

ORIGINAL ARTICLE

Perks and Pitfalls of Performance-Linked Reimbursement for Novel Drugs: The Case of Sacubitril-Valsartan

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BACKGROUND: Rising drug costs have increased interest in performance-linked reimbursement (PLR) contracts that tie payment to patient outcomes. PLR is theoretically attractive to payers interested in reducing the risk of overpaying for expensive drugs, to manufacturers working to improve early drug adoption, and to patients seeking improved access. Multiple PLR contracts were developed for sacubitril-valsartan. We evaluated how the characteristics of a PLR contract influence its performance.

METHODS: We used a published cost-effectiveness model of sacubitril-valsartan. We evaluated hypothetical PLR contracts that adjusted drug payment based on observed therapy effectiveness. Ideally, these contracts reduce the uncertainty around the value obtained with purchasing sacubitril-valsartan. By reducing the financial risk in covering an ineffective therapy, PLR incentivizes insurers to increase patient access. We measured the uncertainty in value as the SD of the incremental net monetary benefit (INMB), an estimate of therapy value incorporating costs and clinical benefits. We evaluated the change in INMB SD under a variety of different assumptions regarding contract design, therapy effectiveness, and population characteristics.

RESULTS: Over 2 years, sacubitril-valsartan led to 0.042 additional quality-adjusted life-years at an incremental cost of \$4916. Using a willingness-to-pay of \$150 000 per quality-adjusted life-year, this led to a mean INMB across simulations of \$1416 (SD, \$1720). A PLR contract that adjusted payment based on cardiovascular mortality reduced the INMB SD moderately by 20.7% while a contract based on all-cause mortality was more effective (INMB SD reduction of 27.3%). A contract based on heart failure hospitalization reduction was ineffective. PLR effectiveness increased with greater uncertainty regarding therapy effectiveness or in sicker cohorts (eg, New York Heart Association Class III/IV heart failure). Contracts required precise estimates of treatment effect in addition to trust or verifiability between manufacturers and payers concerning patient selection.

CONCLUSIONS: The development of accurate prospective estimates of treatment effectiveness using actual enrollee characteristics will be critical for successful PLR. If able to meet these requirements, PLRs could incentivize insurers to expand access to expensive treatments by reducing financial risk.

Key Words: costs and cost analysis ■ drug costs ■ economics ■ heart failure ■ prescription drugs

See Editorial by Rand and Kesselheim

The soaring costs of pharmaceuticals have raised major concerns about affordability and accessibility.^{1,2} Drug manufacturers justify prices with the promise of clinical benefit, sometimes ignoring considerable uncertainty when the clinical evidence is limited.^{3,4}

Even after well-conducted trials that demonstrate significant treatment effects, the magnitude and value of the real-world benefit may remain unclear due to both wide CIs and concerns regarding generalizability of trial findings to the larger population.

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WHAT IS KNOWN

- Novel drugs often have high costs with uncertainty regarding their clinical benefit at the time of introduction.
- Performance-linked reimbursement may be an approach to protect payers from overpaying for low-value drugs while promoting more rapid access for patients.

WHAT THE STUDY ADDS

- Performance-linked reimbursement will be more effective for therapies with potentially large but highly uncertain clinical benefit.
- Performance-linked reimbursement contracts should focus on outcomes that reflect the major benefit of the drug (eg, increased survival) or are strong surrogates of that outcome.
- Successful performance-linked reimbursement will require precise estimates of treatment effectiveness in routine practice.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin converting enzyme
INMB	incremental net monetary benefit
LDL	low-density lipoprotein
NYHA	New York Heart Association
PLR	performance-linked reimbursement
QALY	quality-adjusted life-year

Performance-linked reimbursement (PLR) is a proposed solution to the high prices and uncertain benefits of novel drugs.^{5,6} The pharmaceutical manufacturer assumes partial risk by linking reimbursement to outcomes.⁷ If patients experience less benefit than expected, the manufacturer is paid less. If patients experience more benefit, the manufacturer is paid more. Such 2-sided contracts have been adopted in European countries for drugs including β -interferon for multiple sclerosis, bortezomib for multiple myeloma, and atorvastatin for cardiovascular prevention.⁸ To date, they have been used less frequently in the United States, but the Center for Medicare & Medicaid Services and other American payers have declared interest in piloting such agreements.^{9–11}

PLR contracts hold theoretical appeal to payers and manufacturers. They are designed to ensure payers are paying the right amount for a new therapy's benefit; ideally, the contracts reduce the likelihood of substantial spending on an expensive, new therapy that is minimally effective in practice. In addition to insuring general uncertainty regarding therapies with limited data, PLR contracts may also be useful when the payer and manufacturer disagree regarding expected

benefits. This may occur because a payer suspects the initial clinical trials are not widely generalizable. The payer can pay the amount set forth by the manufacturer, knowing they will obtain a refund if they are right and the therapy ends up less effective. Manufacturers may be willing to assume risk in their per-unit price in exchange for increased early adoption of their product and increased prescription volume given time-limited exclusivity patients. Patients may benefit because an insurer with reduced risk will be more likely to offer that therapy in their formulary. Despite these potential mutual advantages, assessing PLRs in practice is challenging because of limited public availability of data on contract designs and outcomes in practice.^{7,12}

