We next investigated the gene expression in the hearts from untreated and treated Lmna<sup>H11001/H11001</sup> and Lmna<sup>H1222P/H1222P</sup> female mice, because the beneficial effect of SCH00013 was prominent in female mice. In the hearts from untreated Lmna<sup>H1222P/H1222P</sup> mice, Nppa, Nppb, Myb7, and Myl7 messenger ribonucleic acids were significantly increased, and the upregulation of Nppa and Myl7 was significantly reduced in the treated mice (Online Fig. S6). We also found increased messenger ribonucleic acid expression of proto-oncogene Fos and extracellular matrix remodeling–related genes Tgfb1, Tgfb2, and Col1a2 in the untreated Lmna<sup>H1222P/H1222P</sup> mice, whereas these changes were suppressed by the treatment (Online Fig. S6). Left ventricles from the untreated Lmna<sup>H1222P/H1222P</sup> mice showed 2.2-fold and 1.7-fold increases of Nppa and Mlc2 proteins, respectively, as compared with the untreated Lmna<sup>H+++/H+++</sup> mice, and the increased expression was suppressed by the treatment (Online Fig. S7). In addition, we investigated whether the apoptotic signal was induced by the Lmna mutation, because there is an association among apoptosis, cardiac myocyte drop-out, ventricular remodeling, and deterioration of systolic performance in various experimental models of heart failure. However, the number of transferase-mediated dUTP nick-end labeling–positive cells was not increased in the hearts of Lmna<sup>H1222P/H1222P</sup> mice, and western blot analyses showed no or little expression of Fas-L or Fas proteins, respectively, in the Lmna<sup>H1222P/H1222P</sup> mice (Online Fig. S8). These results demonstrated that the apoptosis was not associated with the cardiac phenotypes in Lmna<sup>H1222P/H1222P</sup> mice and suggested that loss of cardiomyocytes was caused by cell death mechanisms other than the apoptosis.

The molecular mechanisms for the beneficial effect of SCH00013 remained unclear, but it might be related to the phosphodiesterase III activity. This possibility is unlikely, however, because SCH00013 inhibited the phosphodiesterase III activity at much higher concentration (IC<sub>50</sub> = 64.9 μmol/l) than the concentration at which it produced the positive inotropic effect (IC<sub>50</sub> = 9.2 μmol/l) in guinea pig hearts (3); and we showed that the plasma concentration of SCH00013 in the Lmna<sup>H1222P/H1222P</sup> mice ranged from 1 to 2 μmol/l, although we did not measure the concentration in the hearts. By contrast, because the Ca<sup>2+</sup> sensitivity of cardiac muscle contraction was not decreased in the Lmna<sup>H1222P/H1222P</sup> mice at 3 months of age (Online Fig. S9), the Ca<sup>2+</sup> sensitizing effect might not play a major role at the early stage, but the Ca<sup>2+</sup> sensitizing effect of SCH00013 was enhanced in the stretched muscles (5), raising a possibility that the Ca<sup>2+</sup> sensitivity in the failed heart might be different. Although the molecular mechanisms should be clarified, our findings implied that the Ca<sup>2+</sup> sensitizer could be a plausible option for preventing disease progression of DCM.

A Meta-Analysis of Remote Monitoring of Heart Failure Patients

Structured disease management improves the prognosis of patients with chronic heart failure and has already been included in the current treatment guidelines. Along with better medication and increased use of defibrillators, planned periodic visits have also become routine in clinical practice. Remote patient monitoring (RPM) is a different type of structured disease management. Although the RPM systems (telephone support, network care, device-assisted monitoring) and health care environments are heterogeneous, the crucial difference from usual care is that RPM enables daily contact with healthcare experts and thus facilitates regular short-term evaluation of the disease status and early intervention. The elaborate meta-analysis by Klersy et al. (1) pointed out considerable benefits to be gained from RPM in terms

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APPENDIX
For supplementary information and supplementary figure legends, please see the online version of this article.

