These effects, germane to quality of life, merit consideration when prescribing or contemplating use of statins, particularly in groups without expected net morbidity/mortality benefit, extending to “high-risk” primary prevention and women and elderly persons (including those with coronary artery disease). There was a significant relation between EnergyFatigEx and actual activity: reduced activity and exertional tolerance (irrespective of activity) in turn predict hard adverse outcomes. Effects may take time to manifest, as may benefits of statin use. Thus, long-term trials are important, if statin use is to be recommended in younger individuals. Meanwhile, physicians should be alert to patients’ reports of exertional fatigue or diminished energy during statin use.

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Vardenafil for the Treatment of Raynaud Phenomenon: A Randomized, Double-blind, Placebo-Controlled Crossover Study

Raynaud phenomenon (RP) is common and occurs with severe symptoms, particularly in patients with connective tissue disease (CTD), in whom RP may lead to digital ulcerations and amputations. Medical therapy in these patients remains unsatisfactory. Administration of phosphodiesterase type 5 (PDE5) inhibitors, which inhibit the degradation of cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells, promote vasorelaxation and are a promising therapeutic approach. However, randomized controlled trials have yielded conflicting results. We previously had conducted an open-label study with vardenafil hydrochloride trihydrate in patients with RP as a proof of concept. Our objective was to confirm our findings in a double-blind, randomized, placebo-controlled trial.

Methods. Patients with primary and secondary RP without active digital ulcers were recruited from the outpatient clinics of the Departments of Dermatology and Angiology at the University Hospital Cologne, from January 2006 through August 2009. We performed a double-blind, single-center, randomized, placebo-controlled, 2-period crossover study for 6 weeks to assess the efficacy and safety of vardenafil (10 mg twice daily) for the treatment of RP. Treatments were switched after a 1-week washout phase. Patients were followed up to 4 weeks after the last drug intake. All vasoactive agents were discontinued at least 1 week before study entry. Inclusion and exclusion criteria can be reviewed in detail online (http://clinicalsite.org/zks-koln/en/trial/490). The study was approved by the Ethics Committee of the Medical Faculty of the University of Cologne. Primary outcomes were changes in the Raynaud condition score (RCS),
The majority of the patients were female (42 of 53 [79%]). Of the 53 patients, 47 (89%) had secondary RP, mainly due to systemic sclerosis, and 6 (11%) had primary RP (eTable).

Adverse events were notably more prevalent with vardenafil treatment and included flush symptoms (12 vs 2; P = .01), headache (14 vs 7; P = .19), dyspepsia (7 vs 1; P = .07), dizziness (9 vs 2; P = .07), nasal stuffiness (7 vs 1; P = .07), and visual abnormalities (4 vs 3; P > .99).

Serious adverse events occurred in 1 patient receiving vardenafil and 2 patients receiving placebo and were not considered to be related to study drug intake and resolved completely.

### Comment
This study is, to our knowledge, the largest randomized controlled trial investigating the efficacy and safety of a PDE5 inhibitor in patients with RP. The findings demonstrate that vardenafil is safe and improves clinical symptoms in these patients. The results are in line with our previous study and 2 other RCTs in patients with RP receiving sildenafil or tadalafil. On the other hand, one study with a 4-week tadalafil therapy in a similar patient population failed to show efficacy, mainly owing to a placebo response. While we also observed a certain placebo response, a significant improvement was present in patients receiving vardenafil. Although representing an established tool in the assessment of RP, the RCS may appear subjective to some extent. The minimally important difference estimates for RCS are considered 1.4 to 1.5 points for improvement on a 0 to 10 visual analog scale in patients with active RP. The mean net RCS reduction at week 6 in our study compared with baseline was −1.07 in patients receiving vardenafil. Because of the short plasma half-life of vardenafil (∼4 h), it was surprising that its effect on