Sacubitril-valsartan—a novel drug that combines a neprilysin inhibitor (sacubitril) and an angiotensin receptor blocker (valsartan)—was shown to reduce cardiovascular mortality and heart failure hospitalizations among patients with heart failure with reduced ejection fraction.¹³ Although costly, we previously found it to be cost-effective (\$47 053 per quality-adjusted life-year [QALY] gained over a lifetime horizon).¹⁴ However, critics initially raised concerns regarding the trial, such as the control group being on an inadequate dose of enalapril. Therapy uptake was subsequently slow with only 13% of patients with heart failure on treatment in an outpatient registry in 2017.^{15–18} Novartis (the manufacturer) then agreed to PLR contracts with Cigna, Aetna, and Harvard Pilgrim, that adjusted payments if the observed treatment effect did not match the clinical trial.^{10,19,20}

We used a cost-effectiveness model to explore how PLR, compared with conventional payment, affected the distribution of value obtained by a payer when adopting sacubitril-valsartan. We used this model to explore key features required for PLR models to reduce the variation in value obtained from pharmaceutical spending more generally. Finally, we demonstrated the potential savings with PLR if therapy effectiveness were systematically overestimated.

STUDY DATA AND METHODS

The model used in this study is available from the corresponding author upon reasonable request.

Cost-Effectiveness Model

We used a cost-effectiveness model to estimate the clinical and economic outcomes of sacubitril-valsartan therapy compared with ACE (angiotensin-converting enzyme) inhibitor therapy in patients with heart failure with reduced ejection fraction. This decision model was based on the findings of PARADIGM-HF, which demonstrated the effectiveness of sacubitril-valsartan.¹³ Model details have been previously published and are included in the supplement.¹⁴ We measured the value of using sacubitril-valsartan compared with an ACE inhibitor by calculating the incremental net monetary benefit (INMB)—a monetized value of the incremental QALYs minus the incremental cost. We used

a monetary valuation of \$150 000 per QALY, a commonly proposed upper bound of the willingness to pay threshold for medical therapies in the United States.^{21,22} A higher INMB indicates better therapy value. In sensitivity analyses, we repeat the primary PLR models with alternate willingness-to-pay thresholds.

We estimated the uncertainty in therapy value by performing 10 000 simulations while simultaneously sampling from the distributions of each model parameter (disease natural history rates, health care costs, quality of life, and treatment effectiveness). We assumed moderate correlations ($\rho=0.50$) between cardiovascular mortality and heart failure hospitalization rates and between the risk reduction in cardiovascular mortality and heart failure hospitalizations with sacubitril-valsartan. For this analysis, we assumed the INMB of each simulation was an estimate of potential drug value with real-world adoption. The INMB distribution across the 10 000 simulations characterized the uncertainty of this value.

Payment Structure

We compared the INMB distribution using conventional payment and PLR. Conventional payment was set as the wholesale acquisition cost of sacubitril-valsartan independent of clinical outcomes.

Novartis has negotiated PLR contracts that adjust payment based on hospitalization and mortality rates among treated patients.^{10,19,20} The contracts will adjust payment if the therapy does not reproduce the effectiveness observed in PARADIGM-HF. Further detail is not publicly available. We assumed payment adjustment was based on the relative risk reduction of cardiovascular mortality or heart failure hospitalization (the primary clinical benefits of therapy) over a 2-year period with sacubitril-valsartan therapy. We varied this duration in sensitivity analyses.

We modeled a 2-sided PLR contract in which payers and manufacturers agreed on a given payment for a given clinical effect. The payment was then modified based on the observed clinical effect. In the base case, we assumed the insurer and manufacturer could precisely determine the observed effectiveness of sacubitril-valsartan; they adjusted payment based on the ratio between observed and expected relative risk reduction. For example, in a simulation with 50% greater relative risk reduction (ie, relative risk reduction of cardiovascular mortality of 31.1% instead of the expected 20.7%), we increased drug payment by 50%. In a simulation with 50% lower-risk reduction, we decreased payment by 50%. If the therapy had no effect on mortality, we set the payment to \$0.

In the primary analysis, we assumed PLR contracts were designed to reduce uncertainty in therapy value and not to drive expected savings. With the uncertainty of therapy effectiveness matching expectations, average spending across the 10 000 simulations equaled conventional payment; in other words, the risk of higher payment than baseline equaled the risk of lower payment than baseline. We performed a secondary analysis in which we assumed a discordance between the contract expectations and actual therapy effectiveness. In this analysis, we assumed the clinical trial, and thereby the PLR contract, overestimated the expected reduction in mortality and hospitalizations in routine practice. This analysis evaluates potential savings for a payer who enters the contract to both reduce uncertainty in therapy value but also because they believe the

therapy will be less effective than suggested by the manufacturer. The manufacturer may still expect the benefit to match the trial, and therefore, the average PLR payment to match conventional payment. For this analysis, we modeled a 20% reduction in the treatment effect (relative risk of cardiovascular death of 0.83 [95% CI, 0.75–0.92] instead of 0.79 [95% CI, 0.72–0.87] in the main analysis).

Our main analyses used 2-sided contracts, in which payers would pay more if the therapy exceeded expectations. One-sided contracts would typically be substitutes for manufacturer rebates.²⁴ In other words, the payer would be increasing spending if the drug met or exceeded expectations. In a sensitivity analysis, we modeled a 1-sided contract based on cardiovascular mortality to demonstrate how it reduces variation in payment but not variation in therapy value compared with a 2-sided contract.

Outcomes

For the payer, a successful contract would reduce the risk of paying excessively for a low-value therapy. Low-value simulations should have negative payment adjustment while high value simulations should have positive payment adjustment. This would narrow the INMB distribution and reduce its SD (Figure 1). We used the SD of the INMB distribution as a measure of the variation in potential therapy value with real-world adoption. We evaluated PLR effectiveness based on the percentage change in SD from conventional payment to PLR. We also evaluated the correlation between baseline NMB and payment adjustment, with a positive association indicating better PLR performance.

