

Impact of Co-pay Assistance on Patient, Clinical, and Economic Outcomes

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Almost half the individuals in the United States are prescribed medicine and nearly a quarter take 3 or more medications.¹ However, many people struggle to take their medications as prescribed. Across clinical conditions and populations, approximately half of patients do not adhere to their prescribed treatments.^{1,2} Such adherence is highly important to achieve the clinical benefits of prescription medicines. There are, however, many barriers to adherence,^{1,2} with cost being a key driver of adherence problems. A number of studies have demonstrated that patients are sensitive to even small adjustments in their out-of-pocket (OOP) costs, which can result in nonadherence.^{3,4} Patient OOP costs have increased over time and may affect an individual's ability to access prescription medications.^{5,6}

Patient assistance programs (PAPs) have been proposed as a potential method to reduce OOP costs. They provide financial assistance, enabling patients to access medications for reduced or no cost. PAPs are sponsored by different entities, including pharmaceutical manufacturers, governments, and other third parties,^{7,8} and may apply to both generic and branded drugs.⁸ Commonly, PAPs are operationalized by the use of prescription discount co-payment (co-pay) cards and coupons distributed by providers or directly to patients, which provide a discount on cost sharing. Alternatively, assistance may include access to free drugs and cash subsidies. Drug manufacturer co-pay cards/coupons have been criticized for potentially increasing total costs.^{9,10} In response to potential cost impacts of the use of co-pay cards, payers have recently offered programs discouraging their use via co-pay accumulator or maximizer initiatives. These discourage the use of coupons by disallowing the value of the coupon to count against a patient's deductible allowance.

Beyond the immediate impact on patient OOP costs, co-pay assistance may affect treatment utilization, such as adherence, with downstream impacts on clinical, economic, or humanistic outcomes (Figure 1¹¹). Given the increased attention paid to co-pay assistance and patient OOP costs,¹² a literature review was conducted to identify peer-reviewed, published literature evaluating the impact of co-pay assistance on the clinical outcomes of adherence to and persistence with treatment, in addition to economic and patient outcomes.

ABSTRACT

OBJECTIVES: Patient assistance programs (eg, co-pay assistance) may reduce patients' out-of-pocket costs for prescription medicines, providing financial assistance to access medicines for reduced or no cost. A literature review to identify peer-reviewed articles on studies evaluating the impact of co-pay assistance on clinical, patient, and economic outcomes was conducted.

STUDY DESIGN: A literature review was conducted by searching Embase and MEDLINE.

METHODS: The population of interest was patients who had received co-pay assistance; the intervention was co-pay assistance; comparator was no co-pay assistance; and outcomes were treatment adherence, compliance, discontinuation, interruption, barriers to adherence, and specific therapeutic outcomes. Articles from the United States published between January 2015 and June 2021 were included.

RESULTS: A total of 1249 initial articles were identified, of which 19 published articles representing 12 studies were included. Most studies were retrospective claims analyses ($n = 10$); there was also 1 randomized controlled trial and 1 prospective and observational study. One article assessed the association between co-pay assistance and patient-reported outcomes, 7 explored the relationship between co-pay assistance and clinical outcomes, and 6 assessed the impact of policy/program changes on co-pay assistance. Co-pay assistance was associated with improved treatment persistence/adherence across various diseases, with limited indirect evidence of this translating into clinical outcomes improvements. Lack of long-term outcomes and uncertainty around program sustainment from co-pay assistance programs are limitations.

CONCLUSIONS: Limited evidence suggests a potential link between co-pay assistance and clinical outcomes; future research addressing study design challenges in measuring the effects of co-pay assistance is needed.

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TAKEAWAY POINTS

This literature review focuses on the impact of patient assistance programs and outcomes. The findings include the following:

- ▶ Some evidence of a positive association between co-pay assistance and adherence, which may suggest an indirect association with outcomes.
- ▶ Limited direct evidence on clinical outcomes, and thus further research is needed to understand the impact of co-pay assistance on clinical outcomes.

METHODS

This literature review was conducted to identify peer-reviewed articles on studies evaluating the impact of co-pay assistance on clinical, patient, and economic outcomes.

Eligibility Criteria

The literature search was guided by a Population, Intervention, Comparator, and Outcomes, or PICO, approach; the population was defined as patients who received co-pay assistance; the intervention and comparator were co-pay assistance and no co-pay assistance, respectively; and the outcomes were treatment adherence, compliance, discontinuation, interruption, barriers to adherence, and specific therapeutic outcomes.

