Prostacyclin Use Among Patients with Pulmonary Arterial Hypertension in the United States: A Retrospective Analysis of a Large Health Care Claims Database

Charles D. Burger, MD, FCCP; Janis A. Pruett, EdD, MSN, FNP-BC; Cassandra A. Lickert, MD; Ariel Berger, MPH; Brian Murphy, MS; and William Drake, III, PharmD

ABSTRACT

BACKGROUND: Prostacyclins play an important role in the management of pulmonary arterial hypertension (PAH). Intravenous prostacyclin was the first disease-specific treatment for patients with PAH. Subcutaneous and nonparenteral (oral or inhaled) formulations have subsequently become available. However, data are lacking on how these different prostacyclin formulations are being used in clinical practice.

OBJECTIVES: To (a) conduct retrospective analyses of a large U.S. health care claims database to describe the characteristics of patients with PAH initiating prostacyclin therapy, and (b) evaluate their treatment patterns, health care resource use, and associated costs.

METHODS: Truven Commercial and Medicare databases were used to define annual cohorts of adults with PAH between January 1, 2010, and October 31, 2015. These patients were identified based on claims with ICD-9-CM diagnoses indicative of PAH (codes 416.0 or 416.8) and claims for PAH-specific medications and PAH-related procedures. Patients with evidence of receiving a prostacyclin were identified, and prostacyclin use was categorized as parenteral versus nonparenteral. Health care costs were assessed alternatively employing an all-cause and PAH-related perspective.

RESULTS: Of 13,633 adults with identified PAH, 3,006 (22.0%) received a prostacyclin during at least 1 year of the study period, and annual prevalence of prostacyclin use ranged from 19.9% to 22.6%. Across calendar years, the median age of prostacyclin users ranged from 56 to 58 years, and 71.9%-75.8% were female. Among prostacyclin users, parenteral prostacyclin use declined from 63.2% in 2010 to 46.5% in 2015, while use of nonparenteral prostacyclins increased from 39.7% to 56.2% over the same period (both $P < 0.001$). Few patients (2.7%-4.1%) received both parenteral and nonparenteral formulations in a given calendar year. Among patients using prostacyclins, receipt of other PAH-specific medications increased from 62.1% in 2010 to 79.2% in 2015. Comparing the 6 months preceding the first prostacyclin prescription (any formulation) to the 6 months subsequent, mean overall health care costs rose from \$61,243 to \$119,283, and PAH-related health care costs increased from \$58,815 to \$116,661, driven mainly by PAH-specific medications, spending on which increased from \$15,053 to \$73,705 (all $P < 0.001$).

CONCLUSIONS: While overall use of prostacyclins was relatively constant from 2010 to 2015, our findings revealed a shift from parenteral to nonparenteral formulations, coupled with increased prescribing of PAH-related medications from other drug classes. Further research is needed to better understand how these changes in patterns of prostacyclin use affect levels of health care resource utilization and costs and patients' overall quality of life.

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What is already known about this subject

- Retrospective analyses of claims databases have reported low rates of prostacyclin use among patients with pulmonary arterial hypertension (PAH) before 2009.
- Treatment options for PAH have expanded rapidly since 2009.

What this study adds

- While the overall proportion of PAH patients receiving prostacyclins has been consistent, there has been a shift away from parenteral formulations to newer, nonparenteral prostacyclins.
- Total costs increased following prostacyclin initiation, primarily attributable to the product costs of prostacyclins, and costs of inpatient and outpatient care tended to remain consistent or decrease over time.
- One third and one half of patients newly started on parenteral and nonparenteral prostacyclins, respectively, augmented treatment with PAH-specific agents from different drug classes.

Pulmonary arterial hypertension (PAH) is a rare and debilitating chronic disease of the pulmonary vasculature, characterized by vascular proliferation and remodeling of the small pulmonary arteries.¹ In the absence of effective treatment, these pathological changes result in a progressive increase in pulmonary vascular resistance, potentially leading to right-heart failure and premature death.¹

Medical management of PAH is based on therapy with 1 or more drugs that target its underlying dysfunctional pathways.^{2,3} The first PAH-specific agent to be approved was intravenous (IV) epoprostenol, a synthetic analog of prostaglandin I₂ (also known as prostacyclin), which remains the gold standard for treating patients with advanced disease.⁴ Since epoprostenol, other prostacyclins have been approved for PAH by the U.S. Food and Drug Administration (FDA), including most recently a formulation of IV epoprostenol with enhanced stability at room temperature, as well as subcutaneous treprostinil and nonparenteral agents such as inhaled and oral treprostinil and inhaled iloprost.⁵ The prostacyclin pathway is also targeted by the novel oral prostacyclin receptor agonist, selexipag, which was approved by the FDA in December 2015.⁶ In addition,

