Chronic kidney disease, SPECT, and coronary angiography: “head of gold and feet of clay?”

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“… and as the toes of the feet were part of iron, and part of clay, so the kingdom shall be partly strong, and partly broken.” Daniel 2:42

Chronic kidney disease (CKD) is now well-recognized as an important coronary risk factor and is considered in our preoperative guidelines as a clinical predictor of perioperative death, myocardial infarction (MI), or the development of congestive heart failure. It can be considered as a coronary disease equivalent, such as a history of prior MI, diabetes mellitus, compensated or prior heart failure, or class I or II angina. Moreover, there is extensive data indicating that cardiovascular disease (CVD) is the chief cause of morbidity and mortality in patients with end-stage kidney disease.

This issue of the Journal has an interesting extension of knowledge in the field of CVD in CKD. Coceani et al. examined the relationship among coronary artery disease (CAD), myocardial ischemia, subsequent death and reduced glomerular filtration rate (GFR) in 650 patients undergoing SPECT perfusion imaging and coronary angiography. Not surprisingly, they documented that a reduced GFR was associated with a greater degree of inducible myocardial ischemia, a higher frequency of significant coronary stenoses on coronary angiography and higher mortality at 5 years. However, the fact that this risk extends to patients with even a mild reduction of GFR (mean of 72 mL/minute/1.73 m²) is new and important information.

While the authors are to be applauded for these observational insights, there are some concerns about the interpretation of their findings. The selection of patients for revascularization, which leads to alteration of cardiovascular outcomes and their definition of “coronary artery disease,” both may mislead those who do not absorb the methodological details. Moreover, selection of coronary angiographic evidence of a 70% stenosis as the definition of CAD or greater is problematic for many reasons.

ANATOMY VS PHYSIOLOGY: A GOLD STANDARD WITH FEET OF CLAY?

The recent publication of the Fractional Flow Reserve versus Angiography for Guiding PCI in Patients with Multivessel Coronary Artery Disease (FAME) trial by Tonino et al. documented the importance of physiological rather than anatomic assessment of coronary stenoses prior to revascularization in order to improve outcomes. Like the current report, there were a significant number of deaths and MIs after revascularization in the FAME trial, but far less in the “ischemia-guided” arm, using routine measurement of fractional flow reserve (FFR).

Fractional flow reserve correlates well with SPECT, and the FAME trial confirms what nuclear cardiologists have been preaching for decades: ischemia-producing lesions have a poor prognosis and lesions that do not induce ischemia have a favorable prognosis, and should not undergo revascularization. This is a culmination of a long trail of critically important science in the area for the past 25 years. In this regard, in my opinion, here are the top 10:

- 1984—White et al. demonstrate that visual analysis of coronary angiograms is unreliable, particularly in the assessment of flow reduction and ischemia production.
- 1987—Glagov et al. introduce the concept of outward coronary remodeling from pathologic
specimens, such that “lumenography” cannot be used as a standard for the presence of mild or moderate CAD, but rather as a measure of severe disease which late in the process encroaches upon the lumen, producing stenoses only when the capability for remodeling is overcome by a massive focal plaque burden.

- 1993—Iskandrian et al.\(^9\) publish that major adverse cardiac events are predicted better by SPECT than by visually analyzed coronary angiograms, and that there was no incremental prognostic value of angiographic data over the SPECT perfusion data, thereby making SPECT a better “gold standard” for patient management.

- 1995—Topol and Nissen\(^10\) confirm in vivo the “Glagov Phenomenon” of coronary remodeling using intracoronary ultrasonography, and emphasize the limitations of clinical decision making based upon “luminology.”

- 1995—Falk et al.\(^11\) analyze data from multiple trials and conclude that the majority of MIs are associated with non-flow limiting, unstable plaques; specifically, using “greater than 70% stenosis” as a definition of CAD would miss the location of 86% of subsequent infarctions.

- 2000—Schachinger et al.\(^12\) confirm that provocative testing with intracoronary acetylcholine to demonstrate flow limiting endothelial dysfunction is superior to routine lumenography in predicting patient outcomes.

- 2002—Shaw et al.\(^13\) demonstrate that “ischemia-guided angiography” using SPECT is more cost effective than routine angiography in patients with stable chest pain.

- 2003—Hachamovitch et al.\(^14\) observed that patients with smaller degrees of reversible ischemia on SPECT perfusion imaging had a survival advantage with medical therapy rather than revascularization, while those with larger amounts of ischemia (>12% of the myocardium) were more likely to benefit from the invasive procedures.