Given that the focus was on original research, review articles, editorials, letters, notes, commentaries, case studies, and non-English publications were excluded. As the investigation sought to assess the situation in the United States only, studies conducted outside the United States were excluded.

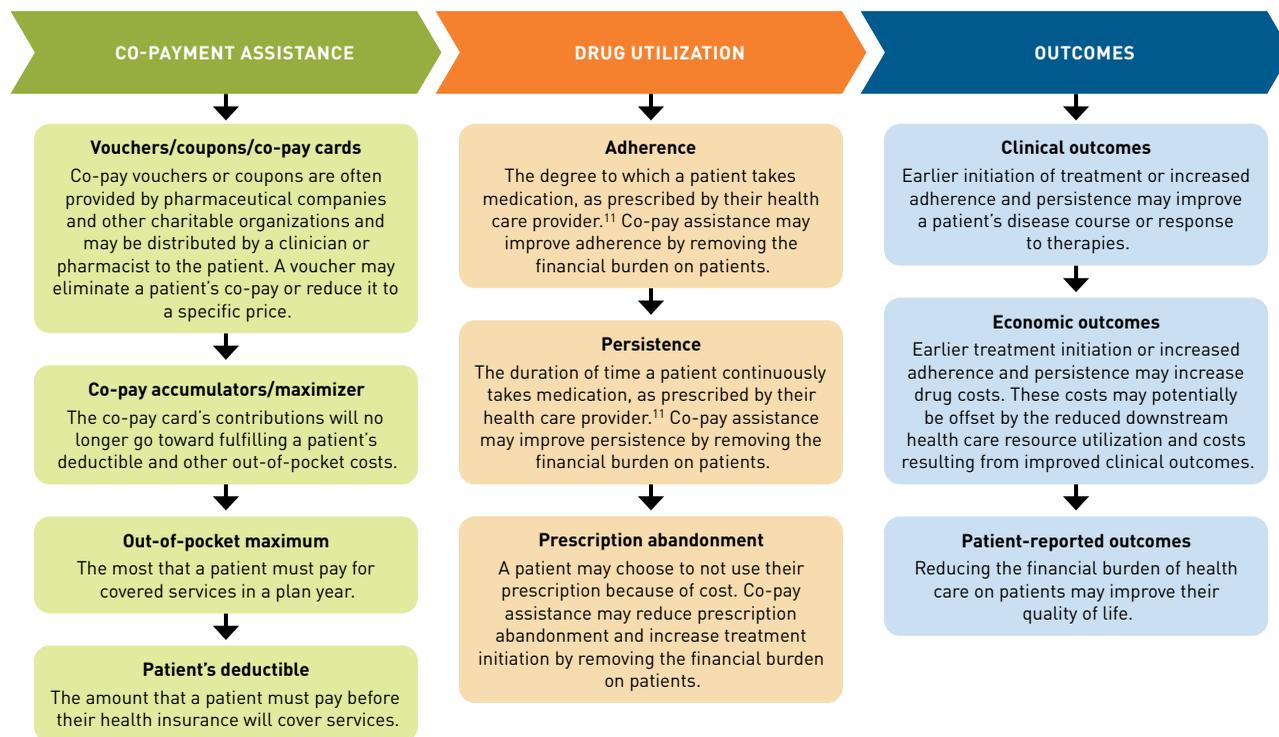
Data Sources and Search Strategy

The electronic literature databases Embase and MEDLINE were searched for papers and conference abstracts using ProQuest Dialog software. The search string used is shown in Figure 2.

Search terms were identified based on studies known prior to the review.¹³⁻¹⁷ Terms were reviewed for completeness, and the search string was modified until all previously known studies were captured. A review identifying conceptual approaches to adherence research

Search results were limited to articles from the United States published between January 2015 and June 2021. Studies not primarily related to co-pay assistance for medications (eg, vouchers incentivizing smoking cessation, co-pay assistance for nondrug services) were excluded. Articles reporting only impacts of co-pay assistance on OOP costs were also excluded, as were those not providing sufficient detail on at least 1 specific outcome of interest.

FIGURE 1. Framework of the Impact of Co-payment Assistance on Clinical Outcomes¹¹



was used to inform the search terms employed describing medication-taking behavior.¹¹

Records identified via other sources included those found through reviewing references and email notifications from journals of new publications.

