1. Title:
The Family History Score and Indices of QT Prolongation

2. Writing Group:
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3. Timeline:
Preliminary analysis to begin March, 1994

4. Rationale:
Long QT syndrome (LQTS) is a disease which was characterized by familial aggregation in its original
descriptions over thirty years ago (Jervell et al 1957; Romano et al 1963; Ward 1964). More recently, linkage
analysis has demonstrated a strong association between LQT and the H-ras-I locus on the short arm of
chromosome 11 (Keating et al 1991). With this modern technique, some of the genetic factors which may
contribute to the clustering of LQTS in families with an autosomal dominant pattern of inheritance have been
elucidated, although autosomal recessive and sporadic patterns also exist. LQTS, as its eponym implies, is
further characterized by prolongation of the QT interval and resultant life-threatening tachyarrhythmias
(Schwartz et al 1993). Indeed, the heart rate-corrected QT interval predicts sudden death in LQTS patients
(Moss et al 1985; Garson et al 1993) and has been used to predict adverse cardiovascular outcome in healthy
subjects (Schouten et al 1991; Goldberg et al 1991), and patients with ventricular fibrillation (Haynes et al
1978), coronary artery disease (Puddu et al 1986), myocardial infarction (Krasnoff 1950; Elek et al 1953;
Wheelan et al 1986; Pohjola-Sintonen 1986), and diverse clinical histories (Algra et al 1991). However, it is
unknown if on a population basis, indices of QT prolongation are continuously associated with familial
frequency of heart disease as quantitatively expressed by the family history score (Hunt et al 1986). The
evidence for familial aggregation of LQTS as described above suggests that such a relationship may exist.
Familial aggregation of risk factors for CHD like diabetes and hypertension, which also appear to be
associated with QT prolongation (Gonin et al 1990; Jermendy et al 1991; Ewing et al 1991; Rautaharju et al
in preparation), may in turn modify this putative relationship.

5. Main Hypotheses:
Indices of QT prolongation are continuously associated with the family history score. The family history
score is an independent predictor of QT prolongation.

6. Analysis:
Analysis will be based on the Visit I 12-lead ECG. Participants without ECG abnormalities known to
influence QT intervals will be included. The heart rate-corrected and the heart rate and QRS-predicted QT
intervals, QTc = QT/(60/HR)^0.5 (Bazett 1920) and QTP = [656/(1+0.01HR)]+0.4QRS (Rautaharju et al
1993), will be calculated. The measure QT interval will be expressed as a percentage of the predicted QT
interval, yielding an index of QT prolongation QTI = (QT/QTP)*100. Associations between QTc, QTI, and
the family history score will be examined.

7. Data:
For Visit I, demographic, ECG composite (including QT), clinical chemistry, medication survey, sitting blood
pressure, lipid, and TIA/Stroke variables. Derived variables including family history score, disease
prevalence, blood glucose level, hypertension, medication use, alcohol use, obesity, and smoking.