Additional Analyses

We varied multiple dimensions of our model uncertainty, the population being treated, and the plan design. We describe these modifications in Table 1. These analyses were designed to provide insight into what influences the outcomes of a PLR plan. These sensitivity analyses are detailed in the supplement.

Analyses were performed using TreeAge 2019 (TreeAge Software, Williamstown, MA) and STATA 14.2 (StataCorp, College Station, TX).

RESULTS

Primary Analyses—Base PLR Models

Our base case model found sacubitril-valsartan led to 0.042 additional QALYs (95% CI, 0.029–0.057) at an additional cost of \$4916 (95% CI, \$3005–\$6371) over a 2-year period. This included \$7847 (95% CI, \$7691–\$8001) in direct expenditures on sacubitril-valsartan offset by a \$2931 reduction in other services. The mean INMB (measure of therapy value) across simulations was \$1416 (95% CI, –\$1657 to \$5059) with a SD of \$1720. The INMB CIs equated to cost per QALY of \$57 645 to \$205 557 over the 2-year time horizon. We refer to the INMB with conventional payment as baseline value—the value before PLR adjustment.

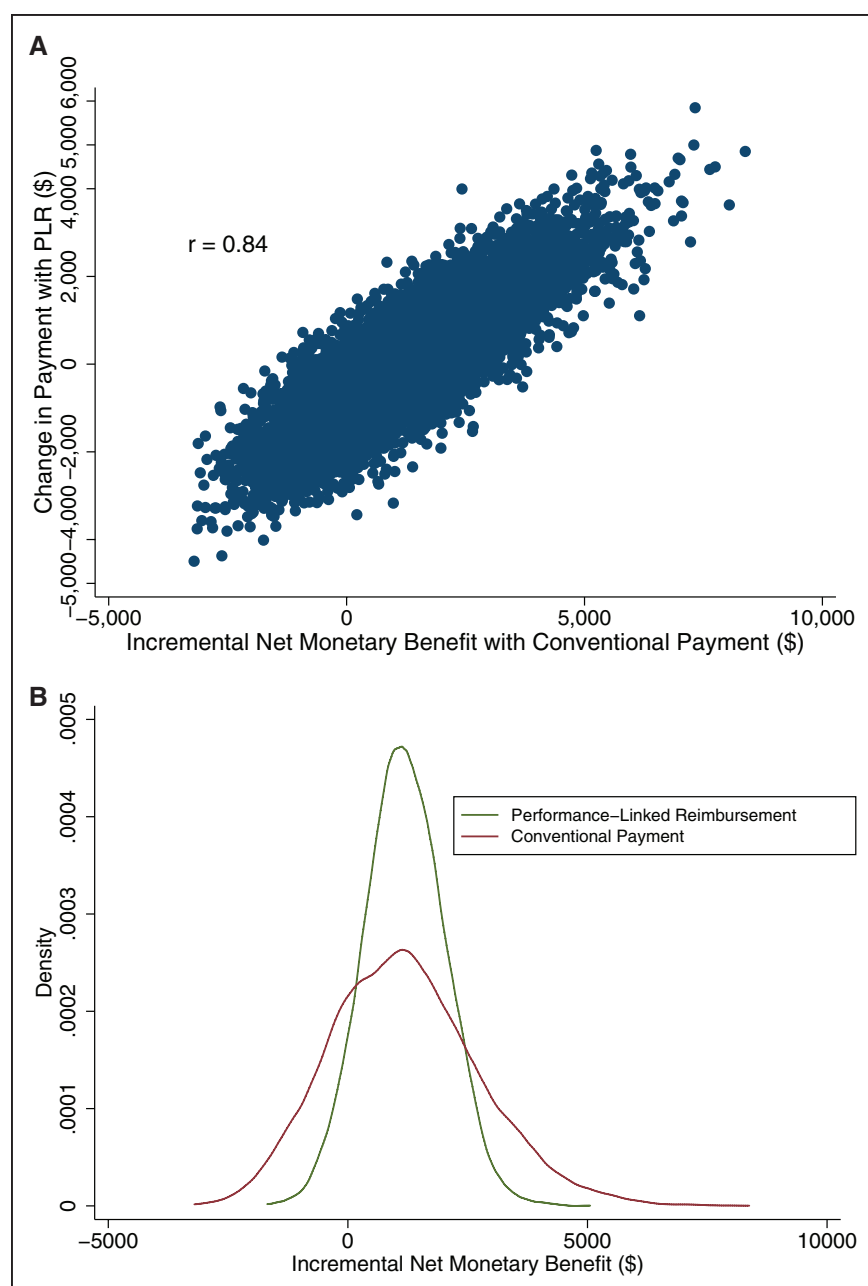


Figure 1. Idealized performance-linked reimbursement (PLR).

This represents an idealized PLR plan across a series of simulations that represent the uncertainty of treatment performance. In **A**, the x axis is the incremental net monetary benefit (INMB) under conventional reimbursement with a larger value indicating higher baseline value. The y axis is the PLR payment change with a positive number indicating increased payment to the manufacturer. With an ideal PLR plan, payment decreases with low baseline clinical benefit and poor value (low INMB with conventional payment). Payment increases with high initial value (high initial INMB). The high correlation between payment change and baseline value is displayed. **B**, Kernel density plot of the INMB (treatment value) with conventional payment and with PLR. PLR should reduce the probability of very low and very high value.