Study Selection

Article titles and abstracts were reviewed by 2 independent reviewers (K.D.P. and W.B.W.), with discussions as necessary during the review process to ensure comparable understanding of selection criteria. Disagreements were resolved by consensus between the 2 reviewers, with a third reviewer being the decision maker if no resolution could be achieved. Articles were classified as relevant, not relevant but related, or not relevant. Those considered not relevant but related (eg, commentary papers) were considered for contextual discussion points. Full-text review was conducted for abstracts that met the initial screening criteria.

Data Collection, Data Items, Summary Measures, and Synthesis of Results

Data for key study design, patient population, demographics, end points, and outcomes of interest were extracted into a spreadsheet, allowing the authors to summarize the key themes.

RESULTS

Study Selection

The search yielded a total of 1249 results, of which 19 published manuscripts/conference abstracts, representing 12 studies, were included in the final sample (Figure 2); 12 articles were relevant and are covered here, and others informed the discussion. A large proportion of studies were excluded because they were not based in the United States (n = 351) or because the outcome (ie, no clinical/humanistic outcome, or economic outcome consists of OOP costs only) or the population (ie, non-medication-related cost sharing) was not of interest (n = 358 and n = 443, respectively). There was 1 conflicting review, which was resolved after discussion and additional scrutiny of the article by both reviewers concurrently.

Study Characteristics

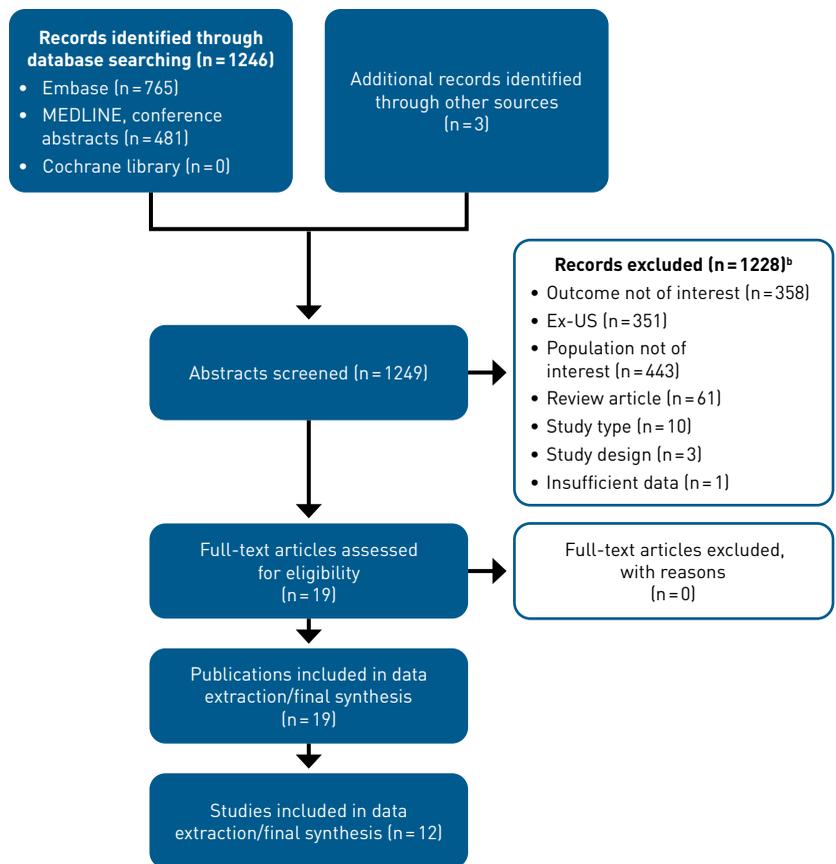
A summary of studies in the final sample is shown in [Table 1](#).¹³⁻²⁸ The majority of studies were retrospective claims analyses (n = 10/12; 83%), 1 study was a randomized controlled trial, and 1 was prospective and observational. The association between co-pay assistance and

the following outcomes was reported: patient-reported outcomes (n = 1), clinical outcomes (n = 7, including 5 measuring treatment persistence/discontinuation or adherence), co-pay assistance policy (n = 6), and co-pay accumulators and maximizers (n = 1). [Table 2](#)^{14,20,23,29,30} provides a summary of the studies identified that addressed direct or indirect measurements of co-pay assistance on outcomes.

