ARIC Manuscript Proposal # 965 (Revised)

PC Reviewed: 11/21/03   Status:    A   Priority:   2
SC Reviewed: 11/24/03   Status:    A   Priority:   1

1.a. Full Title:  Characteristics and Outcome of Troponin Elevation in the Absence of Other Criteria for Myocardial Infarction

b. Abbreviated Title (Length 26 characters): Isolated troponin elev’n

2. Writing Group (list individual with lead responsibility first):

Lead: Teri Manolio, M.D., Ph.D.
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          Writing group members: Sean Coady, Venu Menon, Merle Myerson, Magnus Ohman,
          Camille Pearte, Paul Sorlie, Wayne Rosamond (others more than welcome)

3. Timeline: Analyses will be initiated in fall 2003 and manuscript preparation completed in summer 2004

4. Rationale:

Cardiac troponin is a sensitive and specific marker of myocardial cell necrosis that is replacing creatine kinase MB as the optimal laboratory indicator of myocardial infarction [1]. Given its high sensitivity and strong correlation with irreversible myocardial cell damage [2] troponin has been suggested to identify myocardial necrosis even in the absence of traditional epidemiologic and clinical criteria such as chest pain and electrocardiographic changes [3,4]. Still, troponin elevation is known not to be 100% specific, as several non-ischemic causes have been identified [5]. Although elevated troponin predicts poor outcomes in patients without clearly defined ischemic syndromes [6], its use as a sole diagnostic criterion for myocardial infarction in epidemiologic studies has evoked considerable debate [7], and some have argued against using troponin elevations alone to mandate a diagnosis of MI [2].

Although several studies of patients enrolled in clinical trials suggest an increased risk of death or subsequent MI with troponin elevation in the absence of CK-MB elevation [8] or ST elevation [9], it is not clear whether these patients would have been diagnosed with MI by other clinical and epidemiologic criteria. Data from the Finnish Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (FinMONICA) study, in contrast, failed to demonstrate increased risk related to elevated troponin levels in whom MI is ruled out on other clinical or epidemiologic grounds [10]. Improved laboratory methods have increased the specificity of the measure, potentially reducing the problem of false positives with time [11,12]. Demonstrating that risk of subsequent death in patients with isolated troponin elevations is comparable to that
of patients with MI diagnosed by standard epidemiologic criteria would be a useful indication of
the validity of a troponin-only standard for MI diagnosis.

The ARIC community surveillance component permits comparison of the characteristics and in-
hospital, 30-day, and 1-year mortality of patients with MI by standard epidemiologic criteria [13]
and those with troponin elevations otherwise not meeting ARIC criteria for MI (referred to
hereafter as isolated troponin elevation). This manuscript will:

1) describe the frequency and characteristics of patients with isolated troponin elevation
(with and without “down-coding”), including clinical presentation and reasons for
hospitalization, and compare them to those with ARIC MI and those with neither ARIC
MI nor isolated troponin elevation;

2) describe the in-hospital, 28-day, and 1-year mortality experiences in patients with
isolated troponin elevation and compare them to those with ARIC MI and those with
neither ARIC MI nor isolated troponin elevation; and

3) identify correlates of adverse outcome in those with isolated troponin elevation.

5. Main Hypothesis/Study Questions:

High-risk characteristics at presentation, and subsequent mortality, of patients with isolated
troponin elevation will be less frequent than in patients with ARIC MI but more frequent than in
those with neither ARIC MI nor isolated troponin elevation.

6. Data (variables, time window, source, inclusions/exclusions):

Community surveillance: Hospital information, 28-day and 1-year outcomes from all
surveillance cases with ARIC MI, isolated troponin elevation, and neither ARIC MI nor isolated
troponin elevation, regarding prior CHD, risk factors, condition at presentation, and treatment.
Exploratory analyses show that of 2,385 surveillance cases in which troponin was at least twice
the normal limit (downgraded as necessary by ARIC criteria), 187 or 7.8% had a final diagnosis
of suspected or no MI. Hospital diagnoses of congestive heart failure, sepsis, fluid/electrolyte
abnormalities, and renal failure were more common in these patients when compared to age-sex-
race matched controls with abnormal troponin and ARIC diagnosis of MI.

Cohort: Consider validating findings regarding risk relationships and outcomes in community
data with cohort data, given the richness of these data, the longer extent of follow-up, and the
availability of subclinical disease measures. If the number of isolated troponin elevations is
sufficient in the cohort, utilize comparable data to those available in the communities, plus
cohort data on extent of subclinical disease, prevalence and severity of risk factors, and prior
diagnoses and treatments, to explore the same relationships.

Limitations: Power will be limited in the ARIC cohort and this analysis may not be feasible, but
we would like to explore the possibility. In addition, changing specificity of troponin assays
with time may necessitate adjustment for laboratory method, if such information is available, or
for date of measurement. Down-coding of positive troponins will also complicate analyses; the
impact of down-coding and possible different criteria for applying it, may be able to be explored.
7.a. Will the data be used for non-CVD analysis in this manuscript? __Yes__ __X__ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? __Yes__ __No__
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? __Yes__ __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”? __Yes__ __No__

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://bios.unc.edu/units/cscc/ARIC/study/studymem.html

__X__ Yes _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Manuscript #133, “Serum Enzyme Elevations as Predictors of Mortality after Acute Myocardial Infarction,” is now inactive and the proposers do not appear interested in pursuing the matter further. Manuscript #725, “Prognosis of Hospitalized Myocardial Infarction According to Degree of Injury Assessed by Biochemical Markers and Other Risk Indicators” is also inactive and unlikely to be revisited. Manuscript #713, “Troponin and Event Trends 1987-2000” is well underway and will focus on the impact of increased ascertainment of MI due to troponin assessment. Dr. Rosamond, the lead author on #713, has been involved in developing this proposal and will ensure that overlap is minimal.

11. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References