Next, we simulated the effect of introducing a PLR contract that adjusted payment based on the relative cardiovascular mortality reduction. PLR reduced average payment by \$1124 (14.3% of conventional payment) among the tertile of simulations with the lowest baseline value (lowest INMB with conventional payment) and increased it by \$1083 (13.8%) among high value simulations. This decreased the INMB SD by 20.7% (Figure 2). With conventional payment, 20.8% of simulations had a negative INMB (below the willingness-to-pay of \$150 000 per QALY); with PLR, this decreased to 14.4%. Adjusting payments based on therapy effectiveness increased the variation in drug payments (Table S2).

A contract that adjusted payment based on heart failure hospitalization reduction did not effectively reduce the uncertainty in therapy value. The payment change with PLR had a weaker correlation with baseline value ($r=0.31$ compared with 0.65 for the mortality-based contract; Table 2). The clinical value of sacubitril-valsartan was driven by the reduction in mortality and not hospitalizations because hospitalizations are less severe events with relatively low event rates in the PARADIGM-HF population. If sacubitril-valsartan had no effect on hospitalizations—but still reduced cardiovascular mortality, incremental QALYs gained would decrease by <1%. With a stronger correlation between cardiovascular death and heart failure hospitalizations, a contract based

Table 1. Overview of Analyses

Scenario	Details
Primary analyses—base models	
Base model=CVD*	PLR contract: Payment adjusted by ratio of observed relative risk of CVD with sacubitril-valsartan compared with expected over 2 y period
	Patient population: Based on PARADIGM-HF: average age of 64, 74% NYHA Class II and 26% Class III/IV
	Key model characteristics: Risk of CVD moderately correlated ($r=0.50$) with HFH, reduction in CVD moderately correlated ($r=0.50$) with reduction in HFH; otherwise baseline model from prior CEA
HFH	Payment adjusted by ratio of observed relative risk of HFH with sacubitril-valsartan compared with expected over 2 y period
High HFH correlation	HFH contract with higher correlations between HFH and CVD ($r=0.75$)
All-cause mortality	Payment adjusted by ratio of observed relative risk of all-cause death with sacubitril-valsartan compared with expected over 2 y period
Uncertainty in therapy effectiveness or population natural history	
Therapy uncertainty	Increased uncertainty of sacubitril-valsartan effectiveness (increased variance of the sampling distribution by 50%)
Lower effect (payer savings)	Assumed the contract overestimated the cardiovascular mortality reduction of sacubitril-valsartan by 20%
High natural history uncertainty	Increased uncertainty of the baseline risk of mortality, hospitalizations, and ED visits (increased variance of sampling distributions by 50%)†
Low natural history uncertainty	Decreased uncertainty of the baseline risk of mortality, hospitalizations, and ED visits (decreased variance of sampling distributions by 50%)†
Patient characteristics	
NYHA II	NYHA Class II cohort with lower CVD and HFH risk and better quality of life
NYHA III/IV	NYHA Class III/IV cohort with higher CVD and HFH risk and worse quality of life
Younger	Average age of 54 with lower CVD and non-CVD mortality rates
Older	Average age of 74 with higher CVD and non-CVD mortality rates
Modified selection	NYHA Class III/IV cohort with higher CVD and HFH risk and worse quality of life but based expected CVD risk on base PARADIGM-HF cohort (mix of NYHA Class II and III/IV), leading to lower expected mortality rate than the actual cohort
PLR contract design	
5 y	CVD outcome=5 y horizon
1 y	CVD outcome=1 y horizon
Imprecise effect estimate	Assumed unable to precisely estimate the observed relative risk of CVD with sacubitril-valsartan due to inability to accurately determine the counter-factual. Estimated the relative risk using the average mortality without sacubitril-valsartan across simulations
Absolute reduction	Payment adjusted by ratio of observed to expected absolute reduction of CVD
One-sided contract	Drug cost premium of 7.9% but no payment change if CVD reduction below expected effectiveness. If reduction in CVD exceeds expectations, payment adjusted by ratio of observed to expected relative risk reduction for CVD

CVD indicates cardiovascular death; ED, Emergency Department; HFH, heart failure hospitalization; NYHA, New York Heart Association functional class; and PLR, performance-linked reimbursement.

*The specifications from this analysis were used for all subsequent analyses except for the modifications described.

†The effect of adjusting the range of cardiovascular mortality rate and heart failure hospitalization rate on the CIs of average survival and average heart failure hospitalization rate are displayed in Table S1.

on heart failure hospitalizations also reduced the INMB SD (Table 2).

All-cause mortality has advantages as a PLR metric over cardiovascular mortality. Differentiating between cardiovascular and noncardiovascular mortality can be challenging, and the absolute benefit with sacubitril-valsartan decreases with greater noncardiac competing risks. Tying reimbursement to all-cause mortality strengthened the association between baseline value and the change in payment, so the INMB SD decreased by 27.3% (compared with 20.7% with the cardiovascular mortality metric).

Given manufacturers may be wary of adjusting their reimbursement based on outcomes that their therapy is not intended to affect, we assumed contracts used a cardiovascular mortality metric for the remaining analyses.

