Severe right ventricular dysfunction independent of left ventricular ejection fraction increased the risk of heart failure (HF) and death after myocardial infarction (MI). The association between right ventricular function and other clinical outcomes after MI was less clear. Two-dimensional echocardiograms were obtained in 605 patients with left ventricular dysfunction and/or clinical/radiologic evidence of HF from the VALIANT echocardiographic substudy (mean 5.0 ± 2.5 days after MI). Clinical outcomes included all-cause mortality, cardiovascular (CV) death, sudden death, HF, and stroke. Baseline right ventricular function was measured in 522 patients using right ventricular fractional area change (RVFAC) and was related to clinical outcomes. Mean RVFAC was 41.9 ± 4.3% (range 19.2% to 53.1%). The incidence of clinical events increased with decreasing RVFAC. After adjusting for 11 covariates, including age, ejection fraction, and Killip’s classification, decreased RVFAC was independently associated with increased risk of all-cause mortality (hazard ratio [HR] 1.61, 95% confidence interval [CI] 1.31 to 1.98), CV death (HR 1.62, 95% CI 1.30 to 2.01), sudden death (HR 1.79, 95% CI 1.26 to 2.54), HF (HR 1.48, 95% CI 1.17 to 1.86), and stroke (HR 2.95, 95% CI 1.76 to 4.95), but not recurrent MI. Each 5% decrease in baseline RVFAC was associated with a 1.53 (95% CI 1.24 to 1.88) increased risk of fatal and nonfatal CV outcomes. In conclusion, decreased right ventricular systolic function is a major risk factor for death, sudden death, HF, and stroke after MI. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101:607–612)
end point of VALIANT was all-cause mortality (time to death). Secondary end points included CV death, hospitalization for HF, recurrent MI, sudden cardiac death, stroke, and composites of these.1

All echocardiograms were submitted to the core laboratory at the Brigham & Women’s Hospital, Boston, Massachusetts, for assessment of technical quality and suitability for quantitative analysis. Endocardial borders from end-diastolic and end-systolic frames were digitized manually and left ventricular volumes were assessed using the Simpson’s rule method. Infarct segment size was assessed by manually tracing the akinetic or dyskinetic segment, expressed as a percentage of endocardial perimeter. Left ventricular ejection fraction was derived from calculated left ventricular volumes. The reproducibility of echocardiographic measurements was previously reported.2 Right ventricular function was assessed quantitatively using echocardiographic analysis as percentage of change in cavity area from end-diastole to end-systole. End-diastole was identified by the onset of the R wave from a simultaneously recorded electrocardiogram, whereas end-systole was regarded as the smallest right ventricular cavity size before tricuspid valve opening. Using the apical 4-chamber view, endocardial borders of the right ventricular free wall and septum were traced from base to apex, and the respective right ventricular areas were determined from the average of 3 measurements.3,4 Right ventricular fractional area change (RVFAC) was defined using the formula (end-diastolic area − end-systolic area)/end-diastolic area × 100.2

Echocardiographic measurements were made in triplicate by 1 observer blinded to outcome data using quantitative analysis software. Intraobserver reproducibility for RVFAC was assessed by the primary reader performing 2 sets of measurements in 50 randomly selected patients in a blinded fashion. Pearson’s correlation coefficient (r) between the 2 assessments was 0.94 (coefficient of repeatability 5.3% using the Bland-Altman method). Patients were grouped according to RVFAC into 4 categories (<35%, 35% to 39%, 40% to 45%, and >45%) using clinically relevant cut-off values. Defined time-dependent clinical outcomes included the primary end point of all-cause mortality, the composite CV end point and its individual components of CV death, recurrent MI, HF, stroke, and sudden death. We compared baseline characteristics across groups, and differences were analyzed using analysis of variance and chi-square tests for continuous and categorical variables, respectively. To determine the independent value of baseline RVFAC, we used a multivariable Cox proportional hazards model with 11 candidate variables, inclusive of the most powerful covariate predictors of mortality identified from the overall VALIANT and ejection fraction (derived using echocardiography). These were percutaneous intervention for index MI, history of MI, history of HF, Killip’s classification, history of chronic obstructive pulmonary disease, atrial fibrillation complicating MI, history of diabetes, history of angina, age in years, estimated glomerular filtration rate in milliliters per minute, and left ventricular ejection fraction. Both stepwise elimination and backward selection were used to select the most parsimonious set of predictive variables. Study treatment selection, history of hypertension, baseline end-diastolic left ventricular volume, and non–Q-wave infarction (on baseline electrocardiogram) were included in the adjustment model, but were found not to be significant covariates and were subsequently dropped out of the model. The interaction between left and right ventricular function was tested explicitly to assess whether left ventricular systolic function modified RVFAC. No other formal tests of interaction were performed between other candidate variables. Kaplan-Meier estimates stratified by RVFAC group for all-cause mortality and the CV composite end point were determined and presented as event curves. All p values were 2 sided; p <0.05 was used to determine statistical significance. Statistical analyses were performed using STATA software, version 8.2 (Stata Corp., College Station, Texas).

