The PS-PR patients had a greater postoperative decrease in RVEDV (-47 ± 17 ml/m$^2$ vs. -38 ± 25 ml/m$^2$; p = 0.17) and RV end-systolic volume (-32 ± 17 ml/m$^2$ vs. -20 ± 18 ml/m$^2$; p = 0.023). The RVEF generally increased in patients with PS-PR (46 ± 8% to 53 ± 8%) and remained stable in TOF-PR patients (46 ± 9% to 47 ± 9%; p = 0.011 between groups) (**Figure 1**). Overall, the RVEF increased substantially (>5%) in 63% of PS-PR patients compared with only 24% of TOF-PR patients (chi-square: p = 0.004). Finally, multiple linear regression analysis to adjust for concomitant procedures and preoperative PS was performed. PS-PR remained associated with improved RVEF (adjusted β, 5.9; p = 0.048), whereas concomitant procedures were not (all p > 0.10).

To our knowledge, this is the first study to report CMR-derived hemodynamic effects of PVR in PS-PR patients. The RVEF improved substantially in about two-thirds of PS-PR patients, whereas it generally remained stable in matched TOF-PR patients. Preoperatively, PS-PR patients had higher RVEF and smaller RVEDV when compared with nonmatched TOF-PR patients, similar to a recent report (1). The improvement of RVEF after PVR in PS-PR patients compared with matched TOF-PR patients may be explained by factors such as a less extensive surgical history, absence of previous cyanosis, fewer RV outflow tract aneurysms, and less interventricular dyssynchrony (1,4).

Our retrospective cohort study was limited by a small sample size and missing preoperative or postoperative CMR in a subgroup.

In conclusion, PS-PR patients had superior RV remodeling after PVR when compared with matched TOF-PR patients. Waiting with PVR until symptoms or progressive RV dilation may be considered in PS-PR patients, because a more robust improvement of RV hemodynamic parameters can be expected.

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# Blunted Cortisol Stress Response and Depression-Induced Hypocortisolism Is Related to Inflammation in Patients With CAD

Both depression and psychosocial stress are associated with coronary artery disease (CAD) (1). However, the precise underlying mechanisms have not been elucidated fully. Cortisol is involved in the pathophysiological process of inflammation and atherosclerosis (2), but evidence directly linking depression and social stress with cortisol in CAD patients is limited. Bhattacharyya et al. (3) revealed a flatter diurnal cortisol slope in depressed (+CAD) compared with nondepressed (-CAD) patients, but found no relationship between the diurnal cortisol slope and depression in people without CAD (3). Our study aimed to elucidate the social stress-induced cortisol response in (+CAD) and (-CAD) patients in relation to depressive symptoms and high-sensitivity C-reactive protein (hsCRP). We hypothesized that depressed (+CAD) patients would show a blunted cortisol stress response with a close relation to systemic inflammation.

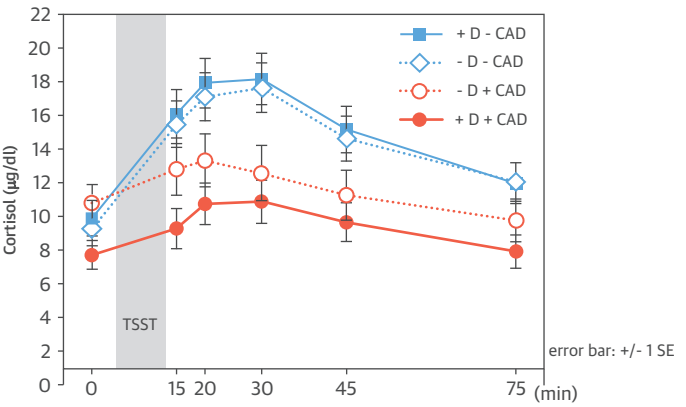
We investigated 91 subjects, 46 of whom experienced CAD with (21 [+D+CAD]) or without depressive symptoms (25 [-D+CAD]) and were compared with 22 depressed patients without CAD (+D-CAD) and 21 healthy subjects (-D-CAD). The German version of the depression subscale of the Hospital Anxiety and Depression scale (HADS) was used to rate symptom

levels of depression (cutoff, <8). In (+D+CAD) and (+D-CAD) patients, *Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Version IV* (SCID-IV) revealed major depression in 25, major depression in the last months in 11, and dysthymia in 7 patients. In the (-D-CAD) and (-D+CAD) groups, SCID-IV showed no abnormalities. Participants were scheduled to the laboratory until 9:00 AM and a venous catheter was inserted before a 60-min resting period. We applied the Trier Social Stress Test (TSST) combining a social and cognitive stressor composed by a 5-min anticipatory stress after a short introduction and a 5-min mock job interview and 5-min mental arithmetic task in front of an audience (4). Blood samples were obtained immediately before (cortisol, hsCRP) and at 1, 5, 15, 30, and 60 min (cortisol) after the TSST, were centrifuged (3,000 rpm, 10 min, 4°C) and stored at -80°C. Cortisol was measured by a competitive immunoassay (Siemens Healthcare, Erlangen, Germany). Using an enzyme-linked immunosorbent assay (IBL International, Hamburg, Germany), hsCRP was measured. Intra-assay and inter-assay variabilities were below 7%.