**Table. Efficacy of Vardenafil Hydrochloride Trihydrate in Patients With RP**

<table>
<thead>
<tr>
<th>Outcome Variable, First Period</th>
<th>Baseline, Mean (SD) Value</th>
<th>Vardenafil, Mean (SD) Value (n=27)</th>
<th>P Value (vs Baseline)</th>
<th>Baseline, Mean (SD) Value</th>
<th>Placebo, Mean (SD) Value (n=29)</th>
<th>P Value (vs Baseline)</th>
<th>P Value (First Period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCS over weeks 1-6</td>
<td>4.66 (2.15)</td>
<td>3.38 (1.98)</td>
<td>&lt;.001</td>
<td>4.14 (3.01)</td>
<td>3.32 (2.17)</td>
<td>.12</td>
<td>.81</td>
</tr>
<tr>
<td>RCS in week 6</td>
<td>3.46 (2.56)</td>
<td>3.46 (2.56)</td>
<td>.90</td>
<td>3.57 (2.44)</td>
<td>3.57 (2.44)</td>
<td>.30</td>
<td>.78</td>
</tr>
<tr>
<td>Raynaud attacks per day, No.</td>
<td>2.90 (1.44)</td>
<td>2.95 (2.04)</td>
<td>.005</td>
<td>2.61 (1.86)</td>
<td>2.61 (1.86)</td>
<td>.11</td>
<td>.66</td>
</tr>
<tr>
<td>Cumulative duration of Raynaud attacks per day, min</td>
<td>67.35 (64.77)</td>
<td>49.82 (60.76)</td>
<td>.006</td>
<td>59.07 (58.07)</td>
<td>42.96 (38.99)</td>
<td>.07</td>
<td>.50</td>
</tr>
<tr>
<td>Digital blood flow in week 6, %</td>
<td>40.3 (13.9)</td>
<td>50.2 (23.8)</td>
<td>.05</td>
<td>41.5 (16.3)</td>
<td>42.9 (14.4)</td>
<td>.48</td>
<td>.48</td>
</tr>
</tbody>
</table>

**Table. Efficacy of Vardenafil Hydrochloride Trihydrate in Patients With RP (Second Period)**

<table>
<thead>
<tr>
<th>Outcome Variable, Second Period</th>
<th>Washout, Mean (SD) Value</th>
<th>Placebo, Mean (SD) Value (n=25)</th>
<th>P Value (vs Washout)</th>
<th>Washout, Mean (SD) Value</th>
<th>Vardenafil, Mean (SD) Value (n=25)</th>
<th>P Value (vs Washout)</th>
<th>P Value (Carryover)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCS over weeks 1-6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.41 (2.44)</td>
<td>3.31 (2.22)</td>
<td>.70</td>
<td>3.32 (2.28)</td>
<td>2.56 (1.84)</td>
<td>.01</td>
<td>.58</td>
</tr>
<tr>
<td>RCS in week 6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>...</td>
<td>3.26 (2.24)</td>
<td>.68</td>
<td>...</td>
<td>2.39 (1.94)</td>
<td>.01</td>
<td>.64</td>
</tr>
<tr>
<td>Raynaud attacks per day, No.&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.49 (1.78)</td>
<td>2.79 (2.17)</td>
<td>.25</td>
<td>2.67 (1.99)</td>
<td>2.05 (1.77)</td>
<td>.003</td>
<td>.66</td>
</tr>
<tr>
<td>Cumulative duration of Raynaud attacks per day, min&lt;sup&gt;d&lt;/sup&gt;</td>
<td>48.06 (58.63)</td>
<td>60.21 (84.60)</td>
<td>.35</td>
<td>38.37 (51.50)</td>
<td>30.48 (42.93)</td>
<td>.01</td>
<td>.70</td>
</tr>
<tr>
<td>Digital blood flow in week 6, %&lt;sup&gt;e&lt;/sup&gt;</td>
<td>45.2 (19.5)</td>
<td>50.3 (20.4)</td>
<td>.29</td>
<td>45.7 (18.7)</td>
<td>51.8 (21.6)</td>
<td>.06</td>
<td>.70</td>
</tr>
</tbody>
</table>

Abbreviations: RCS, Raynaud condition score; RP, Raynaud phenomenon.

