The role of stress testing in the noninvasive evaluation of patients with possible or known coronary artery disease has evolved from functioning as a diagnostic tool to serving primarily as an aid in risk stratification. The results of clinical assessment and stress testing can be combined to estimate individual patient risk and guide subsequent treatment. National guidelines recommend that stress imaging preferentially be performed instead of standard exercise testing in patients with characteristics consisting of inability to exercise adequately, uninterpretable exercise ECG, or previous coronary artery disease revascularization. Aside from these patient subsets, controversy persists concerning the selection of a stress test modality attributable to uncertainty concerning the incremental prognostic value of stress imaging compared with standard exercise testing.

For nuclear myocardial perfusion gated SPECT (MPGS), patient risk can be determined simply by dichotomizing images as normal/abnormal, but risk stratification can be refined by categorizing the images on the basis of summed perfusion scores. These scores include the summed stress score, which is a reflection of the extent and severity of combined infarction and ischemia, and the summed different score, an indicator of the extent and severity of ischemia.

In this issue of Circulation: Cardiovascular Imaging, Candell-Riera et al report on the prognostic value of exercise MPGS in 5672 patients with known or suspected coronary artery disease. The authors apply the c-statistic, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) to examine the incremental prognostic value of MPGS compared with clinical and exercise test variables for predicting the end points of all-cause death and the major cardiovascular end point of combined cardiovascular death and nonfatal myocardial infarction. The authors report 2 major findings: (1) predictive accuracy significantly increased by adding exercise variables to clinical variables for both end points; (2) adding MPGS to the model containing clinical-exercise variables significantly improved predictive accuracy for the cardiovascular end point but not for the end point of overall mortality.

In view of the abundant literature examining the prognostic value of stress MPGS, why publish another article on this topic? The major contribution of the article by Candell-Riera et al is the application of NRI and IDI. The standard approach of examining the association between a variable of interest (in this case MPGS) and clinical outcome consists of applying a series of tests of increasing statistical rigor. The first test determines whether a statistically significant association exists by using simple univariable analysis. The second test evaluates the independent prognostic value of the variable of interest in comparison with other known important prognostic variables in a multivariable model by selecting variables according to strength of association with the end point in a stepwise fashion. The third test examines the incremental prognostic value of the variable. The concept of incremental modeling was introduced by Ladenheim et al and replicates clinical decision-making. The first step includes creating a model containing only clinical variables. In this process, the next step determines whether stress testing variables improve predictive accuracy compared with accuracy provided by the clinical variables alone. The third step examines whether imaging variables add to the value of the clinical-stress test model. Global model \( \chi^2 \) values are calculated at each step. If there is a statistically significant increase in the global \( \chi^2 \) value progressing from 1 model to the next, then the conclusion is that the addition of these variables has added incremental value. The area under the receiver-operating characteristic curve and associated c-statistic can be determined for each model. This approach is well established and has become the standard by which the majority of recent studies have been performed, examining the prognostic accuracy of MPGS compared with standard exercise testing. The results convey important information to the reader, including identification of the variables in each statistical model which contain the most important prognostic information and illustrating whether a model containing MPGS variables is significantly better for predicting outcome compared with the clinical-exercise model. Although an improvement in the global model \( \chi^2 \) or c-statistic can be interpreted as a positive finding, this approach fails to convey clinically important information to the reader. These results do not indicate what percentage of the study population is reclassified as higher or lower risk using MPGS and whether the reclassification results primarily from accurately identifying more high-risk or more low-risk patients. Comparing predictive accuracy between 2 models using NRI and IDI can...
provide this information. Additionally, the results of NRI can
demonstrate how many patients are shifted into different clinical
risk categories (low, moderate, high) by using a different model. The application of these principles is illustrated in the
article by Candell-Riera et al. These authors show the con-
ventional results of their study in Table 1 (univariable associa-
tions between clinical, exercise, and MPGS variables and outcome end points), Table 2 (important variables in each of
the respective multivariable models), and Figure 2 (receiver-
operating characteristic curves and c-statistic results). The
more novel results from applying NRI and IDI are provided
in Figure 3 and Table 3. Figure 3 illustrates the percentage
of the population that is reclassified comparing each model
with the previous model. The $P$ values associated with NRI
and IDI indicate whether the reclassification was statistically
significant. An important result to notice is the reclassification
exercise results in some patient reclassifications that are incor-
rect. Figure 3A demonstrates for the end point overall mortal-
ity that the addition of MPGS to the clinical+exercise model
actually results in more patients being incorrectly reclassi
fied. For patients who died, 4.3% were incorrectly reclassi
fied as lower risk, whereas 3.3% were correctly reclassified
as higher risk, resulting in a net 1% of the population being
incorrectly reclassified. Conversely, for patients who survived,
the addition of MPGS resulted in 7.8% being correctly reclassi
fied and 5.1% being incorrectly reclassified, yielding a net
of 2.7% correctly reclassified. Overall, 1.7% of the popula
tion was reclassified (2.7%–1%), but this small difference was
not statistically significant (NRI=0.017; $P=NS$). For the end
point cardiovascular death and nonfatal myocardial infarction
(Figure 3B), the value of adding MPGS to clinical+exercise
variables was more favorable. Overall 12.2% of the popula
tion was correctly reclassified (2.7% correct reclassifications
for patients with events, 9.5% correct reclassifications for
patients without events). The NRI was 0.122 ($P<0.05$)
and IDI 0.033 ($P<0.001$). Table 3 illustrates shifts between
risk categories (low, moderate, high) determined by these 2
models. In this table, the correct reclassifications are shown
in the cells shaded gray. An important observation is that the
major effect of applying NRI and IDI is correctly reclassify-
ing low-risk patients, primarily by shifting patients who do
not experience events from the moderate-risk category to the
low-risk category, rather than correctly identifying more high-
risk patients. For instance, for the cardiovascular mortality or
myocardial infarction end point, the addition of MPGS to the
clinical+exercise model resulted in 966 patients (671+295)
without an event being correctly reclassified as lower risk,
whereas only 24 patients (1+23) with an event were cor-
rectly reclassified as higher risk. Because the addition of
MPGS resulted in some incorrect reclassifications, the num-
ber of patients with an event who were classified as high-risk
increased very modestly from 86 using the exercise model to
96 using the MPGS model.