Impact of Co-pay Assistance on Patient-Reported Outcomes

De Souza et al¹⁸ examined the effects of patient-level interventions, including co-pay assistance, patient navigators, social workers, financial counselors, support groups, and transportation vouchers, on financial toxicity, defined as an adverse event of cancer treatments. This prospective observational study found that individuals with

FIGURE 2. Flow Diagram of Study Selection Process*



The electronic literature databases Embase and MEDLINE were searched for papers and conference abstracts using ProQuest Dialog software and the following search string: (((TI,AB[copy] OR TI,AB[~co-pay*] OR EMB[~copayment*]) AND [card* OR coupon* OR voucher* OR accumulator*]) OR [coupon* OR voucher* OR accumulator*]) AND [cost* OR economic* OR adherence OR compliance OR persistence OR hospitalization* OR outcome* OR initiat* OR discontin* OR utilization* OR concordance* OR pharmionic*] AND [yr(2015) or yr(2016) or yr(2017) or yr(2018) or yr(2019) or yr(2020) AND yr(2021) (united states*)].

^bDuplicates were excluded by hand searching during the screening process.

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TABLE 1. Summary of Included Studies¹³⁻²⁸

Author (year) [study]; companion publications	Study design	Study size	Population	Demographics	Intervention/comparators	Outcome	Result
De Souza et al (2017) ¹⁸	Prospective observational	308	Patients with cancer receiving co-pay assistance (28% had multiple myeloma)	Not reported	Pre- and post receipt of co-pay assistance	Financial toxicity improvement as measured by cost and HRQOL as measured by FACT-G	Patients with cancer who received co-pay assistance had a significant improvement in financial toxicity over time; however, this was not clearly translated into HRQOL improvements, most likely owing to the multidimensional nature of HRQOL.
Wang et al (2019) ²³ [ARTEMIS]; Fanaroff et al (2020) ²⁰⁻²² [article and abstract] and Doll et al (2020) ¹⁹	Cluster randomized controlled trial	11,001	Acute MI	<p>Age (median)</p> <ul style="list-style-type: none"> • Intervention: 62 years • Usual care: 62 years <p>Sex</p> <ul style="list-style-type: none"> • Intervention: 68.6% male • Usual care: 68.5% male <p>Race</p> <ul style="list-style-type: none"> • Intervention: 89.7% White • Usual care: 86.2% White <p>Private insurance</p> <ul style="list-style-type: none"> • Intervention: 63.1% • Usual care: 65.4% 	Co-pay vouchers for clopidogrel or ticagrelor for 1 year vs no vouchers	Persistence of P2Y ₁₂ inhibitor therapy, MACE (death, recurrent MI, or stroke) at 1 year	Co-pay vouchers for P2Y ₁₂ inhibitors significantly increased patient-reported medication persistence through 1 year (87.0% vs 83.8%), but there was no significant difference in 1-year MACE outcome (HR, 1.07).
Sherman et al (2019) ¹⁶ [article and abstract]	Retrospective claims analysis	603	Patients receiving autoimmune specialty drugs	<p>HSA: 60.5%</p> <p>PPD: 39.5%</p> <p>Age: 43 years</p> <p>Sex: 60% female</p> <p>AGI: \$68,273</p>	Pre- and post CAAP implementation	Adherence (PDC), treatment discontinuation	Implementation of a CAAP was associated with significant reductions in autoimmune specialty drug adherence and a significantly higher risk of treatment discontinuation.
Seetasith et al (2019) ¹⁴	Retrospective claims analysis	3143	Patients prescribed ALKis approved for treatment of ALK-positive NSCLC	<p>Age (mean)</p> <ul style="list-style-type: none"> • Co-pay assistance: 65 years • No co-pay assistance: 60 years <p>Sex</p> <ul style="list-style-type: none"> • Co-pay assistance: 40% male • No co-pay assistance: 44.3% male 	Co-pay assistance for ALKi vs no co-pay assistance	Prescription abandonment rate, time to prescription pickup, persistence with treatment	Patients with co-pay assistance were less likely to abandon their prescriptions, were more likely to pick up their prescriptions sooner, and had a lower risk of discontinuing treatment.
Sullivan et al (2016) ¹⁷	Retrospective claims analysis comparing pre- and post co-pay assistance ban lift in Massachusetts	5783	Commercially insured patients with autoimmune disorders	<p>Lower income</p> <ul style="list-style-type: none"> • Massachusetts: 12% • Control: 14% 	Patients from Massachusetts vs control patients	Uptake of biologic therapies	Positive relationship between co-pay card availability and biologic access, with potentially larger effects for patients on lower incomes.
Seetasith et al (2019) ¹⁵	Retrospective claims analysis comparing pre- and post co-pay assistance ban lift in Massachusetts	699,203	Patients with asthma, chronic heart failure, COPD, inflammatory bowel disease, multiple sclerosis, or rheumatoid arthritis	Not reported	Patients from Massachusetts vs control patients	Disease-related costs, hospitalizations	<ul style="list-style-type: none"> • Significant annual reductions in the number of hospitalizations within all 6 disease areas. • Significant annual reductions in medical costs for 4 of 6 diseases (asthma, irritable bowel disease, multiple sclerosis, and rheumatoid arthritis) in the 5-year period following the amendment.