Letters to the Editor

A Meta-Analysis of Remote Monitoring of Heart Failure Patients

Structured disease management improves the prognosis of patients with chronic heart failure and has already been included in the current treatment guidelines. Along with better medication and increased use of defibrillators, planned periodic visits have also become routine in clinical practice. Remote patient monitoring (RPM) is a different type of structured disease management. Although the RPM systems (telephone support, network care, device-assisted monitoring) and health care environments are heterogeneous, the crucial difference from usual care is that RPM enables daily contact with healthcare experts and thus facilitates regular short-term evaluation of the disease status and early intervention. The elaborate meta-analysis by Klersy et al. (1) pointed out considerable benefits to be gained from RPM in terms
of mortality and hospital stay. This result is misleading. Should we now offer RPM to the millions of heart failure outpatients? The most recent trials (2,3) failed to demonstrate convincing benefits in these end points. What caused the discrepancy? In the era of good baseline medication, growing defibrillator implantation rates, scheduled visits, and good self care, it is essential to identify the patients who might benefit from additional RPM and also those who will not. What are the determinants of outpatient responsiveness? When should RPM be used and for how long? What systems are most suitable? What makes interventions effective? Apart from the diversity of healthcare delivery systems requiring coordination in each country, there might be disease-related determinants of receptivity to RPM. The efforts of future trials should focus on these aspects. The challenge is to identify patients who require daily contact with healthcare experts as well as those who can continue to receive usual care without harm. A very smart technology calls for very intelligent clinical implementation.

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Reply

We thank Drs. Winkler and Koehler for their interest in our report (1) regarding the assessment of effect of remote patient monitoring on the outcome of chronic heart failure patients. We appreciated their provocative thoughts about unmet needs in structured disease management program (e.g., identification of the patients who most likely benefit from the technology, determinants of outpatient responsiveness, what makes interventions effective), which we all share; however, we are afraid that none of these questions might have found an answer, given the lack of published data. As far as the differences in outcome of 2 of the most recently published studies and the results of our meta-analysis are concerned, we believe that they are much less than what Drs. Winkler and Koehler perceived.

The study by Mortara et al. (2) showed a similar outcome between usual care and remote monitoring (indicated in the study as home telemonitoring). However, patients in the Mortara et al. study were at least 5 to 10 years younger than those included in our meta-analysis, and they were in a much lower New York Heart Association (NYHA) functional class (ranging from 34% to 49% in NYHA functional class >3 compared with 54% [randomized controlled trials] and 83% [observation cohorts] in our meta-analysis). Moreover, there was an unexplained imbalance, as already emphasized by Mortara et al., in baseline characteristic in the large Polish cohort as indicated by a more advanced NYHA functional class, significantly lower left ventricular ejection fraction, higher dyspnea score, and much lower sodium plasma level for those patients assigned to home telemonitoring. A post hoc analysis revealed a highly significant interaction between home telemonitoring and country in the association with the number of hospital stays (p = 0.004) and in the combined end point of cardiac death and heart failure hospital stay (p = 0.004). If one would put in perspective the outcome of the Italian cohort of the study by Mortara et al. with the results of our meta-analysis, an impressive similar benefit of remote monitoring compared with usual care would be found.

The study by Dar et al. (3) was a small, prospective, randomized controlled study including 182 patients randomized to usual care versus home monitoring. Although the baseline demographic characteristics of these patients were similar to those reported in the studies included in our meta-analysis, only 74 patients in the home monitoring arm and 79 patients in the usual care completed 180-day follow-up. Thus, the relative weight of the study by Dar et al. (3) in our meta-analysis would be relatively low, and importantly, approximately 50% of the studies we meta-analyzed had a similar duration of follow-up. Of note, there were 14 deaths in the home monitoring arm and only 4 deaths in the usual care group. Overall, this was an extremely high death rate for a very short follow-up but also impressively different between 2 treatments. We were not able to find any comparative study in our meta-analysis reporting similar death rates, which let us question about the reasons (not addressed in the study). Indeed, the death rate at 12 months in all randomized controlled studies we meta-analyzed ranged from 14.1% (95% confidence interval [CI]: 12.8 to 15.4) to 11.7% (95% CI: 10.7 to 12.9) in the usual care and home monitoring arm, respectively, and in observational studies it ranged from 13.0% (95% CI: 10.9 to 15.3) to 6.8% (95% CI: 5.3 to 8.6).

In conclusion, there is no doubt that the studies by Mortara et al. (2) and Dar et al. (3) both represent important contributions to implementation of remote monitoring. Their relative weight needs to be defined in future meta-analysis, keeping in mind some important methodological issues of each study.

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