Impact of Uncertainty in Therapy Effectiveness or Population Natural History

Therapy Effectiveness

Our model estimated the distribution of sacubitril-valsartan effectiveness estimates using results from the

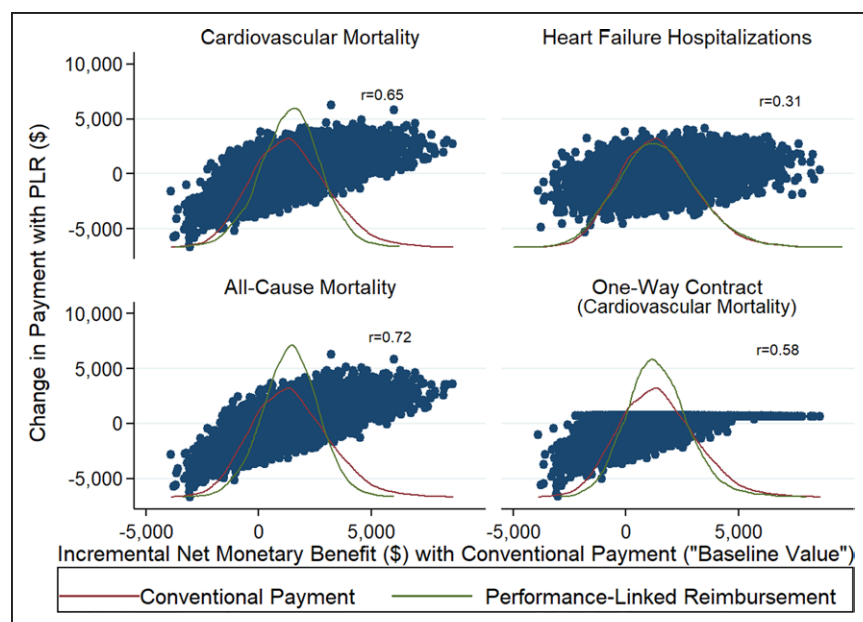


Figure 2. Change in payments with performance-linked reimbursement (PLR) and baseline therapy value. The scatter plot displays the relationship between the incremental net monetary benefit (INMB) with conventional payment (measure of therapy value) and the payment adjustment with the given PLR contract for 10 000 simulations. The correlation is displayed for each contract. The superimposed kernel density plots are the NMBs with conventional payment (red) and PLR (green).

primary clinical trial. This may not capture the uncertainty of real-world therapy adoption. Less precise effectiveness estimates (wider confidence intervals for the mortality effect) increase uncertainty in baseline value (widen the INMB distribution). We found greater efficacy uncertainty increased the reduction in the INMB SD with PLR (26.5% compared with 20.7% with our initial model).

PLR contracts may reduce drug payments if clinical trials systematically overpredict treatment effect in routine practice. This could be related to biased trial design, limited generalizability to a real-world treatment population, or decreased adherence in routine practice. We modeled a scenario in which the PLR contract was based on the findings of PARADIGM-HF but the actual effect on cardiovascular mortality was 20% lower. In this scenario, sacubitril-valsartan only led to an average of 0.038 incremental QALYs over 2 years. Given lower than expected mortality reduction, PLR produced substantial savings. The average payment adjustment was −\$1452 (95% distribution of −\$4706 to +\$1520), which corresponds to an 18.9% reduction in sacubitril-valsartan spending.

Population Natural History

Because PLR contracts adjust payment based on relative risk reduction, they had a larger impact when a greater share of the total uncertainty in value was secondary to uncertainty in treatment effectiveness. These contracts do not insure against other factors that can influence therapy value. With a less defined population, more of the uncertainty in therapy value will be related to imprecision in baseline risk (mortality or hospitalization rates) and less related to therapy effectiveness. We modeled the impact of PLR on cohorts that were either better defined (smaller SD in baseline rates) or less defined (larger SD in baseline rates) than our base

model. We found PLR reduced the INMB SD by 31.1% in the well-defined cohort and by only 6.5% in the less-defined cohort.

Impact of Patient Characteristics

Heart Failure Severity

We evaluated the impact of patient characteristics on the effectiveness of PLR. We modeled using PLR for patient subgroups with more (New York Heart Association [NYHA] Class III/IV) or less severe heart failure (NYHA Class II). The more severe cohort had higher risk of cardiac mortality; therefore, similar therapy effectiveness led to greater absolute treatment benefit and better therapy value. Therapy value having a stronger association with the PLR metric—relative risk reduction—improves the contract's performance. Therefore, PLR was more effective among those more severe heart failure (INMB SD reduction of 28.1% in NYHA Class III/IV versus 20.7% in Class II).

Age

We also varied the average age of the cohort. Older patients have higher rates of cardiovascular and noncardiovascular mortality. Noncardiovascular mortality is a competing risk; in isolation, increasing noncardiovascular mortality would reduce the absolute treatment benefit and therapy value. This would weaken the association between therapy effectiveness and value, impairing PLR performance. However, this was balanced by increased cardiovascular mortality in older patients, which in isolation would improve performance. Hence, PLR effectiveness was overall similar in a cohort that was 10 years older (Table 1). Decreasing the cohort age by 10 years lowered mortality risk from either cause. The decrease