Results

Baseline RVFAC for 522 patients was approximately symmetrically distributed (mean RVFAC 41.9 ± 4.3%; Figure 1). Across RVFAC categories (Table 1), there were no differences with respect to age, gender, pulmonary disease, smoking, hemodynamic variables, Killip’s classification, medications, or infarct location. Individuals in the lowest RVFAC category had a higher incidence of hypertension, previous MI, previous congestive HF, a higher proportion of non–Q-wave MIs, larger left ventricular volumes, and lower left ventricular ejection fractions.

Of 522 patients, 90 (17.2%) died during the follow-up period; 15 of 90 deaths occurred within the first month. Worsening right ventricular function assessed as lower RVFAC was associated with increased mortality (Figure 2). Unadjusted Kaplan-Meier estimates of 3-year mortality rates for the <35%, 35% to 39%, 40% to 45%, and >45% groups were 44.4%, 29.2%, 11.7%, and 10.9%, respectively.

A total of 157 patients (30.1%) experienced the CV composite end point of CV death, hospitalization for HF, recurrent MI, sudden cardiac death, or stroke. The proportion of patients experiencing adverse CV events during the 3-year follow-up consistently increased with lower baseline RVFAC for both the CV composite end point and component events (Figures 2 and 3). With the exception of recur-
rent MI, the trend for increased risk of events with lower baseline RVFAC was significant for both fatal and nonfatal CV outcomes (p < 0.001), including CV death, HF, stroke, and sudden death. Kaplan-Meier estimates for the CV composite end point (Figure 2) showed an early divergence and wide spectrum of risk during the 3-year follow-up, particularly between the higher (RVFAC >40%) and lower groups, with lower RVFAC associated with increasing risk of adverse CV outcomes.

Using the >45% cohort as the reference group, unadjusted hazard ratios for both all-cause mortality and the CV composite markedly increased from mild (RVFAC 40% to 45%) to severe (RVFAC <35%) right ventricular dysfunction (Table 2). Patients with decreased right ventricular function were at increased risk of adverse outcomes, even after adjustment for the 11 candidate variables of percutaneous intervention for index MI, history of MI, history of HF, Killip's classification, history of chronic obstructive pulmonary disease, atrial fibrillation complicating MI, history of diabetes, history of angina pectoris, age in years, estimated glomerular filtration rate in milliliters per minute, and left ventricular ejection fraction (Table 2).

Analyzed as a continuous variable, baseline RVFAC was a potent univariate predictor of all-cause mortality, CV death, HF, stroke, and sudden death (each p < 0.001), but not recurrent MI (p = 0.77). In the adjusted model, each 5% decrease in RVFAC was independently associated with increased risk of all-cause mortality, CV death, sudden death, HF, and stroke (Figure 4). Every 5% decrease in baseline RVFAC was associated with a hazard ratio of 1.53 (95% confidence interval 1.24 to 1.88, p < 0.001) for both fatal and nonfatal CV outcomes based on the CV composite end point. There was no interaction between RVFAC and left ventricular ejection fraction (using echocardiography; p interaction = 0.15).

Discussion

In this analysis, baseline right ventricular function assessed using RVFAC was found to be a significant independent predictor for a broad spectrum of CV outcomes in patients with left ventricular dysfunction and/or HF complicating MI. These results confirmed the importance of right ven-
tricular function after infarction and argue for routine assessment of right ventricular function in high-risk patients.

The concept that impaired right ventricular function after MI was associated with poor outcomes is not novel. In contrast to previous studies in this field, our findings provide contemporary information by involving a larger cohort \( n = 522 \) receiving modern therapies after MI, with a broader spectrum of adjudicated clinical events during a longer follow-up. In addition, the present study showed that right ventricular function was a predictor not just of death and hospitalization for HF, but also of stroke and sudden death, and gradations of worsening right ventricular function, not just severe right ventricular dysfunction, conferred risk.