(continued)

TABLE 1. (Continued) Summary of Included Studies¹³⁻²⁸

Author (year) [study]; companion publications	Study design	Study size	Population	Demographics	Intervention/comparators	Outcome	Result
Daubresse et al (2017) [abstract 2015; full publication 2017] ¹³	Retrospective claims analysis comparing statin coupon users with coupon nonusers	~1.1 million	Commercially insured incident statin users starting atorvastatin or rosuvastatin treatment between June 2006 and February 2013	Age (mean) • Incident coupon users: 49 years • No coupon use: 50 years Sex (% female) • Incident coupon users: 55% • No coupon use: 57%	Coupon users vs coupon nonusers	Utilization, switching, termination, OOP and total costs	<ul style="list-style-type: none"> • Coupon users had similar levels of utilizing and switching to nonusers • Coupon users were 11.1% less likely to discontinue statin therapy than coupon nonusers at 4 years. Length of time until a discontinuation rate of 25% was shorter for coupon nonusers (7 months) than for subsequent coupon users (35 months). • Coupon users had lower OOP costs than nonusers; however, total monthly costs were similar.
Cherikh et al (2019) ²⁴	Retrospective claims analysis for IS medications	949	Adult patients with heart transplants	Age (median): 55 years	The analysis was limited to adult recipients of deceased donor heart transplants performed within a year (± 90 days) prior to the first fill, and who had > 2 pharmacy claims for any IS at least 150 days apart in the 12 months after their first fill during the study period.	Adherence to IS medication	Receipt of some co-pay assistance was associated with a greater likelihood of adherence to IS medications (odds ratio, 0.33; <i>P</i> < .09).
Huang et al (2020) ²⁶	Retrospective claims analysis for drugs with close therapeutic generic substitute	Not reported (claims-level analysis)	Massachusetts' Medicare population and a sample representing ~40% of commercially insured patients in Massachusetts	Not reported (claims-level analysis)	Medicare vs commercially insured patients post availability of coupons in Massachusetts	Use of branded vs generic alternatives	<ul style="list-style-type: none"> • Coupon availability was associated with significantly higher branded drug use in 10 of the 14 drug sets. • Across the 14 sets, spending was on average 18% higher per set than it would have been if commercial members used the generic close therapeutic substitute.
Dafny et al (2017) ²⁵	Retrospective claims analysis for drugs with bioequivalent generics	Not reported (claims-level analysis)	New Hampshire and Massachusetts residents captured in the NHCHIS claims data	Not reported (claims-level analysis)	New Hampshire vs Massachusetts residents	Share of prescriptions filled using generics	Coupons associated with 3.4% higher generic use.
Rome et al (2021) ²⁷	Retrospective claims analysis for drugs facing first-time generic competition	Not reported (claims-level analysis)	Commercially insured patients in California and other Western states	Not reported (claims-level analysis)	California vs Western states	Monthly percentage of generic claims	<ul style="list-style-type: none"> • Coupon ban not associated with changes in generic use (decrease of 0.06%; <i>P</i> = .92) • No significant change in trend over time (<i>P</i> = .77)

(continued)

TABLE 1. (Continued) Summary of Included Studies¹³⁻²⁸

Author (year) [study]; companion publications	Study design	Study size	Population	Demographics	Intervention/comparators	Outcome	Result
Brouwer et al (2021) ²⁸	Retrospective claims analysis	789	KPWA patients with multiple sclerosis	Sex (% female): • No PAP: 72.9% • PAP: 75.5% CCS > 1 • No PAP: 36.4% • PAP: 26.4%	Patients with at least 1 claim with patient assistance vs no patient assistance	Price elasticity of demand	Presence of PAPs did not significantly impact demand ($P = .852$).