Table 2. Results Across PLR Models

	Average INMB with conventional payment (SD \$)	Average payment change by simulation baseline value tertile* (% of average total drug payment with conventional payment)			INMB-payment change correlation†	% change in INMB SD
		Low	Intermediate	High		
Primary analyses—Base PLR models						
CVD	\$1416 (\$1720)	−\$1124 (14.3%)	\$42 (0.5%)	\$1083 (13.8%)	0.65	−20.7%
HFH	\$1416 (\$1720)	−\$422 (5.4%)	\$11 (0.1%)	\$411 (5.2%)	0.31	3.5%
High HFH correlation	\$1415 (\$1753)	−\$667 (8.5%)	\$10 (0.1%)	\$657 (8.4%)	0.43	−2.3%
All-cause mortality	\$1416 (\$1720)	−\$1235 (15.8%)	\$29 (0.4%)	\$1234 (15.7%)	0.72	−27.3%
Uncertainty in therapy effectiveness or population natural history						
Greater effectiveness uncertainty	\$1394 (\$1901)	−\$1543 (19.7%)	\$76 (1.0%)	\$1467 (18.7%)	0.73	−26.4%
Lower effect (payer savings)	\$342 (\$1644)	−\$2764 (35.3%)	−\$1388 (17.7%)	−\$202 (2.6%)	0.73	−27.7%
High natural history uncertainty	\$1350 (\$2357)	−\$16 (0.0%)	\$2 (0.0%)	\$15 (0.2%)	0.43	−6.5%
Low natural history uncertainty	\$1440 (\$1519)	−\$1311 (16.7%)	\$69 (0.9%)	\$1260 (16.1%)	0.77	−31.1%
Patient characteristics						
NYHA II‡	\$923 (\$1503)	−\$1198 (15.2%)	\$47 (0.6%)	\$1151 (14.6%)	0.69	−20.7%
NYHA III/IV‡	\$3225 (\$2045)	−\$1188 (15.4%)	\$52 (0.7%)	\$1136 (14.7%)	0.70	−28.1%
Younger§	\$217 (\$1563)	−\$824 (10.0%)	\$301 (3.8%)	\$1264 (15.8%)	0.58	−7.4%
Older§	\$2828 (\$2214)	−\$1018 (13.4%)	\$102 (1.3%)	\$916 (12.1%)	0.58	−18.1%
Modified selection	\$3225 (\$2045)	−\$7653 (99.2%)	−\$7383 (95.7%)	−\$6543 (−4.8%)	0.60	−18.3%
PLR contract design						
5 y Contract	\$11 218 (\$5345)	−\$2475 (15.7%)	\$144 (0.9%)	\$2331 (14.8%)	0.69	−26.7%
1 y Contract	\$90 (\$772)	−\$553 (13.1%)	\$24 (0.6%)	\$529 (12.5%)	0.60	−7.6%
Imprecise effect estimate	\$1416 (\$1720)	\$1447 (18.4%)	\$0 (0.0%)	−\$1447 (18.4%)	−0.28	216.1%
Absolute reduction	\$1416 (\$1720)	−\$1832 (23.3%)	−\$104 (1.3%)	\$1741 (22.2%)	0.87	−45.7%
One-sided	\$1416 (\$1720)	−\$647 (8.2%)	\$195 (2.5%)	\$528 (6.7%)	0.58	−18.6%

CVD indicates cardiovascular death; HFH, heart failure hospitalization; INMB, incremental net monetary benefit; NYHA, New York Heart Association; and PLR, performance-linked reimbursement.

*We performed 10000 simulations. We divided the simulations into tertiles by the INMB with conventional payment. With a successful PLR plan, payment would decrease in simulations with lower INMB with conventional payment.

†Correlation coefficient between the change in payment with PLR and the INMB with conventional payment.

‡In subgroups, NYHA Class III/IV with higher risk of CVD, HFH, lower quality of life, and greater health care costs than NYHA Class II.

§Younger cohort has a higher risk of CV and non-CV mortality and lower health care costs. Older cohort has a higher risk of CV and non-CV mortality and greater health care costs.

||The one-sided plan only reduces payment depending on therapy effectiveness. It includes a premium of 7.9% of sacubitril-valsartan cost compared with conventional payment. The listed average payment changes across simulations incorporates the sacubitril-valsartan premium.

in cardiovascular risk attenuated the benefit of the PLR contract substantially (reduced INMB SD by 7.4%).

Patient Selection

PLR contracts create financial incentives for patient selection. If payers focus on higher-risk patients than the mix specified in the contract (increasing expected mortality) without adjustment of the baseline expected mortality, the measured risk reduction and manufacturer payment would decrease. We modeled unilateral payer enrollment of a higher-risk cohort (eg, only treating NYHA class III/IV as opposed to the expected mix of NYHA class II and III/IV). We assumed the contract did not account for the higher expected 2-year cardiovascular mortality risk of 17.6% compared with 13.8% in the base case, leading to underestimation of the observed treatment effect. In a simulation with observed cardiovascular mortality of 13.4%, the

contract incorrectly estimated a relative risk reduction of 2.5% and reduced payment by over 80%. With the correct expected mortality rate, the calculated risk reduction exceeded the expected effect, and hence would not warrant payment reduction. In this scenario of asymmetric patient selection, payment was reduced by an average of \$7194 (93.2% of total drug costs).

Impact of PLR Contract Design

Time Horizon

Contract effectiveness is also dependent on the time horizon. For chronic diseases, the impact of a therapy's effectiveness on value grows over time. A longer observation period will capture more events and increase payment adjustments. A 5-year contract reduced the INMB SD more than the initial 2-year contract (Table 2). Conversely, PLR effectiveness decreased with a 1-year

contract. However, increasing contract durations introduces other potential consequences. Drug manufacturers expose themselves to long-term obligations based on an unpredictable changing environment. Payers may incur prolonged monitoring costs and the technical challenges of frequent insurance turnover.

