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EDITORIAL COMMENT

The Ethnic Rosetta Stone

Translating Risk Factors, Plaque Scores, and Mortality*

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The discovery of the Rosetta stone in 1799 by Napoleon's forces digging a fort in el-Rashid (Rosetta) had a profound impact on translating the lost Egyptian language of hieroglyphics into Greek, a more easily comprehended modern-day language.

Translating population-based cardiovascular (CV) risk factors into individual preventive care paradigms is often like looking at hieroglyphics—to date there are hundreds of factors that can influence personal CV risk, and more appear in the published literature each year. Calculating a Framingham risk point score (1) is a common initial approach to translating these variable factors into an estimation of global CV risk. However, in point of fact, this scoring system merely defines the median risk for a population of similar total point scores, meaning that 50% of the same group is at a higher personal risk and 50% of the same group is at a lower personal risk. This is a partial, but incomplete, translation.

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Coronary artery calcification (CAC) quantification (calcium score) using noncontrast computed tomography has been shown in clinical and pathological studies to provide an "estimation" (partial translation) of the atherosclerotic plaque burden (2–4); furthermore, it has been shown in clinical studies to be incremental to and independent of conventional (Framingham designated) CV risk factors (5–8).

Often these 2 methods of estimating personal CV risk are at odds with each other when individual translations are disparate and in line when individual translations are in accord. Thus, 2 camps are frequently found, one stating that CAC is "no better than risk factors" and the other stating CAC "is better than risk factors." The answer, in my opinion, lies in between, but the more complete translation for an individual requires improvement.

Research has long shown that ethnic factors both dependent and independent of conventional CV "risk factors" play an important role for heart attack and stroke risk in the ethnically diverse population of the U.S. Even socioeconomic factors such as level of primary and secondary education affect long-term CV risk (9). These factors, which likely are amplified by genetics, cannot be reflected or modeled properly into conventional point risk scoring, but may be factors already incorporated into baseline CAC estimates of coronary atherosclerotic plaque burden.

The Framingham risk score was largely (but not exclusively) derived from long-term data on enrollees that were non-Hispanic whites (NHW). To complicate the matter, the prognostic information derived from CAC to date, both as a total score and percentile rank score, was also largely (but not exclusively) derived from long-term data on enrollees that were also primarily NHW. If we have this much confusion in translation for one major ethnic group, then 'heaven help us' in our attempts to translate these hieroglyphics into broad-based ethnic CV risk assessments.

Prior publications on CAC prevalence and scoring from different ethnic groups in the U.S. have been variable. Our original CARDIA (Coronary Artery Risk Development in Young Adults study) publication (10) indicated the prevalence of any CAC in younger populations was highest in African American (AA) men compared with NHW men, and that the prevalence of any CAC was higher in AA women compared with NHW women. A later publication from otherwise healthy and young (age 40 to 45 years) soldiers refuted these finding, saying that CAC was less prevalent in AA than NHW (11), thus casting confusion into the potential value of CAC across ethnic borders. The Dallas Heart study, specifically designed to include 50% AA and 50% NHW, perhaps put these issues to rest by balancing the numbers of subjects included. In that publication (12), the authors found the prevalence of any CAC to be similar in men and women of both ethnic groups. Importantly, the absence of CAC (a "zero" score) in this largely middle-aged population was 62% for AA and 67% for NHW, which is a bit higher than other broad-based studies done in screening populations (~50% with zero scores). The "zero" score has occupied a very important position as study after study demonstrated a low-to-very-low medium-term (3- to 5-year) CV risk, regardless of mitigating risk factors (5–8).

All these epidemiologic data were, however, difficult to resolve in terms of CV prognosis or mortality because, in general, AA have a much higher incidence of nonlipid risk factors including smoking, diabetes, and hypertension; historically, AA have been shown to be at significantly higher overall CV risk than NHW (13) (and other ethnic groups, e.g., Asians and Hispanics). The critical issue is that prior prognostic studies looked at either/or for the independent

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variables of risk factors and CAC and did not really consider the impact on future CV events using both risk factors and CAC.

