Statistical Analysis of Noncommensurate Multiple Outcomes

Armando Teixeira-Pinto, PhD; Laura Mauri, MD, MSc

Abstract—Many studies collect multiple outcomes to characterize treatment effectiveness or evaluate risk factors. These outcomes tend to be correlated because they are measuring related quantities in the same individuals, but the common approach used by researchers is to ignore this correlation and analyze each outcome separately. There may be advantages to consider the simultaneous analysis of the outcomes using multivariate methods. Although the joint analysis of outcomes measured in the same scale (commensurate outcomes) can be undertaken with standard statistical methods, outcomes measured in different scales (noncommensurate outcomes), such as mixed binary and continuous outcomes, present more difficult challenges. In this article, we contrast some statistical approaches to analyze noncommensurate multiple outcomes. We discuss the advantages of a multivariate method for the analysis of noncommensurate outcomes, including situations of missing data. A real data example from a clinical trial, comparing bare-metal with sirolimus-eluting stents, is used to illustrate the differences between the statistical approaches.


Key Words: noncommensurate outcomes ■ multivariate methods ■ missing data ■ statistical methods ■ joint modeling

Clinical trials and observational studies involving multiple outcomes are common in cardiovascular research. Disease complexity is often not adequately characterized by a single outcome, and several aspects of the patient’s response, either to a treatment or to a risk factor, must be considered. The concept of multiple outcomes applies to repeated or longitudinal measurements of a specific variable, such as systolic blood pressure, and to measurements of different variables in the same individual, such as target lesion recanalization, binary restenosis, and diameter stenosis after coronary stenting. Statistical methods for repeated measures and longitudinal data comprising multiple observations of a single variable are well established, and there is vast literature addressing both theoretical and applied aspects of the method. Recently, 2 articles1,2 published in the Statistical Primer for Cardiovascular Research series have focused on methods for the analysis of such data. In this article, we will focus on the setting where different response variables are measured in the same individual and the term multiple outcomes will be used in this context.

Background

One of two statistical strategies is usually adopted for the analysis of multiple outcomes. Either the outcomes are combined into a single composite end point using a variety of pooling rules and scoring algorithms or, alternatively, the outcomes are analyzed separately using univariate statistical tools for each outcome.

Several types of composite end points exist, such as taking a simple average of the outcomes or using conjunctive or compensatory rules.3,4 An example of the latter commonly used in cardiovascular research is the major adverse cardiac event end point. The major adverse cardiac event is defined as the occurrence of 1 of the following clinical events: all-cause mortality, nonfatal myocardial infarction, target lesion recanalization, or target vessel revascularization. The pooling strategy has the disadvantage of reducing the information collected and potentially attenuating important features of the data. For example, 2 interventions may present no differences in the composite end point major adverse cardiac event, but they can have different mortality rates that would be masked by grouping the outcomes. Another major drawback of pooling multiple measurements is that it fails when the outcomes are of different natures or are measured on different scales (ie, noncommensurate outcomes). For example, combining a binary outcome (eg, the presence of a symptom) and a continuous outcome (eg, a well-being score) would require dichotomization of the continuous outcomes and a consequent waste of information. Finally, any missing observations in 1 of the outcomes may reduce the sample size if a complete case analysis is adopted or even produce biased estimates if the missing mechanism is dependent on the other outcomes.5

Analyzing each end point separately does not require the outcomes to be measured on the same scale because each outcome is treated independently of the others. Although the simplicity of such an approach is appealing, the correlation...
between the outcomes is effectively ignored. This could result in a loss of efficiency in the analysis, leading to lower power to detect treatment effects (or the effect of other covariates of interest) and larger CIs for the estimates. Also, if some outcomes are missing, separate analyses may produce biased estimates of the covariate effects on the outcomes. Finally, when several outcomes are clinically related, one might want to combine all the evidence of treatment effect into a single global test of significance. This test would provide an overall statement to declare whether there are any differences between the treatments before proceeding to the individual tests for each outcome; however, separate analyses do not provide such a global test. Furthermore, testing of the treatment effect for each outcome will increase the probability of a significant result by chance (type I error), which usually requires adjusting the significance level for multiple testing.

