ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #301

1. Title:
Low Heart Rate Variability and Mortality

2. Writing Group:
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3. Timeline:
ECG measurements March 1995 - Feb 1996
Analysis: March 1996, Draft: Summer 1996

4. Rationale:
Decreased heart rate variability (HRV) is accompanied by high risk of sudden death in myocardial infarction patients and in subjects referred for Holter monitoring. Also patients with heart failure, hypertensive cardiovascular disease, and atherosclerosis have been reported to show less HRV than healthy controls. This has been explained by a shift of autonomic cardiac control towards sympathetic dominance. An increase of sympathetic activity, usually with concomitant lowering of parasympathetic activity, leads to reduction of total HRV, primarily in the breathing-related component. Experimental studies have demonstrated that respiratory sinus arrhythmia is parasympathetically mediated. Because sympathetic dominance lowers the ventricular fibrillation threshold, it may be an important factor underlying the observed high risk of sudden death in patients with low heart rate variability.

However, we also recently observed increased risk of non-coronary heart disease mortality, including cancer, in men with low HRV in a 25-year follow-up study of middle-aged Dutch men. Possible explanations include a relation between autonomic nervous system function and immune system function, or low HRV being an indicator of compromised general health.

In the ARIC study extensive information has been collected on risk factors for coronary heart disease, including 2-minute rhythm strips, and follow-up of cause-specific mortality is available. This information may contribute to our understanding of the nature of the association between low HRV and mortality risk.

5. Main hypothesis:
Low HRV is associated with risk of mortality from all causes, including cancer.

6. Data (variables, time window, source, inclusions/exclusions):
Design: (follow-up data): Case-cohort**: Random sample of 1000 men and 1000 women (without prevalent heart disease) and all deaths. Expected: a total of plus or minus 3000. HRV will be taken from the rhythm-strips.

Analysis: As measures of heart rate variability the frequency of the occurence of a difference of more than 50 msec between 2 successive beats, the mean difference of successive intervals, and the standard deviation will be evaluated. The predictive value of each of these derived measures for cause specific mortality will be studied by multivariate survival analysis using poisson regression for the case-cohort design (Schouten).

Other covariates: (Visit 1 data) age, systolic and diastolic blood pressure, Body Mass Index, height, weight, cholesterol subfractions, smoking, physical activity, triglycerides, waist-hip ratio, insulin, glucose, ECG-data,

rhythm disturbances, use of medication (beta-blockers), carotid artery wall thickness, prevalent disease variables

*Incidence data won't be published until released by ARIC.
*This proposal overlaps, in part, with ARIC manuscript #277. However, somewhat different information is obtained by our method, and we will combine the HRV with ECG characteristics taken from this rhythm strip. We intend to compare our results with those of #277, if we have sufficient overlap in our study samples.

**The case-base or case-cohort design is similar to the nested case-control design. The difference between the two is that in the case-cohort design, the referent sample is drawn from the total cohort instead of a non-case sample. The advantage is that this cohort sample can be used for every outcome that is investigated. An additional advantage is the case-cohort design allows the estimation of incidence density ratio's (Schouten, Prentice), in contrast to the case-control design which does not. If the size of this cohort sample is a four or five fold of the number of cases, loss of precision is very low (Miettinen).

REFERENCES:
1. Miettinen OS. Design options in epidemiological research. An update. Scand J Work Environ Health 1982; 8:suppl 1:7-14
2. Prentice RL. A case-cohort design for epidemiologic and cohort studies and disease prevention trials. Biometrika 1986; 73:1-11.
3. Schouten EG, Dekker JM, Kok FJ, le Cessie S, van Houwelingen HC, Pool J, Vandenbroucke JP. Risk ratio and rate ratio estimation in case-cohort designs: hypertension and cardiovascular mortality. Stat in Med 1993; 12: 1733-45