AGI, adjusted gross income; ALK, anaplastic lymphoma kinase; ALKi, ALK inhibitor; CAAP, co-pay assistance accumulator program; CCS, Charlson Comorbidity Index Score; COPD, chronic obstructive pulmonary disease; FACT-G, Functional Assessment of Cancer Therapy - General; HRQOL, health-related quality of life; HSA, health savings account; IS, immunosuppressant; KPWA, Kaiser Permanente Washington; MACE, major adverse cardiovascular events; MI, myocardial infarction; NHCHIS, New Hampshire Comprehensive Health Care Information System; NSCLC, non-small cell lung cancer; OOP, out-of-pocket; PAP, patient assistance program; PDC, proportion of days covered; PPO, preferred provider organization.

TABLE 2. Summary of Direct and Indirect Measurements of Co-pay Assistance on Outcomes^{14,20,23,29,30}

Drug class	Population	Effect of co-pay assistance on drug utilization	Effect of co-pay assistance on clinical outcomes	Direct or indirect measurement of clinical outcome
P2Y ₁₂ inhibitors	Acute MI: ITT	Increased persistence (adjusted OR, 1.19; 95% CI, 1.02-1.40) ²³	No significant difference in MACE at 1 year (adjusted HR, 1.07; 95% CI, 0.93-1.25) ²³	Direct
P2Y ₁₂ inhibitors	Acute MI: stratified by risk of voucher use	Dependent on risk [OR [95% CI] for 1-year persistence, intervention vs usual care: 1.25 [1.05-1.47] for low likelihood, 1.31 [1.10-1.56] for intermediate likelihood, and 1.86 [1.48-2.33] for high likelihood) ²⁰	Dependent on risk [low likelihood: HR, 1.17; 95% CI, 0.98-1.39; intermediate likelihood: HR, 1.58; 95% CI, 1.18-2.11; and high likelihood: HR, 0.80; 95% CI, 0.56-1.16] ²⁰	Direct
ALKis	ALKis in NSCLC	Time to treatment was shorter by ~3 weeks (2.6 days vs 25.7 days) ¹⁴	> 3 weeks' delay associated with increased risk of death (adjusted HR, 2.05; 95% CI, 1.13-3.71) ³⁰	Indirect
ALKis	ALKis in NSCLC	Reduced risk of treatment discontinuation (HR, 0.76; 95% CI, 0.66- 0.88) with difference in median time to discontinuation of 43 days ¹⁴	43 days of treatment duration associated with 18% lower risk of disease progression or death and 43% lower risk of death ²⁹	Indirect

ALKi, anaplastic lymphoma kinase inhibitor; ITT, intention to treat; MACE, major adverse cardiovascular events; MI, myocardial infarction; NSCLC, non-small cell lung cancer; OR, odds ratio.

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cancer who received co-pay assistance for their treatments had a significant improvement in financial toxicity over time, with 89% of patients experiencing an improvement over 3 months. However, improvements in financial toxicity did not clearly translate into significant improvements in health-related quality of life (HRQOL), probably owing to the multifaceted nature of HRQOL (ie, effects of disease outweighing improvement in financial toxicity).

Impact of Co-pay Assistance on Clinical Outcomes

The impact of co-pay assistance on clinical outcomes was assessed in 7 articles. The impact on objective clinical outcomes is likely to be mediated by intermediate outcomes, such as adherence to or persistence with treatment (Figure 1¹¹). Five studies related to the ARTEMIS trial (NCT02406677) were identified that measured associations between co-pay assistance and intermediate outcomes, such as treatment adherence and persistence, as well as hard clinical outcomes, such as major adverse cardiovascular events (MACE).

In ARTEMIS, patients using P2Y₁₂ inhibitors were randomized to receive vouchers (with a median value of \$137 for a 30-day medication supply) or usual care with no vouchers. The use of vouchers to offset the cost of medication co-payments for P2Y₁₂ inhibitors significantly increased patient-reported medication persistence at 1 year compared with the control group (87.0% vs 83.8%; $P < .001$; observed increase, 3.3%; 95% CI, 1.0%-5.5%); however, voucher use did not significantly decrease MACE. A post hoc analysis of ARTEMIS found that the effect of vouchers on medication persistence and MACE was dependent on the likelihood of voucher use, with the greatest improvements in medication persistence and reduction in MACE seen in patients most likely to use them.²⁰ A secondary analysis from this study demonstrated that nonpersistence was associated with a higher risk of MACE at 12 months than persistence.²¹

One study examined the impact of coupons on incident statin utilization and costs through a retrospective claims analysis.¹³ The study found that coupon users had \$5 lower average monthly OOP costs at 1 year than coupon nonusers; however, this difference was

not statistically significant. Statin utilization and switching were similar for coupon users and coupon nonusers, but coupon users were 11.1% less likely to terminate statin therapy than coupon nonusers at 4 years. Additionally, this study identified an association between the level of coupon use and statin utilization, with high levels of coupon use resulting in greater statin utilization and a lower likelihood of treatment switching and discontinuation.

