

# Long Term Follow Up of the Early Repolarization Pattern in Participants in the West of Scotland Coronary Prevention Study

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## Abstract

*The West of Scotland Coronary Prevention Study was a primary prevention trial aimed at assessing the effects of pravastatin in middle aged males with hypercholesterolemia but no history of myocardial infarction. As part of that study, baseline 12 lead ECGs were recorded in digital form around 1990.*

*The aim of the present study was to analyse these ECGs to look for the early repolarization pattern (ERP) and to see if there was any adverse outcome associated with ERP during 15 years of follow up.*

*At baseline, 6595 men aged 45-64 (mean age  $55.2 \pm 5.5$ ) were recruited. Subsequent hospitalizations and/or death were recorded centrally. Twelve lead ECGs were recorded and stored on a Mingocare system. 6575 ECGs were recently retrieved and analysed with the University of Glasgow ECG Analysis Program, which incorporates criteria for the detection of ERP. A health census of participants was taken 15 years after entry into the study. Analysis was undertaken of the difference in outcome for those with versus those without ERP.*

*ERP was found in 1398 cases. Kaplan-Meier analysis of the 15 year outcomes data showed no significant difference between those with and without ERP for the outcome of i) non-fatal myocardial infarction or coronary heart disease death, and ii) all cause mortality ( $P=0.65$ ).*

## 1. Introduction

The definition and identification of the early repolarization pattern (ERP) in ECGs has been an area of much recent research activity. Different investigators have used different definitions for ER. The classical definition was based on the presence of both ST segment elevation and end QRS notching or slurring [1]. Some cardiologists have interpreted the presence of ST-segment elevation alone as signifying ER [2]. The current definition requires end QRS notching or slurring and does not require ST segment elevation [3]. An example of an ECG with ERP, as newly-defined, in leads II, aVF, V4, V5 and V6 is shown in Figure 1.

While the classically defined early repolarization was generally considered to be a benign phenomenon, the presence of end QRS notching or slurring particularly in subjects with syncope has been associated with idiopathic ventricular fibrillation [4].

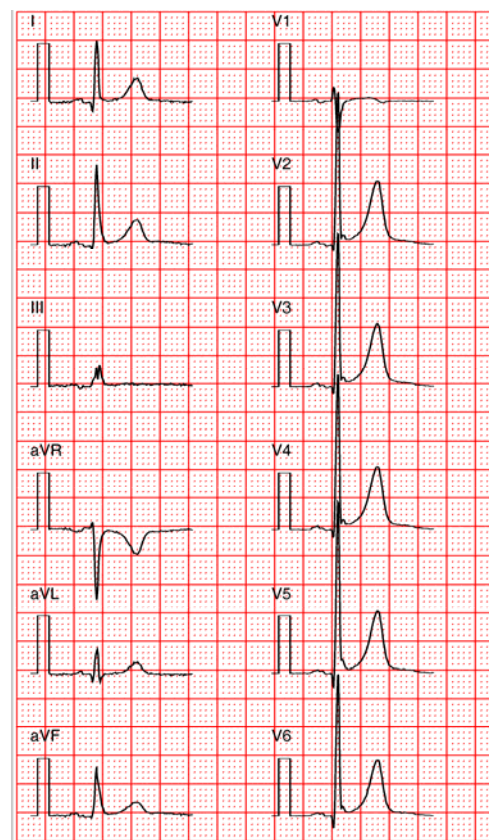


Figure 1. The 12 lead ECG of a 48-year old male. Note end QRS slurring in leads II, aVF and end QRS notching in V4-V6.

The West of Scotland Coronary Prevention Study (WOSCOPS) [5] was a primary prevention clinical trial which assessed the effects of pravastatin in middle aged males with hypercholesterolemia but no history of

myocardial infarction. The 5 year trial period of treatment with pravastatin versus placebo was succeeded by 10 years extended follow-up [6]. At the end of the 5 year trial, the participants were returned to the care of their primary care physicians and subsequent use of statin therapy was decided by these physicians. For all participants, the baseline 12 lead ECGs had been recorded in digital form between 1989 and 1991.