Treatment effect (Hills-Armitage approach) with parametric 95% CIs (vardenafil minus placebo, Welsh modified) and nonparametric P value (Wilcoxon rank sum test):

- Change: −0.45 (95% CI, −0.90 to 0.01) (P=.03) (subgroup analyses—primary RP [n=6]; −1.61 [95% CI, −3.43 to 0.20] [P=.05]; and secondary RP [n=47]: diffuse cutaneous systemic sclerosis [n=13], −0.36 [95% CI, −1.47 to 0.75] [P=.34]; limited cutaneous systemic sclerosis [n=25], −0.69 [95% CI, −1.38 to −0.01] [P=.04]; overlapping syndromes [n=6], 0.28 [95% CI, −2.01 to 2.57] [P=.99]; and undifferentiated connective tissue disease [n=3], 0.16 [95% CI, −1.46 to 1.78] [P>.90]).
- Change: −0.49 (−1.09 to 0.11) (P=.15) percentage of patients with complete values per week: first period, 92.5% (weeks 2-5) to 67.9% (week 6), second period, 92.5% (week 3) to 58.5% (week 6); last observations were carried forward for imputation.
- Change: −0.51 (95% CI, −0.90 to −0.12) (P=.005).
- Change: −11.43 minutes (95% CI, −20.79 to −2.07 minutes) (P=.003).
- Change: 4% (95% CI, −2% to 10%) (P=.14).

**Results**
Vardenafil significantly reduced the RCS on average by −0.45 compared with placebo (P=.03) and decreased the number (−0.51 vs placebo; P=.005) and cumulative duration (−11.43 minutes vs placebo; P=.003) of Raynaud attacks per day. The improvement of clinical symptoms by vardenafil was associated with a nonsignificant improved digital blood flow (+0.04 vs placebo; P=.14). Subgroup analyses revealed an increased efficacy of vardenafil in patients with primary RP and secondary RP with limited cutaneous systemic scleroderma compared with other subsets of patients with secondary RP (Table).

Interestingly, in patients receiving vardenafil first, the RCS remained low during the washout phase and the entire second phase of the study when patients received placebo, suggesting a prolonged drug effect (eFigure 2). However, statistical testing for a carryover effect did not yield significant results.

The majority of the patients were female (42 of 53 [79%]). Of the 53 patients, 47 (89%) had secondary RP, mainly due to systemic sclerosis, and 6 (11%) had primary RP (eTable).
clinical symptoms persisted throughout the washout phase and even beyond. Prolonged functional effects of PDE5 inhibitors, which exceed their plasma half-life, have also been found by others.\textsuperscript{5,8} The fact that a single-dose of a PDE5 inhibitor is insufficient to increase digital blood flow or attenuate cold-induced vasoconstriction in patients with RP indicates that the beneficial effect may involve mechanisms other than pure inhibition of cold-induced vasoconstriction.\textsuperscript{9}

In conclusion, vardenafil appears safe and effective in improving clinical symptoms and digital blood flow in patients with RP. Surprisingly, clinical efficacy is prolonged after discontinuation of the drug.

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Communicating With Physicians About Medical Decisions: A Reluctance to Disagree

Effective patient-physician communication is essential for shared decision making, considered by some to be the “pinnacle” of patient-centered care.\textsuperscript{1} Many health care decisions have multiple options and no correct choice. These are called preference-sensitive decisions, and the optimal decision is one that takes into account patient preferences and values in a collaborative process with the physician, known as shared decision making. We sought to describe patients’ intentions to engage in shared decision-making communication behaviors in response to a hypothetical preference-sensitive clinical scenario and to examine the effects of underlying patient beliefs on these behaviors.

Methods. An online panel of 1340 patients older than 40 years who had visited a physician within the last year read a hypothetical scenario about treatment of heart disease and were surveyed about 3 behaviors key to reaching a shared decision: (1) asking questions, (2) discussing preferences, and (3) voicing disagreement, when relevant. The survey was theoretically grounded and drew on the psychosocial constructs of the Integrative Model of Behavioral Prediction,\textsuperscript{2,3} which posits that 3 respondent characteristics influence, for purposes of our study, a patient’s intention to engage in a health-related communication behavior: (1) patient attitudes, (2) patient-perceived social

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