Candell-Riera et al also include cost estimates (and appro-
priately recommend cautious interpretation) for each reclas
sification of $4078.00 for the cardiovascular end point and
$12480.00 for the mortality end point. The reader should
appreciate that the major benefit of this additional cost of
applying MPGS instead of exercise testing alone in the entire
population is correctly identifying low-risk patients. These
cost estimates reflect only the cost of imaging and do not
address the cost of invasive downstream procedures, such as
coronary angiography or revascularization. Even assuming
that the correct reclassification of some patients into a higher-
risk category could lead to an intervention that could be life-
saving, the cost per year-of-life-saved would be substantially
higher than the imaging costs of reclassification provided by
Candell-Riera. The concept of applying nuclear imaging for reclassify-
ing patient risk is not new. More recently, this concept
has been popularized through the work of Pencina et al and
the introduction of the terms NRI and IDI. Only a handful
of recent nuclear cardiology publications have applied this
approach. The present study by Candell-Riera et al can be
added to this small group of important studies.

The application of NRI and IDI provides a superior method
for analyzing the incremental value of performing a presum-
bably better technique in place of a less accurate technique. In
contrast to the traditional but more abstract concepts of com-
paring global $\chi^2$ and c-statistic values, this new methodology
illustrates the percentage of a population that is accurately
reclassified, providing clinically meaningful results rather
than only statistically significant differences between $\chi^2$
and c-statistic values. The results of reclassification can be
especially useful to address questions related to cost-effectiveness.
For low-risk patients, can enough patients be accurately
reclassified as low-risk to avoid unnecessary catheterizations
and revascularization procedures to offset the initially higher
cost of performing MPGS versus exercise testing alone in
the population? For high-risk patients, can enough high-risk
patients be accurately reclassified to justify the higher cost of
MPGS versus exercise testing according to accepted standards
expressed as the cost per year-of-life-saved? NRI and IDI have
been applied to other areas besides stress imaging and should
represent the new standards to judge the incremental risk
stratification accuracy added by more expensive technologies
versus less expensive techniques.

Disclosures

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