these changes to cardiac mortality. In addition, every opportunity should be taken to include serial ECG recordings in all larger randomized controlled trials examining cardiovascular and mortality outcomes. Risk stratification models that incorporate echocardiographic, electrocardiographic and laboratory parameters together will likely lead to more sensitive and specific risk prediction. Finally, the serious and potentially treatable bradyarrhythmias being detected by implantable loop recording in dialysis patients would itself justify a more regular and perhaps protocolled use of ECG in these populations.

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