A retrospective cohort study of oral anaplastic lymphoma kinase inhibitors (ALKis) in patients with ALK-positive non-small cell lung cancer (NSCLC) found associations between co-pay assistance for incident ALKi users and outcomes, such as the proportion of patients with a prescription abandonment, time to prescription pickup, and treatment persistence.¹⁴ Co-pay assistance decreased OOP costs for a patient's first ALKi prescription by an average of \$1930. In an adjusted analysis, patients with co-pay assistance were more likely to pick up their ALKi prescriptions than those without it (88.2% lower risk of prescription abandonment of their first approved claim), picked up their prescriptions approximately 3 weeks sooner than those without co-pay assistance (2.6 days vs 25.7 days), and were more likely to remain on treatment, with a 24.3% lower risk of discontinuing therapy and an increase in median time to discontinuation of 43 days compared with those without co-pay assistance.

Finally, a retrospective claims analysis for immunosuppressant medications suggested that co-pay assistance was positively associated with adherence in transplant recipients (odds ratio, 1.33; $P = .09$).²⁴

Impact of Co-pay Assistance Policies

The impact of co-pay assistance policies on clinical outcomes was assessed in 6 articles,^{15,17,25-28} with a focus on Massachusetts, which was one of the first states to prohibit manufacturer co-pay assistance under its antikickback statute. In July 2012, the antikickback statute was amended to allow temporary manufacturer co-pay assistance for medicines without a generic equivalent. A study examining the coupon ban found that coupons were associated with increased use of branded drugs facing entry of generic therapeutic alternatives,²⁵ whereas 2 studies assessing the impact of the policy amendment on drug utilization found that it was associated with increased use of autoimmune biologics¹⁷ and branded drugs with close generic therapeutic substitutes.²⁶ A third study assessed medical costs and health care resource utilization associated with the policy across 6 disease areas and found that in the 5-year period following the amendment, the rise in availability of co-pay assistance programs was associated with a significant reduction in the annual number of hospitalizations and annual medical costs in 4 of the 6 disease areas compared with before the antikickback statute amendment.¹⁵ In contrast to some of the findings in Massachusetts, Rome et al²⁷ found no significant changes in generic substitution in the first year after the California ban on co-payment coupons for brand-name drugs with generic competition, and Brouwer et al²⁸ found that PAP use within a regional integrated health system had no effect on drug demand.

Impact of Co-pay Accumulators and Maximizers

Co-pay accumulators and maximizers have been relatively new tools for pharmacy benefit managers. These discourage the use of co-pay cards by restricting the amount on the card that counts against a patient's deductible and OOP cost maximum. Only 1 study on co-pay accumulators was identified, which found associated reductions in adherence and persistence.¹⁶ Sherman et al¹⁶ found that the implementation of a co-pay accumulator adjustment program (CAAP) was associated with significant reductions in autoimmune specialty drug adherence and that the risk of treatment discontinuation was significantly higher following CAAP implementation than before it.

DISCUSSION

The findings of this literature review highlight the limited evidence and the heterogeneous nature of studies in this area. Results of the studies identified suggest that co-pay assistance may have a positive impact on persistence with and adherence to treatment across a range of diseases, with some indirect evidence indicating improvements in clinical outcomes. Although previous reviews on this topic have examined adherence or PAPs as part of a suite of services,^{31,32} our review is unique in that we focused specifically on the effect of PAPs alone on clinical, economic, or humanistic outcomes, and the dearth of evidence indicates that future research is warranted, especially in diverse patient populations and settings.

Impact of Co-pay Assistance on Clinical Outcomes

Adherence to long-term treatment is a complex behavior influenced by a variety of factors and associated with improved outcomes.³³ Although the study on ALKis in NSCLC lacked a direct measurement of clinical outcomes,¹⁵ subsequent studies revealed a potential indirect association (Table 2^{14,20,23,29,30}) between the impact of co-pay assistance and progression-free survival and overall survival. A delay of greater than 3 weeks in filling prescriptions for patients without co-pay assistance (compared with those with co-pay assistance) may be associated with shorter overall survival and a 2-fold increase in the risk of death.³⁰ Furthermore, poor treatment persistence in those without co-pay assistance has been shown to have a clinical bearing. The authors of one retrospective database study reported that each additional month on ALKi therapy was associated with a 13% lower risk of disease progression or death and a 32% lower risk of death.²⁹ Applying these reduced risks per month to the difference of 43 days in treatment duration observed by Seetasith et al,¹⁴ co-pay assistance for ALKi therapy may be associated with an 18% lower risk of disease progression or death and a 43% lower risk of death.