An alternative strategy, for the analysis of multiple outcomes using multivariate methods, can also be considered. These methods present, at least from a conceptual point of view, the appropriate and natural statistical framework for this type of problem and may overcome some of the problems previously described. However, multivariate approaches have been rarely used in observational studies or clinical trials, with the exception of repeated-measures or longitudinal studies in which multivariate methods, such as mixed models and generalized estimating equations, are commonly used. In this tutorial, we present a multivariate method that simultaneously analyzes all outcomes by accounting for their correlations, while allowing mixtures of different types of outcomes (eg, binary and continuous outcomes). Other approaches have been proposed to analyze noncommensurate outcomes in a multivariate framework, with some limitations regarding the settings where they can be applied. In section 2, we introduce a real-data example that will be used throughout the article. In section 3, we present the multivariate model and contrast the findings using individual analysis of the outcomes with those using multivariate methods; in section 4, we provide the software code to fit the multivariate model. We conclude in section 5 with some general recommendations.

1. Restenosis After Coronary Stenting Using Bare-Metal and Sirolimus-Eluting Stents

Data used in this tutorial arise from the Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions (SIRIUS) trial, which compared bare-metal with sirolimus-eluting stents. We are interested in estimating the treatment effect and identifying the baseline risk factors predictive of poor outcome after the stenting procedure.

Patients at risk for coronary restenosis were randomized to standard bare-metal or sirolimus-eluting stenting. Several baseline characteristics were recorded, but in this example, we will limit the analysis to patient’s age, clinical history (diabetes and prior myocardial infarction), and angiographic pre-stenting characteristics (length of lesion, reference vessel diameter, minimum lumen diameter, and diameter stenosis). In addition, the covariate group identifies the enrollment arm (bare-metal or sirolimus-eluting stent) of each patient.

Three outcome variables, 1 measured 1 year after stenting and 2 measured at 9 months after stenting, are considered for this example:

1. Any clinically driven repeat percutaneous intervention, denoted as target lesion revascularization (TLR), during the first year after stenting. A clinical events committee that had access to clinical and angiographic laboratory data designated the TLR. This is a binary outcome, and it was observed in all patients.

2. Binary restenosis (BR) was defined as 50% diameter stenosis at 9 months after stenting. The percentage of diameter stenosis was computed as follows: 1-(minimum lumen diameter/reference vessel diameter). Binary restenosis is a binary outcome, and it was only assessed in a subgroup of patients who had follow-up angiography planned according to study protocol.

3. Late lumen loss (LL) is the difference between the diameters of the stented segmented right after the stenting procedure and the follow-up angiogram at 9 months. This is a continuous outcome measured in the subgroup of patients who had follow-up angiography planned according to study protocol.

A total of 1052 patients were enrolled in the trial. Twenty-six observations (2.5%) were excluded from this analysis because of missing values in some of the covariates, leaving 1026 patients to be analyzed. In addition, according to the trial protocol, only the first 850 patients enrolled in the trial were chosen for angiographic follow-up at 9 months. For several reasons, the angiographic follow-up was performed in only 699 of these patients. Although the initial choice of patients for follow-up should not represent a source of selection bias, the same may not be true for the actual observed data, for which 151 patients failed to complete the follow-up protocol. Therefore, there are no guarantees that the 699 patients with follow-up represent an unbiased sample of the patients enrolled in the trial. In summary, TLR was assessed for 1026 patients, but BR and LL were available in only 699 patients.

Another important characteristic of these data is the strong correlation observed between the outcomes. The correlation between TLR and BR is 0.70; TLR and LL, 0.60; and BR and LL, 0.72. Table 1 provides some general description of the variables used in the example for each arm of the trial.

This analysis does not intend to be a thorough analysis of the SIRIUS data; instead, it intends to be a didactic example of application of the joint modeling approach to multiple noncommensurate outcomes.

2. Statistical Methods

2.1. Separate Analyses of Each Outcome

As previously discussed, 1 common statistical approach to studies with multiple outcomes is to analyze each outcome separately by modeling each outcome as a function of the covariates of interest. The regression models depend on the type of the outcome that is being modeled. For example, for continuous outcomes, a linear regression model is typically assumed, whereas for binary outcomes, logistic or probit
regression models are common choices. Some model-building strategy may be used to select the covariates that are associated with each outcome, such as stepwise selection.