All data (mean ± standard error) were controlled for age, gender, body mass index, β-blockers, and antidepressants as covariates. Greenhouse-Geisser correction for repeated measures was applied. Other cardiovascular medications were tested separately to eliminate potential medication-related effects. Univariate analyses of covariance (ANCOVAs) revealed significant differences in baseline cortisol between (+D+CAD) and (-D+CAD) patients (+D+CAD [7.70 ± 0.85], -D+CAD [10.78 ± 1.10], +D-CAD [9.96 ± 1.01], -D-CAD [9.30 ± 0.98]), $F(1;43) = 6.07$, $p = 0.019$. Using ANCOVAs for repeated measures with four characteristics (4 groups, independent variable) and cortisol (6 repetitions, repeated dependent variable), we found significant group and group-by-stress effects. Both (+CAD) groups showed a blunted cortisol stress response compared with the (-CAD) groups (**Figure 1**). We found no group differences in hsCRP (3.33 ± 0.89 mg/l [+D+CAD], 2.09 ± 1.07 mg/l [-D+CAD], 1.61 ± 1.12 mg/l [+D-CAD], and 1.50 ± 1.19 mg/l [-D-CAD]). Partial correlations revealed that HADS depression scores were negatively related to baseline cortisol in (+CAD) ($r = -0.346$, $p = 0.031$) compared with (-CAD) patients ($r = -0.005$; $p$ = NS), whereas no relation was found between HADS depression and hsCRP ([+CAD] $r = 0.078$; [-CAD] $r = 0.046$; $p$ = NS). Baseline cortisol was negatively related to hsCRP ($r = -0.431$; $p = 0.027$) in the (+CAD) groups, but not in the (-CAD) groups ($r = -0.103$; $p$ = NS).

Our findings indicate that a blunted cortisol stress response and depression-induced baseline hypocortisolism in (+CAD) patients may play a key role in the progression of atherosclerosis and mortality due to an increased vulnerability to inflammation and autoimmunity (5). Strengths of our study include the comparisons of 4 groups in a well-validated stress paradigm, which makes it possible to delineate unique effects of CAD and depression. Further research is needed to evaluate our cross-sectional findings in a longitudinal study design.

**FIGURE 1 Analyses of Covariance for Repeated Measures Revealed a Blunted Cortisol Stress Response in (+CAD) Compared With (-CAD) Patients**




| | group effects | group-by-stress effects |
|---|---|---|
| all | F(3; 78) = 4.14 p = 0.009 | F(7.82; 203.18) = 2.60 p = 0.011 |
| (+D+CAD) – (+D-CAD) | F(1; 35) = 8.88 p = 0.005 | F(2.34; 81.71) = 3.76 p = 0.022 |
| (+D+CAD) – (-D-CAD) | F(1; 36) = 9.29 p = 0.004 | F(2.87; 103.40) = 6.21 p = 0.001 |

Values are mean ± standard error (SE).

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# Coronary Artery Calcification Testing

## A Platonic Certainty

In a recent issue of the *Journal*, Nasir et al. (1) used the concept of number needed to treat (NNT) to rationalize the statin therapy decision. The study indicated that 40% of subjects eligible for statin therapy had no coronary artery calcification (CAC), which was associated with a lower incidence of atherosclerotic cardiovascular events (ASCVEs), yielding a higher NNT and theoretically preventing the need for statin therapy.

Although the authors appropriately suggest that "among candidates for statin therapy, clinicians should consider the role of CAC," we suggest a further appraisal of the study's results to avoid overestimation of CAC testing utility.

In the study, candidates for statin therapy with no CAC had a NNT of 64 to prevent 1 ASCVE compared with an NNT of 28 in those with any CAC. Although it is a significant NNT gradient, a traditional risk score would certainly identify subgroups of particular baseline risks and different NNTs. Therefore, within this wide risk range, comparing CAC score stratification with no clinical stratification may have overestimated CAC testing utility.

Second, the need for testing should be evaluated by comparing post-test probability with pre-test probability of events, representing performing versus not performing testing. In those at intermediate risk, the incidence of events was 8.2%, leading to a pre-test NNT of 41. Thus, a better description of the value of CAC testing would be the comparison of an NNT of 64 (no CAC) with the pre-test NNT of 41, a smaller gradient.

Finally, reclassifying individuals is not a guarantee of improving prediction. The analysis must take into account the net of correct versus incorrect reclassifications (2). As opposed to contemporary studies, the authors did not provide this analysis.

A century ago, William Osler (3) stated that "medicine is a science of uncertainty and an art of probability." CAC testing is definitively useful for cases in which statin therapy is a decision dilemma. However, routine consideration of CAC testing would be a demonstration that the medical mind normally seeks for a platonic certainty.

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# REPLY: Coronary Artery Calcification Testing

## A Platonic Certainty

We thank Drs. Correia and Lemos for their interest in our paper describing significant heterogeneity in atherosclerotic cardiovascular disease (ASCVD) risk among statin therapy candidates and highlighting the role of absent coronary artery calcification (CAC) in reclassifying risk to a category in which the guideline no longer recommends treatment (1). Overall, 49% of individuals with a 10-year ASCVD risk range of 5% to 20% was determined on the basis of clinical information, and as a result, candidates for statin therapy had CAC = 0 and a reclassified risk lower than the threshold suggested for treatment consideration (1). Although further clinical information may refine risk in these categories, the revised estimates with CAC testing reported in our paper, however, already accounted for risk factor-based pre-test probabilities.