PAH-specific agents are currently available from other drug classes, as follows: endothelin receptor antagonists (ERAs; oral ambrisentan, bosentan, and macitentan); phosphodiesterase type-5 inhibitors (PDE-5i's; oral sildenafil and tadalafil); and the soluble guanylate cyclase (sGC) stimulator, oral riociguat.^{5,6}

IV epoprostenol is the only drug therapy to have shown a survival benefit in a controlled trial,⁷ as subsequent placebo-controlled trials with other agents assessing mortality as an endpoint could not ethically be performed.⁸ Consequently, the most recent PAH clinical practice guidelines continue to recommend parenteral prostacyclins for high-risk cases in World Health Organization Functional Class (FC) IV as well as those patients in FC III who have rapid disease progression or other markers of a poor prognosis.^{2,3} In the United States, nonparenteral prostacyclins are currently recommended primarily in combination with agents from other drug classes for PAH patients in FC III or IV.²

Several retrospective claims database studies reported PAH treatment patterns in the United States,⁹⁻¹² but those studies covered time periods before 2009, preceding the availability of the most recently approved agents, namely, inhaled and oral treprostinil, macitentan, riociguat, and selexipag.^{5,13} Similarly, data are lacking to identify whether the prescribing of prostacyclins has increased following the availability of more convenient inhaled and oral forms.

Among patients receiving prostacyclins, even less is known about the real-world use of combination therapy with drugs from different classes, a concept that is increasingly prominent in clinical practice guidelines.^{2,3,14} There is limited real-world evidence on the use of parenteral prostacyclins in the United States other than that based on enrollees in REVEAL (Registry to Evaluate Early And Long-Term PAH Disease Management)—the largest prospective registry of PAH patients—in which approximately 43% of patients were receiving a parenteral prostacyclin and 14% a nonparenteral prostacyclin at time of death (either alone or in combination with an ERA or a PDE-5i).¹⁵ To address this information gap, this study was conducted to assess relatively current patterns of use of prostacyclins and other PAH-specific agents in a large sample of commercially insured adult Americans.

Methods

Data Source

The data sources for this study were the Truven (formerly Medstat) MarketScan Commercial Claims and Encounters Database and the Truven MarketScan Medicare Supplemental Coordination of Benefits Database. These large databases are nationally representative for commercially insured health plan enrollees with medical and pharmacy coverage, have been widely used to conduct retrospective observational research, and are the basis for more than 1,100 peer-reviewed articles published since 1990,¹⁶ including some specific to PAH.^{11,17,18}

The databases included approximately 15 million covered lives during the study period, which spanned January 1, 2010–October 31, 2015 (the latest date for which data were available at the time of analysis). These data have been anonymized and are fully compliant with the Health Insurance Portability and Accountability Act Privacy Rule.

Available demographic and insurance data included age, gender, coverage type, and dates of plan eligibility. Medical claims data available for analysis included disease diagnoses (recorded as *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes); procedures (ICD-9-CM, Current Procedural Terminology-4, and Healthcare Common Procedure Coding System codes); provider specialty; and charged and reimbursed amounts for services.

Pharmacy claims data included details of dispensed drugs (with identification by National Drug Code numbers) and reimbursed amounts.

Study Design and Cohort Selection

Claims data do not contain sufficient detail, such as findings from right heart catheterization (RHC), to confirm a PAH diagnosis. In the absence of such data, and given the nonspecificity of the ICD-9-CM diagnostic codes for PAH (vs. other forms of pulmonary hypertension [PH]),¹⁹ an algorithm was used to identify patients with PAH that was based on similar methods used in previous retrospective database studies in this therapeutic area.^{9,17,20,21}

To increase the sensitivity of ascertainment, broad criteria were applied in the first step, whereby data were extracted from the Truven databases for patients with a diagnosis suggestive of PAH (ICD-9-CM code 416.0 or 416.8) or nonspecific pulmonary heart disease (ICD-9-CM code 416.9); any claim for a PAH-related procedure (RHC or left heart catheterization, cardiac surgery, echocardiogram, and lung/heart-lung transplants); or any prescription for a PAH-specific medication (prostacyclin, prostacyclin receptor agonist, ERA, PDE-5i, and sGC). Database codes are presented in Appendix A (available in online article). No selexipag use was ascertained, since this agent became available after the study period.