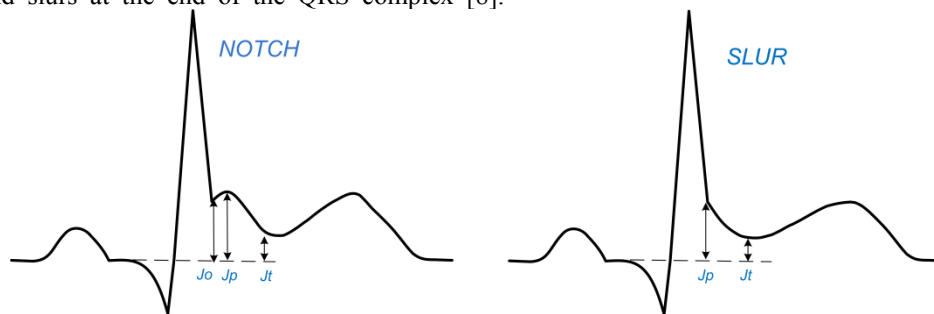
The aim of the present study was to analyse the baseline ECGs of participants in WOSCOPS to look for the newly-defined ERP, based solely on end QRS notching or slurring, and to see if there was any adverse outcome associated with this ECG abnormality during the 15 year follow-up period from the baseline ECG recording.

## 2. Methods

The baseline 12 lead ECGs for the 6595 men enrolled in the WOSCOPS study had been recorded using a Siemens Sicard 440 ECG machine and stored on a Mingocare system. On enrolling in the study, individuals were flagged with the Scottish Government Record Linkage System so that any hospitalizations and/or deaths were recorded centrally. For the purposes of the study, data on hospitalisations and deaths were censored at approximately 10 years post trial termination. All participants were included in the long-term follow-up for clinical outcomes. Data for primary and secondary outcomes was recorded. These included death from definite coronary heart disease while all cause mortality was also an end point of interest.

The digital data for the baseline ECGs were retrieved from the database and were re-analysed using the 2014 development version of the University of Glasgow ECG Analysis Program [7].

This version incorporates logic to detect and measure notches and slurs at the end of the QRS complex [8].



- The last component of the QRS complex is an R wave
- The R wave duration > 40 msecs
- There is a notch or slur on the downward slope of the R wave
- The notch or slur has a minimum allowed amplitude ( $J_p$ ) of 0.1mV and a maximum of 0.5mV

Figure 2. Schematic illustration of a notch and a slur showing J onset (Jo), J peak (Jp), and J termination (Jt) and the criteria used in the program.

Terminology and criteria used to define a notch and a slur are illustrated in Figure 2.

The criteria used for reporting ERP, based on the presence of notching or slurring in the downslope of the R wave in two contiguous leads, are given in detail in Figure 3.

- There is a notch or slur on the R wave at the end of QRS complex in 2 or more contiguous leads in the inferior leads II, aVF III; the lateral leads I, aVL or the anterolateral leads V4, V5, V6.
- There is no LBBB, RBBB or Brugada pattern.
- The QRS duration  $\leq 120$  msecs.
- There is no acute Q wave infarction at the relevant site.

Figure 3. Criteria for reporting ERP.

The analysis results for the ECGs were examined for the presence of the diagnostic statement reporting ERP. An array indicating the presence of ERP for each ECG was obtained and this was used to see if there was any difference in outcome over the 15 years from the baseline ECG recording, irrespective of treatment. The statistical analyses were undertaken at the Robertson Centre for Biostatistics, University of Glasgow. The outcomes considered were i) all cause mortality and ii) non-fatal myocardial infarction or death from coronary heart disease.

The analyses were carried out with and without adjustment for other variables which included age, body-mass index, systolic blood pressure and social deprivation scale [5]. Analyses of the outcomes for the 15 years from trial initiation to 10 years following the trial termination were undertaken using the Kaplan-Meier method.