For TLR and BR, both binary outcomes, we use a logistic regression to estimate the crude and adjusted odds ratio (OR) of the covariates. For the continuous outcome, LL, we choose a linear model. For each regression, we used backward stepwise selection to select the covariates significantly associated with the outcomes. Results for each outcome are presented in Tables 2, 3, and 4. Patients in the bare-metal stent group, with a clinical history of diabetes and a previous episode of myocardial infarction had higher loss in the lumen at 9 months after stenting. Age and minimum lumen diameter were negatively associated with LL (Table 5).

### 2.2. Multivariate Approach Using a Latent Variable

Rather than modeling each outcome separately, a multivariate approach that models the 3 outcomes in a similar way as the separate models discussed in section 3.1 but that also accounts for the correlation between the outcomes should be considered. Why would an investigator want to adopt this analytic strategy? When the study outcomes have no missing values (or they are missing completely at random), analyzing each outcome separately will provide unbiased estimates for the treatment effects, even if the outcomes are correlated. In this case, the separate models for each outcome will give correct effect estimates of the covariates but some may have larger SEs than if the correlations among outcomes were considered.13

One exception to this last point is the situation of multivariate linear regression, when all the outcomes are modeled using the same set of covariates, with complete observations for all subjects. In this case, the correlation between the outcomes does not improve the precision of the estimates, and the results of the multivariate model are the same as fitting individual linear regressions.13 However, this is not the case when some of the outcomes are not continuous and we have to use a nonlinear model, such as the logistic model.14 In any case, with sufficiently large sample sizes, investigators may not be concerned, so that the tradeoff between simplicity of the analysis procedure and larger errors might favor the simple one-outcome-at-a-time approach.

However, what happens in the more common case when data are missing in some of the outcomes? In the SIRIUS data, not all the patients underwent angiography at 9 months. Therefore, the binary restenosis and late luminal loss were not assessed for these patients. In addition, there were twice as many patients with no angiographic measures at 9 months in the group of patients with no TLR than in the group with TLR (36% versus 18% for a total of 897 and 129 in each group, respectively; table 2). This unbalance of missing data suggests that the effects computed in the individual analysis of each outcome may be estimated with bias. By modeling all the outcomes jointly, we may be able to correct for this bias through the correlation between the outcomes obtained from the complete cases, in which all the outcomes are observed.5 There are several other alternatives to deal with missing data, such as the use of propensity scores or imputation methods (a recent review of such approaches was published in a series of statistical interpretation of methods).9

When the outcomes are measured in the same scale (commensurate outcomes), there are some modeling options

### Table 1. Descriptive Statistics for the Variables Involved in the Analysis of the SIRIUS Data Used in the Example

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (N=1026)</th>
<th>Sirolimus Eluting (n=519)</th>
<th>Bare Metal (n=507)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.2 (11.0)</td>
<td>62.0 (11.2)</td>
<td>62.3 (10.9)</td>
</tr>
<tr>
<td>Clinical history*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>314 (31)</td>
<td>146 (28)</td>
<td>168 (33)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>270 (26)</td>
<td>127 (24)</td>
<td>143 (28)</td>
</tr>
<tr>
<td>Pre-stent angiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of lesion</td>
<td>14.4 (5.8)</td>
<td>14.4 (5.8)</td>
<td>14.4 (5.8)</td>
</tr>
<tr>
<td>Reference vessel diameter</td>
<td>2.8 (0.5)</td>
<td>2.8 (0.4)</td>
<td>2.8 (0.5)</td>
</tr>
<tr>
<td>Minimum lumen diameter</td>
<td>1.0 (0.4)</td>
<td>1.0 (0.4)</td>
<td>1.0 (0.4)</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td>65.4 (12.4)</td>
<td>65.1 (12.7)</td>
<td>65.6 (12.1)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target lesion revascularization*</td>
<td>129 (13)</td>
<td>26 (5)</td>
<td>103 (20)</td>
</tr>
<tr>
<td>Restenosis*</td>
<td>133 (19)</td>
<td>11 (3)</td>
<td>122 (36)</td>
</tr>
<tr>
<td>Late LL, mm</td>
<td>0.5 (0.6)</td>
<td>0.2 (0.5)</td>
<td>0.8 (0.7)</td>
</tr>
</tbody>
</table>

Data are given as the mean (SD) unless otherwise indicated. Of the initial 1092 patients randomized for Sirolimus-eluting or bare metal stenting, 28 observations were excluded from this analysis because of missing data.