Accuracy of Treatment Effect Assessment

Accurately estimating treatment effect is critical to PLR. We assumed the contracting parties could precisely determine the hypothetical expected mortality risk with ACE inhibitor therapy (the counter-factual) to calculate treatment effectiveness. However, variability in patient selection, the effect of unmeasured variables, and other temporal changes in treatment patterns may render estimation difficult. We evaluated the impact of decreased precision in treatment effect estimation. If the contract estimated an expected 2-year cardiovascular mortality of 13.8% (model average) but the uncertainty of their estimate matched the distribution of our model (95% CI, 9.8%–17.7%), calculated treatment effectiveness was only moderately correlated ($r=0.37$) with actual treatment effectiveness. This commonly led to inappropriate payment adjustment and the INMB SD increased with PLR relative to conventional payment. Greater precision in estimates of baseline cardiovascular mortality risk (95% CI, 12.8%–14.9%) improved the correlation between estimated and actual treatment effectiveness ($r=0.80$) but remained insufficient precision to reduce the INMB SD because PLR still over-adjusted a large number of simulations. Reducing the magnitude of PLR adjustments improved performance with imprecise effect estimates (details in supplement).

Relative Versus Absolute Treatment Effect

Given therapy value is determined by absolute benefit, a contract that adjusted payment based on absolute benefit would better connect payment adjustment and baseline value. A contract centered on the absolute risk reduction of cardiovascular mortality reduced the INMB SD by 45.7%. However, similar to an all-cause mortality contract, manufacturers may be wary of entering a contract in which they would be penalized if physicians and insurers select a cohort that is less likely to benefit due to a low cardiovascular risk or substantial risk from noncardiac comorbidities.

One-Sided Contract

Finally, we modeled a one-sided contract in which payment was only adjusted downward if sacubitril-valsartan under performed. We assumed the payer paid a 7.9% premium, in return for unilaterally reducing risk, such that the average payment across simulations remained unchanged. In this case, the PLR contract only reduced INMB SD by 18.6%. However, the one-sided contract reduced the variation in payment for sacubitril-valsartan

(SD of \$955 versus \$1566 with 2-sided contract). If the one-sided contract was enacted without an increased drug price, the average savings would be \$621 per patient over 2 years.

DISCUSSION

PLR has been lauded as a promising tool to assist payers in approaching novel pharmaceuticals with intimidating prices and to assist manufacturers with improved early utilization of therapies.^{9,23–26} For payers, these agreements facilitate patient access to novel therapies by reducing the risk of overpaying for ineffective treatments.^{10,27} With more expedited FDA reviews, there may be marked limitations in the data available at the time of price negotiations.²⁸ Pharmaceutical manufacturers face greater difficulty introducing new products given pharmacy benefits managers and decreased access to physicians.²⁹ Therefore, they are willing to bear the financial risk of PLR contracts to expedite treatment uptake with the expectation that this will increase total revenue.^{7,9,30,31} We found the effectiveness of PLR for payers was highly dependent on the treatment cohort and the contract structure. To be a worthwhile endeavor for payers, they must select a therapy with substantial uncertainty in the absolute clinical benefit and must base the contract on an outcome that can be precisely measured and is strongly tied to overall therapy value.

The PLR plan had a larger impact when there was more uncertainty regarding the absolute treatment effect. High-risk populations, such as those with NYHA class III/IV heart failure, had higher potential variation in treatment value (the INMB SD). This led to PLR having a larger effect in reducing this variation than among lower-risk patients. This suggests PLR contracts should target therapies for high-risk populations and with imprecise effectiveness estimates. Estimates of therapy effectiveness derived from limited trial data

Table 3. Selected Factors Affecting PLR Effectiveness in Reducing Variation in Treatment Value

Improve PLR effectiveness	Reduce PLR effectiveness
Strong association between treatment effect and outcome measure	Weak association between outcome measure and overall clinical benefit/value
More uncertainty regarding treatment effect	Difficulty measuring/arbitrating outcome measure
More precise natural history	Larger competing risk (ie, non-CVD mortality)
Higher baseline risk of outcome measure	Inaccurate untreated event rate estimates
Longer time horizon	Asymmetric patient selection
Greater payer risk aversion	Higher payer turnover
	Cost of implementing and monitoring contract

CVD indicates cardiovascular death; and PLR, performance-linked reimbursement.

may underestimate uncertainty by not accounting for design bias, generalizability concerns, limited long-term follow-up, or real-world adherence. More uncertainty with real-world therapy adoption increases the potential benefit of PLR contracts.

Our primary analysis assumed payer's main goal with PLR was to reduce the risk of overspending on low-value therapies and not necessarily to reduce spending. Manufacturers may only offer 1-sided PLR contracts as a substitute for existing rebates. In most industries, money-back guarantees come at the cost of higher starting prices.²³ In a secondary analysis, we demonstrated that contracts can lead to expected savings if the PLR contract systematically overestimated the treatment effect compared with what is observed in routine practice. If the payer and manufacturer disagree regarding trial generalizability, PLR contracts can facilitate agreement. If the payer is right, they save money in addition to reducing the variability of the value obtained with their purchase.

Therapy value is dependent on multiple factors in addition to effectiveness and cost: baseline risk, competing risks, baseline quality of life, and chronic health care costs. PLR contracts only guarantee therapy value based on a given metric of effectiveness (eg, relative risk reduction of cardiovascular mortality). We demonstrated PLR performance improved when more of the potential variation in value was related to that metric. Factors that strengthened the link between value and estimated therapy effectiveness—higher baseline risk (cardiovascular mortality), lower competing risk (noncardiovascular mortality), precise estimates of natural history, and increased uncertainty in treatment effectiveness—improved the performance of PLR (Table 3).

Certain factors that reduce the impact of PLR, such as a lower baseline risk or greater imprecision in the natural history, would be less influential if contracts were based on absolute therapy benefit rather than relative effectiveness. This would largely shift the risk of treating a low-risk population with high competing risks from the payer to the manufacturer. However, manufacturers may be wary of accepting such risk given their limited ability to influence patient selection for postmarket monitoring.