- 2004—von Mering et al.\(^15\) added that women in the WISE trial with “false positive” noninvasive studies, such as SPECT perfusion imaging, leading to coronary angiography showing “no significant” stenoses, often had endothelial dysfunction documented in the cath lab with adenosine or acetylcholine infusion; impaired coronary vasomotor function was linked to adverse cardiovascular outcomes regardless of coronary angiography anatomic findings.

- 2009—The FAME trial\(^5\) confirms the prognostic impact of physiologic assessment to document ischemia prior to performing revascularization.

These data are compelling and its implications are critical for our field. We should no longer use coronary lumenography, without accompanying physiological assessment of ischemia, as an indicator of the accuracy of tests for ischemia, such as SPECT perfusion imaging, or as the best available evidence for how well patients will fare with revascularization in addition to medical therapy.

**CORRELATION WITH OUTCOMES: SELF-FULFILLING PROPHECY?**

In this report, Coceani et al. used the “70%” stenosis on angiography as the arbiter of CAD, and found that this correlated with outcomes better than SPECT ischemia. While they explain their findings as possible “post-test referral bias” or inclusion of only patients with SPECT evidence for ischemia, there are other factors that must be considered.

First, if successful, a test can be judged by its downstream impact on patient outcomes. The clinicians caring for these patients were not blinded to the noninvasive study results, and presumably aggressively medically managed patients with ischemia, such that one cannot simply measure the correlation of SPECT and subsequent death, but rather SPECT-followed-by-medical-therapy and subsequent death.

Second, there were patients with only mild-to-moderate degrees of ischemia, based on their summed difference scores (SDS, maximum was 8, corresponding to 11.8% ischemic myocardium). No patients reached the Hachamovitch criterion\(^14\) of >12% myocardial ischemia. In this population, there should be a relative few events expected over a 5-year period, particularly with aggressive medical management.

This concept is further confirmed by the correlation of the summed stress score (SSS) with subsequent death in the Coceani study, similar to their other independently correlating variables, age and ejection fraction. SSS reflects both ischemia and myocardial scarring, with the degree of scarring is less modifiable with treatment. The ejection fraction is similarly less modifiable when there is little reversible ischemia. In sum, milder degrees of ischemia and measurement of therapeutic impact impairs the correlation of SDS with subsequent death, while the inexorable consequences of age and myocardial scarring, the latter expressed by a higher SSS and/or reduced ejection fraction, will indeed correlate with a poor outcome.

Finally, since the degree of ischemia in their population was only mild-to-moderate, in many institutions, many of these patients would not have undergone coronary angiography, and would not have the consequent “oculo-stenotic reflex” induced revascularizations. Revascularization of such patients could potentially lead...
to subsequent restenosis (angina) or acute stent thrombosis (infarction) that may not have occurred with aggressive medical management. From a statistical viewpoint, this would increase the apparent “prognostic” value of the finding of “CAD” on coronary angiography, a self-fulfilling prophecy. Thus, again, one cannot simply measure the relation between angiography and outcomes here, but rather the correlation between angiography-followed-by-intervention and subsequent outcomes.

**CONCLUSIONS**

Coceani et al. report that mild reductions in GFR may be associated with an increase the prevalence of CAD, and that coronary angiographic definition of CAD as a >70% stenosis correlates with subsequent death, better than SPECT indices in patients with mild-to-moderate degrees of ischemia.

While this is not a totally unexpected result, the methods within their message serve as a reminder that in mature clinical specialties, such as nuclear cardiology and coronary angiography, with clear patterns of post-test clinician behavior, the test results can drive interventions that obscure correlation between the original test results and the ultimate patient outcome.

Furthermore, it reminds us that we should continue to push for evidence-based selection of any “gold standard.” In this era when multimodality appropriateness criteria and comparative effectiveness data may ultimately determine our diagnostic testing patterns, we should not continue to sell SPECT short, and should even avoid using the terms “sensitivity and specificity” relative to invasive coronary angiographically defined CAD.

Indeed, invasive coronary angiography still retains its “golden head” when used as a technical guide for intervention, e.g., the size and length of an intracoronary stent. However, until physiological assessments are routinely performed in the catheterization laboratory, invasive angiography will always have “clay feet” in the determination of the intervention worthiness of coronary stenoses. This should be the role reserved for SPECT myocardial perfusion imaging and other methods of identifying the presence of reversible myocardial ischemia.

**References**