In this study, we observed a higher than expected prevalence of right ventricular dysfunction after MI compared with that reported previously.\(^5\) The reason for this discrepancy may be related to the high-risk cohort involved in our study, but more importantly, most post-MI registries and studies mainly relied on qualitative assessment of right ventricular function. Echocardiographic quantitative assessment of right ventricular function was limited because the methods used to determine left ventricular volumes and function were not applicable to the right ventricle owing to its complex geometry.\(^5,7\) Moreover, qualitative assessment of right ventricular function remains subjective and variable. RVFAC, which is methodologically easy to perform, may be a better echocardiographic descriptor of right ventricular systolic function than existing methods, evidenced by its strong association with clinical outcomes independent of left ventricular function, and is recommended as the preferred method for right ventricular assessment in the most recent American Society of Echocardiography guidelines.\(^8\)

Decreased right ventricular systolic function was associated with the development of HF\(^9–11\) and was an independent predictor of outcome in patients with chronic HF.\(^9,12–14\) This may be explained because the right ventricle is sensitive to changes in ventricular loading conditions. Increases in left ventricular end-diastolic pressure reflected back to the right ventricle will cause right ventricular enlargement and decreased right ventricular systolic function.\(^15,16\) Right ventricular function after MI may thus serve as an indirect surrogate of left ventricular end-diastolic pressure.

We observed that decreased right ventricular function was an independent predictor for risk of stroke even after adjustment for factors associated with stroke, such as age, diabetes, and atrial fibrillation.\(^17–19\) This appears to be a novel finding. The mechanism for this relation is unknown. Right ventricular function may be a sensitive measure of left atrial pressure, and decreased right ventricular function may reflect chronically increased left atrial pressures, associated with larger atria and atrial stasis, risk factors for atrial thrombus formation and stroke.\(^18,20\)

Several limitations of this study should be noted. The method used to quantify right ventricular function was dependent on image quality and was not a true volumetric-based method. Nevertheless, in a validation study, this method correlated well with magnetic resonance imaging-based volumetric assessments of right ventricular ejection fraction.\(^21\) The time course of recovery of right ventricular function after MI is unclear; although most baseline echocardiographic measurements were performed within the first week after MI, differences in timing of the baseline measures of RVFAC may have influenced our findings. Finally, because VALIANT studied only patients with left ventricular dysfunction, HF, or both after infarction, we do not know whether right ventricular function would be as im-

![Figure 2. Kaplan-Meier curves for (A) all-cause mortality and (B) CV composite stratified by RVFAC category.](image)

![Figure 3. Proportions (Kaplan-Meier estimates) of adverse CV outcomes at 3 years’ follow-up stratified by RVFAC category. CHF = congestive HF; SD = sudden death.](image)
Table 2
Hazard ratios (HRs) for all-cause mortality and cardiovascular composite at 3 years’ follow-up stratified by right ventricular fractional area change (RVFAC) group

<table>
<thead>
<tr>
<th>Variable</th>
<th>RVFAC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;35% (n = 27)</td>
</tr>
<tr>
<td>Death</td>
<td>44.4%</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>5.26 (2.39–11.56)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>3.56 (1.07–11.90)</td>
</tr>
<tr>
<td>Composite outcome*</td>
<td>70.4%</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>5.15 (2.81–9.44)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>2.72 (1.26–5.87)</td>
</tr>
</tbody>
</table>

Adjustment model included percutaneous intervention for index MI, history of MI, history of HF, Killip’s classification, history of chronic obstructive pulmonary disease, atrial fibrillation complicating MI, history of diabetes, history of angina pectoris, age in years, estimated glomerular filtration rate in milliliters per minute, and left ventricular ejection fraction.

* Composite outcome was all-cause mortality, CV death, resuscitated sudden death, recurrent MI, hospitalization for HF, and stroke.

Figure 4. Adjusted hazard ratios for adverse outcomes calculated for every 5% decrease in baseline RVFAC. Adjustment model: percutaneous intervention for index MI, history of MI, history of HF, Killip’s classification, history of chronic obstructive pulmonary disease, atrial fibrillation complicating MI, history of diabetes, history of angina pectoris, age in years, estimated glomerular filtration rate in milliliters per minute, and left ventricular ejection fraction. CV = cardiovascular.

important a predictor of outcome in patients after MI with normal left ventricular function.