The lack of impact on clinical outcomes in the ARTEMIS study highlights the challenges of studying the effects of co-pay assistance. A number of potential reasons were noted for the lack of alignment between persistence with treatment and clinical outcomes in this study.³⁴ The introduction of vouchers led to only limited differences in guideline-preferred therapies between groups, and relatively

low adherence levels were detected based on prescription fill data; both may have contributed to challenges in detecting differences in clinical outcomes, especially in the context of the sample sizes and adherence levels. Additionally, in this study, 27% of patients randomized to the intervention group failed to use their vouchers. Taken together, co-pay assistance was shown to be a factor in improved persistence with P2Y₁₂ therapy. However, a multifactorial approach including co-pay assistance may be required to improve clinical outcomes in this disease area.

Limitations and Implications for Future Research

This review was limited to the past 6 years, given the rapid changes in the policy environment, and focused specifically on co-pay assistance programs and policies, which form part of a larger body of literature examining other related aspects. Several studies have demonstrated that higher OOP costs are associated with prescription abandonment, lower adherence, and/or higher rates of discontinuation.^{5,35,36} Furthermore, studies have examined different mechanisms to reduce or eliminate co-payments, but the effectiveness (and practicality of implementing these) have varied. For example, Volpp et al³⁷ found no effect of eliminating antihypertensive co-pays via post hoc rebates on blood pressure control. In contrast, studies examining the impact of patient support programs³⁸ or financial navigators,³⁹ both of which may include co-pay assistance, have found associations with improved quality of life, adherence/persistence, and costs. Given the multifaceted nature of these interventions, however, the extent to which these effects are attributable to co-pay assistance is unclear. Nonetheless, co-pay assistance programs represent a relatively practical mechanism to achieve lower OOP costs, and thus are the focus of this review.

The small number of studies identified is a limitation, indicating the need for future research, particularly on longer-term outcomes. However, a number of obstacles to collection and analysis of these data remain, including access and study design challenges, such as selection of the appropriate control group. For instance, despite ARTEMIS being a prospective randomized controlled trial, there were challenges in evaluating the impact of co-pay assistance because of difficulties selecting the appropriate study population (ie, individuals likely to use co-pay assistance in the real world). Use of secondary data sources may be a more practical approach to evaluate effects of co-pay assistance, but this is not without challenges. These include (1) few data sources, mostly limited to open claims, to identify co-pay assistance while also making it challenging to measure adherence/persistence due to the lack of enrollment data; and (2) claims data linked to electronic health records may be required, although sufficient sample sizes may be challenging. Lastly, identification of the appropriate counterfactual cohort may be challenging (ie, individuals who may be eligible for co-pay assistance but did not receive it) because data for variables that might indicate eligibility, such as income, are often unavailable. Future work on enhancing and linking data sets is required to capture the relevant data points needed to advance research in this area.

Lastly, additional research may support ongoing health policy discussions around access to co-pay assistance programs. Studies have found conflicting results on the impact of generic utilization,^{26,27} and further research is needed to inform future policies. Additionally, several policy changes have been made in response to the co-pay accumulators, with some states banning the use of such programs. Evolving policy includes the HHS Notice of Benefit and Payment Parameters for 2021,⁴⁰ which allows health plans flexibility in whether to count manufacturer co-pay assistance toward deductibles or OOP maximums—a reversal of the previous year's policy of requiring plans to count co-pay assistance toward deductibles and OOP maximums. Well-designed research would inform these evolving policies.

CONCLUSIONS

Although existing literature on the relationship between co-pay assistance and outcomes is limited, there is a signal that co-pay assistance can have a positive impact on treatment persistence and adherence across clinical conditions, with indirect evidence suggesting clinical outcome benefits. These findings should be considered in context, as studies have yet to evaluate long-term outcomes and program sustainment. Additional data measuring the direct link between co-pay assistance and clinical outcomes are needed. Future research should address the numerous study design challenges involved in measuring the effects of co-pay assistance. ■

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