also other approaches to improving Treg numbers and function in autoimmune diseases and GVHD and inhibiting them in cancer. The design of these trials will need to take into account the challenge of interpretation of data in patients who are receiving complex therapies. Alternatively, combinations of interleukin-2 with other directed immunotherapies, such as the infusion of ex vivo expanded Treg cells, might be used. Finally, mechanistic studies must be included, notably signaling assays (such as signal transducer and activator of transcription 5 phosphorylation) coupled with immune phenotyping. These studies may identify populations of patients who will have a response to the therapy to ensure that the pleiotropic effects of the drug, and specifically its ability to promote effector and memory T-cell responses, can be precisely evaluated.

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Improving Adherence — Money Isn't the Only Thing

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Interventions that both improve outcomes and save costs are unusual, but the provision of lifesaving medications to survivors of myocardial infarction is one such example.[1] In the past, physicians' poor compliance with evidence-based guidelines was a major reason for suboptimal use of such medications. Now, with help from the dissemination of quality metrics, cost-saving medications such as beta-blockers, aspirin, and angiotensin-converting–enzyme (ACE) inhibitors are nearly universally prescribed to eligible patients after myocardial infarction,[2,3] so the focus has switched from physician prescribing to patient adherence. The concept of value-based insurance design,[4] which is encouraged by the Patient Protection and Affordable Care Act of 2010, is to use lower copayments in order to encourage patients to adhere to high-value, potentially cost-saving treatments.

In this issue of the *Journal*, Choudhry and colleagues[5] report their findings from a controlled trial, sponsored by Aetna, that assessed whether the elimination of copayments for statins, beta-blockers, ACE inhibitors, and angiotensin-receptor blockers for recent survivors of an acute myocardial infarction could improve adherence, reduce future cardiovascular events, and save costs. The elimination of copayments, which averaged about $13 to $25 per month per medication, significantly increased adherence, by 4 to 6 percentage points above the rates of 36 to 49% in the control group.

The elimination of copayments did not significantly reduce the risk of the primary end point, a first major vascular event or revascularization procedure (17.6 per 100 person-years in the full-coverage group vs. 18.8 per 100 person-years in the usual-coverage group; hazard ratio, 0.93; P=0.21). However, the incidence of two prespecified secondary end points, all major vascular events or revascularizations and the time to

the first major vascular event, declined significantly by nearly 2 percentage points. All reductions were within a plausible range, given changes in adherence and the expected benefits of the medications.[6] The 11% relative reductions in overall and cardiovascular-specific spending with free medications were not significant, although patients' out-of-pocket spending for prescription drugs was reduced (relative spending, 0.70; P<0.001).

Perhaps the most sobering findings were both the low baseline adherence and the small improvement in adherence in what should have been a highly motivated group of patients after myocardial infarction. Adherence to prescribed medications varies depending on the frequency of administration (a four-times-daily regimen is associated with a relative reduction of nearly 40% in adherence, as compared with a once-daily regimen), as well as on psychological problems, cognitive impairment, treatment of an asymptomatic disease, side effects, and cost.[7] Strategies for improving poor adherence have addressed these issues but generally have reported baseline rates of adherence and changes in adherence similar to those in the study by Choudhry et al., regardless of whether the intervention eliminated copayments or was behaviorally focused.[8,9]

Because of the relative paucity of trials to assess the worthiness of value-based insurance interventions, the business community has been slow to adopt this approach. For example, a recent Mercer national survey of health plans sponsored by large employers showed that less than 20% of plans now have such value-based components, even though more than 80% say they plan to offer them in the future.[10] The reduction in events and the trend toward lower costs in this study should foster great interest among employers and other payers, even if the business case does not yet indisputably confirm lower costs for them.

Value-based insurance design may be a useful complement to the health savings accounts and consumer-driven health plans that are increasingly being offered in the market. Employers have sought to shift health care costs to the beneficiary through higher deductibles or higher copayments at the time of service. The goal of these plans is to foster greater cost-consciousness by consumers, deter utilization, and lower the cost of care. The challenge is that patients are often poor judges about the relative or absolute benefits of different health care services. Value-based insurance design can provide important signals that identify high-value services, as well as financial incentives to encourage their use.

Reducing or eliminating the costs of highly beneficial medicines is almost certainly one key component of increasing adherence, even if its absolute benefit is distressingly modest. More comprehensive insurance coverage also has appeal, but it is likely to raise the costs of care. For patients who have had a myocardial infarction, currently available generic formulations are already far less expensive than the average copayments faced by patients in the study by Choudhry et al. For example, generic statins cost $4 per month,[11] as compared with their average copayment of $25 per month. Pharmaceutical companies should not expect that the elimination of copayments for costly proprietary preparations will be considered a sensible alternative when low-cost generics are available.

In some instances, it surely makes sense to align financial incentives with high-value care. However, a rational health care system must not only incorporate financial considerations but must also investigate and develop additional ways to improve adherence. Since health insurers, both private and public, have a huge stake in the outcomes, their sponsorship of research should be a good investment, not only for them but also for the people whom they insure.

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