* Data are given as number (percentage) of each group.

### Table 2. Distribution of Missing Data in BR or Late LL According to the Diagnosis of TLR (N=1026)

<table>
<thead>
<tr>
<th>Target Lesion Revascularization</th>
<th>No Missing Data on BR and Late LL (n=684)</th>
<th>Missing Data on BR or Late LL (n=342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>578 (64)</td>
<td>319 (36)</td>
</tr>
<tr>
<td>Yes</td>
<td>106 (82)</td>
<td>23 (18)</td>
</tr>
</tbody>
</table>

Data are given as number (percentage) of each group.
available to researchers. For example, for normally distrib-
uted outcomes, we can use a multivariate linear regression;
for multiple binary outcomes, we can use a generalized linear
mixed model.\textsuperscript{10,16,17} However, with outcomes that are not
measured on the same scale (noncommensurate outcomes),
there is no simple approach to model these outcomes in a
multivariate fashion. The difficulty arises because there is no
obvious way to express the multivariate distribution for the
mixed type of outcomes.

What can be used instead? The main trick is to include a
common unobserved (or latent) variable for all the regression
equations or, using the mixed-models terminology, a random
intercept common to all the outcomes. This latent variable
establishes the link between the regression equations: the
outcomes are measured on the same individuals so the latent
variable induces the needed correlations among the outcomes.

We assume the latent variable completely specifies the
correlation among the outcomes (ie, given the latent variable,
the outcomes are assumed to be independent). This permits
examination of the outcomes as independent of each other by
accounting for the correlation through the latent variable.\textsuperscript{5,14}

The latent variable is assumed to have a normal distribu-
tion with mean 0 and some variance, and it has to be scaled
(multiplied by a value that has to be estimated) for each
outcome to accommodate the different nature of the out-
comes. One restriction regarding the correlation is that the
outcomes have to be positively correlated. If some of the
correlations are negative, they can easily be changed to
positive by inverting the outcome scale or, in the case of
binary outcomes, by reversing the coding of the 2 categories.

Also, if the number of outcomes being analyzed simulta-
neously is \( >3 \), this approach assumes some structure in the

\begin{table}
\centering
\caption{ORs for the Association Between Covariates and the Binary Outcome, TLR}
\begin{tabular}{llllll}
\hline
Variable & Unadjusted Estimates (I) & & Separate Regressions (II) & & Multivariate Latent Variable Model (III) \\
& OR (SE) & \( P \) Value & OR (SE) & \( P \) Value & OR (SE) & \( P \) Value \\
\hline
Stent group (bare metal vs sirolimus eluting) & 4.89 (1.12) & <0.001 & 5.23 (1.23) & <0.001 & 3.54 (0.70) & <0.001 \\
Age & 1.00 (0.01) & 0.984 & \ldots & \ldots & \ldots & \ldots \\
Clinical history & & & & & & \\
Myocardial infarction & 1.36 (0.27) & 0.123 & \ldots & \ldots & \ldots & \ldots \\
Diabetes & 1.89 (0.37) & 0.001 & 1.73 (0.36) & 0.008 & 1.59 (0.31) & 0.017 \\
Pretest angiography & & & & & & \\
Length of lesion & 1.04 (0.02) & 0.015 & 1.04 (0.02) & 0.012 & 1.02 (0.01) & 0.092 \\
Reference vessel diameter & 0.56 (0.12) & 0.007 & \ldots & \ldots & \ldots & \ldots \\
Minimum lumen diameter & 0.63 (0.63) & 0.064 & 0.15 (0.09) & 0.002 & 0.14 (0.08) & <0.001 \\
Diameter stenosis & 1.01 (0.01) & 0.472 & 0.95 (0.02) & 0.006 & 0.95 (0.01) & <0.001 \\
\hline
\end{tabular}
\end{table}

