"I do not imagine that electrocardiography is likely to find any very extensive use in the hospital. It can at most be of rare and occasional use to afford a record of some rare anomaly of cardiac action" Augustus Desiré Waller (1856-1922).

Since Waller's first recording of the human ECG in 1887, it is quite clear he had no preconception that the simple ECG would become one of the cornerstones of modern medicine making him one of the most humble cardiologists of all time. The utilisation of ECG markers to predict SCD has a long history spanning QRS and QT prolongation, heart rate, T wave alternans and QRS fractionation. However, despite some evidence of high negative predictive accuracy for some biomarkers e.g. T wave microvolt alternans, ECG features have struggled to predict risk in the general population and outperform crude ejection fraction in heart failure. However, increased computational power and advances in signal processing techniques have renewed interest in the field especially as the standardised 12 lead ECG is so cheap and easy to acquire in populations as opposed to imaging.

Left ventricular hypertrophy (LVH) is associated with myocyte enlargement, fibroblast and collagen accumulation, and apoptosis. This distorted myocardial architecture, acts as a substrate for the initiation and maintenance of re-entrant ventricular arrhythmias. Increased sympathetic activity, sub-endocardial ischaemia and wall stress will also promote degeneration of ventricular tachycardia into fibrillation. LVH ECG diagnostic criteria, as described by Sokolow and Lyon (SL) in 1949, incorporate QRS voltage information namely R and S wave amplitudes, representing depolarisation of the main ventricular myocardial mass and hence describe some substrate features. Thus far, various electrocardiographic criteria have differing sensitivities and specificities for LVH detection depending on the population age and ethnicity studied-as they also utilise

different precordial and/or limb leads they are likely to differ in their SCD predictive power [1].

In this issue of IJC, Porthan et al make important progress to unpick this problem in a population-based study. Cornell voltage (CV), SL and Peguero-Lo Presti criteria were significantly associated with an increased risk of SCD in multivariate analyses as continuous variables. CV and a composite of SL and CV (HR 1.82; 95% 1.2 – 2.7) were the only features to reach significance when analysed as dichotomised variables, possibly due to a reduction in statistical power. However, the inclusion of 'possible SCD' cases in the analysis is a potential source of error reflecting the limitations of such studies in the SCD field which demand rigorous evaluation of the cases. Predicting SCD risk is also becoming more challenging as mortality is reducing with disease modifying drugs e.g. in dilated cardiomyopathy, mortality has fallen from 6% per annum to 4% with increased prescription of beta-blockers, ACE-I, ARBs and neprilysin inhibitors [2].

The predictive value of a single ECG variable for SCD is comparatively lower than some other modalities, such as left ventricular ejection (LVEF) (HR 5.99 (95% 2.73 – 13.14)) [9]. When testing the independent predictive value of new ECG parameters for SCD, established markers should be included in multivariate analyses to ensure new markers independently affect risk. This study omitted a number of such markers including prolongation of QRS and QT intervals (QT: HR 2.5; 95% 1.3 – 4.7) [3].

Multiple variables will be required to improve risk prediction. The Multicentre Unsustained Tachycardia Trial, identified the association between reduced LVEF and arrhythmic death or cardiac arrest (HR 1.19; 95% 1.07 – 1.37 per 5% decrease in EF) [4]. Absence of non-sustained ventricular tachycardia within 10 days of coronary artery bypass grafting, was also an independent predictor (HR 1.86; 95% 1.02 – 3.40). Yet a key

finding from the study was the risk of such events at 2 years, was low in individuals with an LVEF < 30% with no other risk factors (<5%), but greater in individuals with EF > 30% and other risk factors such as interventricular conduction delay on ECG. Thus a single variable in isolation does not effectively predict risk. Aro et al recently demonstrated an association with increased risk of SCD per additional abnormal ECG parameter in a combined ECG risk score-a variety of different measures in the model included prolonged QTc and QRS intervals, heart rate, QRS-T angle > 90° and electrocardiographic LVH. A combination of ≥ 4 ECG abnormalities was associated with a HR of 4.84 (95% 2.34 – 9.99) [5], thus confirming the importance of composite risk scores.

Novel ECG features are now being investigated- an abnormal spatial QRS-T angle (the angle between the mean ventricular depolarisation and repolarisation vectors), is associated with a significant increase in SCD risk; even after inclusion of other ECG parameters like QT interval or lipid levels in the multivariate model (HR 3.4; 95% 1.9 – 6.0)[6]. Indeed, there is also hidden information in the resting ECG - dynamic oscillations in the T wave angle caused by increased sympathetic tone are emerging as an independent biomarker of sudden death risk bring in a new biomarker of autonomic nervous system activity[7].

Beyond ECG markers, genetic risk scoring is also emerging as an additional easily accessible discriminator. A proof of concept genetic risk score study of 966 SCD cases using single nucleotide polymorphisms associated with SCD in previous genome wide association studies, identified a 1.5 fold greater risk of sudden cardiac death in the highest risk quintile compared with the lowest. Whilst the effects were modest, next generation sequencing, inclusion of variants associated with other traits and greater sample sizes, may improve risk prediction using polygenic risk scores [8].

It remains to be seen whether pooling of electrocardiographic & simple clinical markers with genetic data will not only improve SCD risk prediction in left ventricular hypertrophy, but also enable personalised risk reduction strategies in the general population. One thing is for certain, the simple ECG still holds a rich source of potential prognostic information for the foreseeable future.

References

1. Laszlo R, Kunz K, Dallmeier D, Klenk J, Denkinger M, Koenig W, et al. Accuracy of ECG indices for diagnosis of left ventricular hypertrophy in people >65 years: results from the ActiFE study. Aging Clin Exp Res. 2017;29(5):875–84.

2. Pathak RK, Sanders P, Deo R. Primary prevention implantable cardioverter-defibrillator and opportunities for sudden cardiacdeath risk assessment in non-ischaemic cardiomyopathy. Eur Heart J. 2018 Aug 14;39(31):2859-2866.

3. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol. 2006 Jan 17;47(2):362-7.

4. Buxton AE, Lee KL, Hafley GE, Pires LA, Fisher JD, Gold MR, Josephson ME, Lehmann MH, PrystowskyEN; MUSTT Investigators.
Limitations of ejection fraction for prediction of sudden death risk in patients with coro naryartery disease: lessons from the MUSTT study. J Am Coll Cardiol. 2007 Sep 18;50(12):1150-7

5. Aro AL, Reinier K, Rusinaru C, Uy-Evanado A, Darouian N, Phan D, et al. Electrical risk score beyond the left ventricular ejection fraction: Prediction of sudden cardiac death in the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study. Eur Heart J. 2017;38(40):3017–25.

6. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. Eur Heart J. 2003 Jul;24(14):1357-64.

7. Rizas KD, Nieminen T, Barthel P, Zürn CS, Kähönen M, Viik J, Lehtimäki T, Nikus K, Eick C, Greiner TO, Wendel HP, Seizer P, Schreieck J, Gawaz M, Schmidt G, Bauer A. Sympathetic activity-associated periodic repolarization dynamics predict mortality following myocardial infarction. J Clin Invest. 2014 Apr;124(4):1770-80

8. Huertas-Vazquez A, Nelson CP, Sinsheimer JS, Reinier K, Uy-Evanado A, Teodorescu C, Ayala J, Hall AS, Gunson K, Jui J, Samani NJ, Chugh SS. Cumulative effects of common genetic variants on risk of sudden cardiac death. Int J Cardiol Heart Vasc. 2015 Jun 1;7:88-91.