The Current Investigation

In this issue of the *Journal*, Nasir et al. (14), representing the combined efforts of 5 academic centers, have perhaps given us a glimpse of the ethnic CV risk Rosetta stone scripting data from conventional assessment and plaque imaging (CAC) with regard to long-term all-cause mortality in initially asymptomatic individuals.

In the study under discussion, a total of 14,812 individuals were initially referred by their primary care physicians between 1991 and 2004 for CAC measures using electron-beam computed tomography (EBT). Conventional risk factors, along with primary ethnicity, were determined from patient interview, referring physician contact, and existing medical records. These individuals were followed for all-cause mortality over a mean of 6.8 years (range 0.7 to 14.5 years) through verification via the National Death Index (NDI). The NDI essentially defines mortality as permanent retirement of an individual's social security number. Four risk groups were examined: AA, NHW, Hispanics, and Asians.

The prevalence of a family history of premature disease and hyperlipidemia was highest in NHW, whereas the prevalence of smoking, diabetes, hypertension, and female gender were highest in AA. Coronary artery calcification scores (as estimates of initial plaque burden) were divided into low (0 to 10), mild (11 to 100), moderate (101 to 400), high (401 to 1,000), and very high (>1,000). The prevalence of a low score was 50% in NHW and approximately 60% in AA, Hispanics, and Asians.

Examining all-cause mortality across a decade, a low calcium score consistently demonstrated a low-to-very-low mortality rate across all ethnic subgroups (0.2% to 0.5%/year), consistent with prior published CV event rates using CAC as the primary variable. However, the all-cause mortality data were disparate in the presence of mild to very high CAC scores when looking at each ethnic subgroup. As has been shown in prior studies, the higher the CAC score, the worse the prognosis regardless of ethnicity, but the finding of mild or more CAC in NHW conferred an all-cause mortality of up to one-half that documented for AA, the Hispanics following closely the NHW statistics with Asians showing the least all-cause mortality of all ethnicities.

The Rosetta Stone

How can we "translate" this information into clinical practice? That is, how do these data help make sense of confusing hieroglyphics into understandable Greek? First of all, CAC score is proven again to be a powerful discriminator for individual all-cause mortality and thus CV mortality, regardless of ethnic origin. Additionally, the absence of CAC on EBT scanning described a low-to-very-low risk group, independent of conventional risk factors, but what about the disparity for all-cause mortality with increasing CAC scores, being greatest in AA and least in Asians?

Coronary artery calcification is an estimator of plaque burden; the severity of coronary atherosclerosis regardless of whether it is estimated by the number of stenosed vessels or extent of disease by intravascular ultrasound predicts with increasing severity a higher CV event rate, so the findings of the current investigation are consistent with that principle. However, estimates of plaque burden are not necessarily predictors of plaque instability. The fact that risk factors are predictive of CV events at all lies in the fact that the greater the number of potentially inflammatory influences (including genetic/family predisposition), the greater the likelihood of plaque instability, although influenced as shown in the current investigation by the underlying milieu (i.e., the atherosclerotic plaque burden). The findings are reflected in the higher frequency of no risk factors in the Asians across ethnic subgroups and the higher frequency of ≥3 risk factors (almost double that of Asians) in AA.

This principle underlies the SHAPE (Screening for Heart Attack Prevention and Education) paradigm (15) in which we advocated estimating the atherosclerotic plaque burden (using carotid ultrasound and/or CAC scoring) in an individual first followed by a thorough investigation and therapy of the proinflammatory milieu, guided by the extent of disease, rather than defining risk factors first (conventional approach) and looking for plaque only if the median population risk is intermediate/indeterminate.

As with all translational research, the current study is but one more step in understanding the nature of coronary atherosclerosis and its individual consequences. I look forward to more attempts to unravel the risk factor hieroglyphics into an understandable language applicable to the expanding and complicated kinetics of the American culture.

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