In model I, unadjusted ORs for each covariate were obtained by individual logistic regressions for each covariate; in model II,
separate regressions, adjusted ORs were obtained by a logistic model with selected covariates (backward stepwise with remove criteria \( P>0.1 \)); and in model III, multivariate latent variable model, adjusted ORs were obtained for the same covariates selected in model II but the TLR was modeled jointly with 2 other outcomes, BR (Table 4) and late LL (Table 5).

\begin{table}
\centering
\caption{ORs for the Association Between Covariates and the Binary Outcome, BR}
\begin{tabular}{llllll}
\hline
Variable & Unadjusted Estimates (I) & & Separate Regressions (II) & & Multivariate Latent Variable Model (III) \\
& OR (SE) & \( P \) Value & OR (SE) & \( P \) Value & OR (SE) & \( P \) Value \\
\hline
Stent group (bare metal vs sirolimus eluting) & 17.15 (5.59) & 0.002 & 18.16 (6.04) & <0.001 & 11.43 (2.83) & <0.001 \\
Age & 0.99 (0.01) & 0.496 & \ldots & \ldots & \ldots & \ldots \\
Clinical history & & & & & & \\
Myocardial infarction & 1.31 (0.27) & 0.180 & \ldots & \ldots & \ldots & \ldots \\
Diabetes & 2.34 (0.47) & <0.001 & 1.73 (0.36) & <0.001 & 1.89 (0.41) & 0.004 \\
Pretest angiography & & & & & & \\
Length of lesion & 1.04 (0.02) & 0.015 & 1.05 (0.02) & 0.012 & 1.04 (0.02) & 0.024 \\
Reference vessel diameter & 0.71 (0.15) & 0.407 & 0.57 (0.14) & 0.012 & 0.54 (0.10) & 0.001 \\
Minimum lumen diameter & 0.62 (0.16) & <0.001 & \ldots & \ldots & \ldots & \ldots \\
Diameter stenosis & 1.01 (0.008) & <0.001 & \ldots & \ldots & \ldots & \ldots \\
\hline
\end{tabular}
\end{table}

In model I, unadjusted ORs for each covariate were obtained by individual logistic regressions for each covariate; in model II,
separate regressions, adjusted ORs were obtained by a logistic model with selected covariates (backward stepwise with remove criteria \( P>0.1 \)); and in model III, multivariate latent variable model, adjusted ORs were obtained for the same covariates selected in model II but the BR was modeled jointly with 2 other outcomes, TLR (Table 3) and late LL (Table 5).
correlation between the outcomes. However, in our experience, this structure is flexible enough to accommodate most practical situations in which the number of outcomes is not large.

In the SIRIUS data example, the multivariate model using a latent variable becomes

\[
\begin{align*}
\logit(P(TLR = 1|u)) &= a_1 + b_{1\text{group}} + \ldots + u \\
\logit(P(BR = 1|u)) &= a_2 + b_{2\text{group}} + \ldots + \lambda_3 u \\
\text{LL}|u &= a_3 + b_{3\text{group}} + \ldots + \lambda_3 u + \varepsilon,
\end{align*}
\]

where \( \varepsilon \sim N(0, \sigma^2_{\text{LL}}) \).

The notation "|u" indicates that the models are conditional on the latent variable, \( u \), which is inducing the correlation between the 3 outcomes. The coefficients \( \lambda_2 \) and \( \lambda_3 \) represent the scaling factor for each outcome. The scale factor for 1 of the outcomes (in this case, for TLR) can be fixed to be 1, meaning that the latent variable \( u \) will be in the appropriate scale for this outcome and has to be scaled for the other outcomes.

For the joint analysis, we used the same covariates selected in the separate analysis to facilitate the comparison of the methods. However, a characteristic that has not been fully exploited in the statistical literature is the potential benefit of selecting the covariates, usually referred to as model building, by considering all the outcomes at the same time.