### 3. Results

Of the 6595 participants aged 45-64 (mean age  $55.2 \pm 5.5$ ), 20 baseline ECGs were missing from the database. For a further 2 cases, no matching outcome data was found relating to the patient identifier on the baseline ECG. Of the remaining 6573 cases, the ERP was reported in 1398 cases (21.3%). An example, where notching was identified in leads V4, V5 and V6 and slurring in leads II and aVF, is shown in Figure 1. The waveforms are from a baseline ECG of a WOSCOPS participant. The Kaplan-Meier survival analysis showed that the presence of ERP was unrelated to the outcome of non-fatal myocardial infarction or death due to coronary heart disease, unadjusted or adjusted for other variables. There were also no significant differences ( $P=0.65$ ) between those with and without ERP for the outcome of all cause mortality (Figure 4).

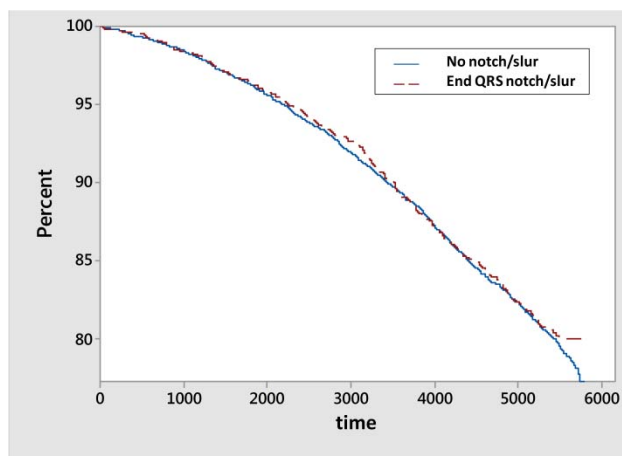


Figure 4. Survival plot for all cause mortality.

### 4. Discussion

In their 2008 study [4], Haïssaguerre et al found that there is an increased prevalence of early repolarization in patients with idiopathic ventricular fibrillation accompanied by syncope. The definition of ERP used in that study was broadly in line with the criteria for ERP now formally described in the 2015 Consensus paper [3].

Following the association of ERP and ventricular fibrillation, there have been many studies investigating

the prognostic significance of ERP, and Wu et al [9] performed a meta-analysis in 2013 to summarize the results. Their conclusions were that ERP is associated with increased risk of arrhythmia death but not cardiac death or all-cause mortality. Where our method differs from those earlier studies is that we have used automated detection rather than visual detection of the newly-defined ERP. The accuracy of the automated detection method had been verified prior to this study [8].

Another study which used automated detection of ER is that by Agard [10] in 2014. However in this case, the investigators used automated detection of classically defined ERP and then visual detection of notches or slurs. Agard et al found that this classical ER was not associated with increased risk of death. This study used a large population ( $> 200,000$ ) of both males and females ranging from 18 to 75 years.

Another recent study by Quattrini et al [11] of a mainly Caucasian population of age  $25 \pm 4$  years, found that ERP was not a risk factor for adverse cardiac events. It looked at the significance of ERP in highly trained athletes with a mean follow-up of 6 years. It is known that ERP is more common in athletes and there has been concern about possible increased risk of sudden cardiac death in this group.

There has been a suggestion that the high prevalence of ERP indicates that it is non-specific and, in the conclusion of the 2015 Consensus paper, the authors stated that, “pending further research, in the absence of syncope or a strong family history of juvenile cardiac death, the finding of early repolarization pattern does not merit further investigation” [3]. The findings of our study reinforce this point of view.

As has been indicated in the consensus paper, it may be necessary to modify the definition of ERP if it is found to be too sensitive. Notches and slurs may need to be considered separately or the definition extended to include ST-segment slope as suggested by Tikkanen [12]. It is interesting to note that none of the ECGs for the healthy athletes in the Quattrini study which had end QRS notching/slurring showed a downward sloping ST segment.

### 5. Conclusion

In the population of males with no history of myocardial infarction but raised plasma cholesterol levels, it was found that the ERP is of no prognostic significance with respect to i) non-fatal myocardial infarction or death from coronary heart disease; ii) all cause mortality. The prevalence of ERP was high and it may be worth investigating further the criteria for end QRS slurring as used in the automated approach as they may be more sensitive than a subjective impression of a notch as used in visual interpretation.

## 6. Limitations

In the study population, approximately half the participants were being treated with pravastatin and half with a placebo. We did not look at the results for these two groups separately.

Furthermore, the population consisted only of males and family history was not utilised in the present study.

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