Risk-sharing agreements require easily measured outcomes strongly associated to primary treatment benefits.^{7,27} For oncological drugs, therapy response may be detectable in the short-term and linked to long-term survival.⁹ For heart failure, reductions in mortality or hospitalization are currently easier to broadly measure than benefits centered on quality of life. However, distinguishing between cardiovascular and noncardiovascular death may present challenges and opportunities for contract manipulation. Payers should consider incorporating all-cause mortality into contracts because it is easier to objectively measure and takes into account potential variation in competing risks. Although sacubitril-valsartan does not directly

affect noncardiac mortality, that risk still affects the value obtained with therapy. Therefore, PLR with an all-cause mortality metric provided better insurance than a contract centered on cardiovascular mortality.

A contract based on cardiovascular mortality outperformed a similar contract centered on heart failure hospitalizations because sacubitril-valsartan's clinical benefit was driven by mortality reduction. The stronger the association between heart failure hospitalization and cardiovascular mortality, in terms of both baseline risk and therapy reduction, the better the contract based on hospitalizations. Surrogate outcomes that are modifiable, observable in the short-term, and strongly correlated to the outcomes that drive value (ie, mortality) can be used.^{7,27} For example, Merck previously offered 6 month refunds for individuals without adequate LDL (low-density lipoprotein) cholesterol lowering with simvastatin.³¹ For statin therapy, LDL cholesterol reduction is a strong surrogate for clinical benefit that is easily measured. However, like LDL reduction with some non-statin medications, surrogate measures may not universally predict long-term outcomes with novel therapies.³² Additionally, financial incentives encourage manipulation of softer end points.

Identifying a well-defined population is critical because accurate estimation of risk without therapy is essential to estimate treatment effect and appropriately adjust payment. However, the precision required to estimate effectiveness will be challenging to obtain. Evolving treatments, comorbidities, and outpatient care intensity all simultaneously affect outcomes. Clinical trials providing treatment data often underrepresent real-world variability. Developing effective PLR contracts for diverse, real-world populations will require accurate predictions of event rates using risk models based on enrollee characteristics and historical controls. Manufacturers and payers may prefer shorter contract durations to better isolate the impact of therapy; however, we found short durations also reduce the impact of these contracts. This emphasizes the critical role of risk prediction.

Risk-sharing plans are based on the assumption that payers want to invest in interventions that improve clinical outcomes and have risk aversion towards investing in new therapies with uncertain clinical benefit. This risk aversion is likely enhanced by short-term budgetary concerns when payers are suddenly faced with expensive drugs for large patient populations. Smaller budgets may increase interest in PLR. However, these payers may also require greater administrative cost per patient. Time burden and administrative costs have been cited as major implementation challenges.²⁴ Unless PLR contracts are carefully designed, the costs of negotiating contracts, monitoring the program, and transferring payments may eclipse benefits.²⁸ Additionally, we demonstrated PLR contracts will increase budgetary uncertainty effect given

payments could increase if the drug exceeds expectation. While this is reduced with one-sided contracts, we also demonstrated one-sided contracts are less effective at insuring therapy value.

PLR agreements will need to protect manufacturers from the risk of asymmetric information. Unilateral enrollment of a higher risk cohort could penalize manufacturers substantially. Contracts will need to mitigate this risk by detailing the intended treatment cohort and constructing a mechanism by which manufacturers can verify enrollee characteristics, for example, retrospective calculation of baseline risk based on actual case-mix—to reduce the possibility of such patient selection. The incorporation of accurate prospective estimation of expected event rates based on observed enrollee characteristics may be a critical component to developing contracts that are less susceptible to patient selection. These safeguards may raise the cost of administering the contract and reduce its desirability. If more subtle forms of asymmetric selection still occurred, it could discourage manufacturers from future participation.

Our analysis has important limitations. First, PLR contracts for sacubitril-valsartan are not publicly available. We modeled plausible contracts and varied our assumptions in sensitivity analyses. Our analysis used contracts with 2-sided risk to focus on the requirements for PLR to effectively reduce the uncertainty in therapy value. Second, the costs of administering actual PLR contracts is unclear. We were thereby unable to directly compare costs and benefits. Finally, we used a willingness-to-pay threshold of \$150 000 per QALY. While the willingness-to-pay threshold will be critical for determining the value of a therapy to a payer, it was less critical for our analysis as we focused on understanding how PLR design and therapy influenced plan effectiveness rather than classifying absolute therapy value.

Patient access to expensive, novel therapies is often limited by concerns regarding the uncertain value of these treatments. PLR has been hailed as an exciting opportunity to shift this risk to drug manufacturers to improve patient access. Ideally, however, PLR could benefit the manufacturer in addition to the payer and patients. The payer's risk of overpaying for a low-value therapy is reduced; the manufacturer assumes risk on a per-unit basis while increasing the overall volume of sales and expected revenue via early adoption, and patients gain earlier access to therapies with expected clinical benefit. We explored the potential gains and risks of such contracts from the perspectives of the payer and the manufacturer. Developing a contract that optimally insures therapy value requires careful selection of the outcome measure and treatment cohort. Even with such a design, successful implementation of PLR will require innovation around precisely estimating actual treatment effect in real-world settings and additional contract features that mitigate the risks of

asymmetric information and selection. PLRs could serve a valuable role of guaranteeing appropriate payment for therapies with high evidence uncertainty; however, if they are unable to address the many challenges illustrated in this analysis, they will likely be ineffective or unsustainable.

ARTICLE INFORMATION

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Supplemental Material

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