Another advantage of the multivariate approach is the possibility of testing for a global treatment effect on the outcomes (ie, testing if the treatment has an effect on any of the outcomes), as suggested for trials with multiple outcomes.8 For example, in the SIRIUS trial, we might be interested in answering the following question: “Is there a difference between the 2 types of stents in any of the outcomes (TLR or BR or LL)?” In statistical notation, this would mean to test the null hypothesis \( H_0: b_1 = b_2 = b_3 = 0 \). In this case, the global test is highly significant (\( P<0.001 \)), indicating that the 2 types of stents have a different effect on, at least, 1 of the outcomes. This test is usually more powerful than individual tests for a treatment effect on each outcome. Also, multiple individual testing carries the problem of inflating the type I error, which typically requires some adjustment to the significance level, such as the Bonferroni correction.

### 2.3. Interpretation of the Regression Parameters

The regression equations used in the latent variable approach are conditional on the latent variable. For this reason, the regression parameters in the latent variable model also have to be interpreted somewhat differently than when fitting separate models. However, investigators are most interested on the unconditional effects, similar to the usual interpretation in regression models. For the continuous outcomes, the regression parameters can be interpreted in the same manner as those from a separate analyses approach. For the binary outcomes, this is not the case; in particular, for the logistic model, we can only approximate the unconditional effects. A similar situation has been largely debated in the literature of mixed models under the topic of population-average and subject-specific effects.18 To compute the effects that are approximately comparable to those obtained from a separate analysis, the regression coefficients are divided by the square root of 1+(0.346 times the variance of the latent variable) and the SEs are computed accordingly. The justification for this transformation is based on the approximation between the logistic and the probit function, and it is beyond this tutorial; however, interested readers should consult Hu et al18 for more on this topic.

In Tables 2 and 3, the coefficients for the multivariate model are already transformed and can be compared with the results obtained by modeling each outcome independently. Some of the estimated effects are different in the approach in which the 3 outcomes are modeled individually and the approach that accounts for the correlation between them and models the outcomes jointly. For example, for the need of TLR, the estimated OR for metal versus sirolimus-eluting stents was 5.23 in the separate modeling approach and 3.54 in
the multivariate approach. One possible explanation for this difference is that the separate analysis ignores the unbalanced proportion of missing data, whereas the multivariate approach will consider it (Table 2).

In Tables 2 through 4, several SEs associated with the ORs decreased when the outcomes were modeled jointly. This can be explained by the extra information contained in the correlation between the outcomes that is effectively ignored in the individual analysis of the TLR, BR, and LL. Some P values increased in the joint analysis, which may seem to be in contradiction with the reduction of the SEs. However, the decrease in the significance of some covariates coincides with effects that were smaller in the joint analysis. Despite the higher precision (lower SEs), smaller effects may lead to larger P values. As previously mentioned, the pattern of missing data may be responsible for the differences in the estimated effects obtained from the separate and joint analysis. In any case, when the estimated effect is identical in both methods, the P value typically decreases for the joint model. For example, the diameter stenosis is significantly associated with BR (OR, 0.95), but the decrease in the significance of some covariates coincides with the line referring to the distribution of the tentvar and the corresponding scale parameters (scale3), as well as the line that approximates the marginal odds-ratio.

It is necessary to specify initial values for the model. In our experience, the successful convergence of the algorithm is sensitive to this choice. One option is to use the estimates obtained by fitting separate models to each outcome as starting values and to try different values for the variances components (sigma3, sigma_latent, scale2, scale3). It might also be necessary to tune-up the options QPOINTS and GCONV of Proc NLMIXED. For more details on this, refer to the Proc NLMIXED manual.19

By removing the latent variable from the likelihood (latentvar) and the corresponding scale parameters (scale2 and scale3), as well as the line referring to the distribution of the latent variable (random latentvar ~ normal (0, sigma_latent**2) subject=MID; latent variable), the result is equal to fitting separate regressions to each outcome. As indicated by 1 of the reviewers, this might be a convenient way to check if the code is correct.

/* Example of SAS code for using the PROC NLMIXED to fit the joint model for three outcomes (y1, y2, y3) using the latent variable approach.

y1 and y2 are binary outcomes and y3 is a continuous outcome.
*/
PROC NLMIXED data =nameofmydata QPOINTS=15 GCONV=1E-15; *initial estimates that can be obtained from the separate regressions for each outcome;
PARMS a1=4.0 b1=3.0 c1=3.0
a2=1.7 b2=.76 c2=.87
a3=2.0 b3=-5.0 c3=-1.0 sigma3=4
sigma_latent=2;
*constrains the std deviations and the scale factors to be positive;
BOUNDS sigma3>0.0001, sigma_latent>0.0001, scale2>0.0001, scale3>0.0001;
*constant used to obtain the marginal effects for the binary outcomes;
stdconst=sqrt(1+0.346*sigma_latent**2);
*construction of the log-likelihood;
p1=exp(part1)/(1+exp(part1))
p2=exp(part2)/(1+exp(part2))
mean_y3=a3+b3*covariate1+c3*covariate2+scale3*latentvar;
ll1=y1*log(p1)+(1-y1)*log(1-p1);
ll2=y2*log(p2)+(1-y2)*log(1-p2);
ll3=-.5*log(2*pi*sigma3**2)+.5*((y3-mean_y3)/sigma3)**2;
ll=ll1+ll2+ll3; *log-likelihood for complete observations;
if missing (y2) and missing (y3) then ll1=1;
if missing (y2) and not missing (y3) then ll1=ll2;
if missing (y2) and not missing (y3) then ll2=ll1;
if missing (y2) and not missing (y3) then ll=ll1+ll2;
if missing (y2) and not missing (y3) then ll=ll1+ll3;
if missing (y2) and not missing (y3) then ll=ll1+ll3;
model y1 ~ general(ll);
random latentvar ~ normal(0, sigma_latent**2) subject=MID; latent variable;
*approximates the marginal odds-ratio;
estimate b1_mar=exp(b1/sqrt(1+0.346*sigma_latent**2));
estimate c1_mar=exp(c1/sqrt(1+0.346*sigma_latent**2));
estimate b2_mar=exp(b2/sqrt(1+0.346*(scale2*sigma_latent)**2));
estimate c2_mar=exp(c2/sqrt(1+0.346*(scale2*sigma_latent)**2));
*global test for the treatment effect H0: b1=b2=b3=0;
contrast "H0: b1=b2=b3=0" b1, b2, b3;
contrast "H0: b1=b2=b3=0" b1, b2, b3;

4. Concluding Remarks
The use of multivariate methods for the general linear model used to require complete data, and an assumption that the multiple outcomes of interest had jointly normal distributions (ie, multivariate normality). Although this restricted their application to continuous and normally distributed outcomes, the advantage of the multivariate approach was that it provided more parsimonious hypothesis tests and interval estimates than a series of univariate tests. With the development of generalized nonlinear mixed-effects regression models that can accommodate missing data under fairly general statistical assumptions, the advantages of the multivariate approach can be extended to a reduction in bias produced by missing data; as illustrated herein, these methods can be applied to outcomes measured on different scales, including a mixture of discrete and continuous outcomes.

We have presented a multivariate strategy to model mixed types of outcomes. This approach is an alternative to analyz-
ing each outcome separately, which disregards the potential correlation between the outcomes and to pooling information into a composite end point, which loses information contained in the data. The data set used as an example illustrates the advantage of the latent variable model regarding the more efficient use of the data, which usually translates in smaller CIs (smaller SEs). Also, it easily accommodates the situation in which some outcomes are not observed for all patients. In such cases, modeling the outcomes separately may produce biased estimates of the regression parameters.

The latent variable approach has some disadvantages. The model is implemented only in a few statistical packages, such as MPlus\textsuperscript{20} and AMOS.\textsuperscript{21} Although most statistical software does not have this procedure available, a simple program can be written to provide model estimates. The latent variable model makes some assumptions that are not easily verifiable, such as the assumption that the latent variable arises from a normal distribution (although there have been some recent developments regarding this last point\textsuperscript{22}). Because of the frequent use of multiple outcomes in cardiology studies, however, the potential benefits in terms of increases in precision of estimation and power of testing by adopting a multivariate approach are extremely promising.

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**References**