Two sets of analyses were performed, one that included all patients with PAH identified in any given year of the study period (“prevalence-based”), the other focused on PAH patients newly initiating prostacyclin treatment (“incidence-based”). For the prevalence-based analyses, patients with PAH were ascertained on the basis of any 1 of the following algorithms: (a) 2 or more outpatient claims with PAH diagnoses (ICD-9-CM codes 416.0 or 416.8) at least 30 days apart and at least 1 prescription for a PAH-specific medication; (b) at least 1 inpatient claim with a PAH diagnosis and at least 1 prescription for a PAH-specific medication; (c) at least 1 outpatient claim with a PAH diagnosis and 2 or more prescriptions for

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TABLE 1 Ascertainment of Prevalence-Based Cohorts of PAH Patients, by Year

Number (%) of patients with:	Year							P Value
	2010	2011	2012	2013	2014	2015 ^a	2010-2015 ^a	
≥ 2 outpatient claims with diagnoses of PAH ≥ 30 days apart and ≥ 1 claim for a PAH-specific medication	3,645	4,470	4,573	4,056	4,067	2,800	12,073	–
≥ 1 inpatient claim with diagnoses of PAH and ≥ 1 claim for a PAH-specific medication	1,662	1,977	2,008	1,820	1,792	1,007	7,766	–
≥ 1 outpatient claim with diagnoses of PAH and ≥ 2 claims for PAH-specific medications	3,972	4,821	5,008	4,394	4,374	3,265	12,538	–
Claim for RHC followed within 1-60 days by ≥ 1 claim with PAH diagnosis, then ≥ 1 claim for a PAH-specific medication	1,108	1,301	1,335	1,116	1,032	607	5,397	–
Total with evidence of PAH	4,525	5,444	5,576	4,971	4,841	3,543	14,430	–
Aged ≥ 18 years	4,298	5,166	5,315	4,733	4,592	3,358	13,633	–
Received prostacyclin	905 (21.1)	1,119 (21.7)	1,109 (20.9)	960 (20.3)	1,038 (22.6)	667 (19.9)	3,006 (22.0)	0.637
Received ERA	2,019 (47.0)	2,318 (44.9)	2,311 (43.5)	1,945 (41.1)	1,910 (41.6)	1,558 (46.4)	5,669 (41.6)	0.002
Received PDE-5i	2,826 (65.8)	3,531 (68.4)	3,804 (71.6)	3,524 (74.5)	3,322 (72.3)	2,443 (72.8)	10,111 (74.2)	<0.001

^aThrough October 31, 2015, only.

ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RHC = right heart catheterization.

PAH-specific medications; or (d) a claim for RHC followed by at least 1 claim with a PAH diagnosis followed by at least 1 prescription for a PAH-specific medication, where the claims for PAH and the PAH-specific medication were both required to be within 60 days of the date of RHC. Six calendar-year cohorts of prevalent PAH patients were constructed across the 2010-2015 study period, each consisting of all patients meeting any 1 of the aforementioned 4 algorithms in the corresponding year. Within a given calendar-year cohort, patients younger than 18 years at the start of the year were excluded.

For the incidence-based analyses, all patients with evidence of receipt of a prostacyclin (any form) during the study period were identified. The earliest date of receipt of prostacyclin during this period was designated the “index date,” and to allow identification of first use of a prostacyclin, patients were required to have a minimum of 6 months of continuous enrollment in their health plan before this date. Patients also were required to have any 1 of the following: (a) 1 or more claims with a PAH diagnosis within the 3-month period before index date; (b) at least 1 prescription for a PAH-specific medication other than a prostacyclin within this 3-month period; or (c) 1 or more claims with a PAH diagnosis within the 4-week period following the index date.

Statistical Analysis

Descriptive statistics were used to describe patients' baseline characteristics and the prescribing patterns for PAH-specific agents across the study period, using counts and percentages for discrete variables, and mean and standard deviation or median and interquartile range for continuous variables. The

Charlson Comorbidity Index (CCI) was constructed from all relevant conditions (each assessed with appropriate ICD-9-CM codes) using standard methods.^{22,23}

Cochran-Armitage tests were used to assess the statistical significance of trends over time in receipt of prostacyclins, ERAs, PDE-5i's, and sGC. Trends in use of these agents were assessed for each therapeutic class (e.g., prostacyclins; ERAs) as well as for selected agents within each class (e.g., epoprostenol, iloprost, treprostinil; ambrisentan, bosentan, macitentan). As necessary, these analyses also were conducted on specific branded products and their generic counterparts (e.g., the trend of epoprostenol prescribing was assessed, as were the trends in prescribing of Flolan [original IV epoprostenol], Veletri [room-temperature-stable formulation], and generic epoprostenol). Two-sided *P* values were used for each of these tests, as there were no a priori hypotheses concerning whether prescribing of any particular agent(s) increased or decreased over the study period.

For the incidence-based analyses, health care costs were assessed alternatively employing a total (i.e., all-cause) and PAH-related perspective. The former was based on all claims for medical care (inpatient or outpatient) and all prescription pharmacotherapy; the latter, on all claims involving a PAH diagnosis, PAH-specific medications, ancillary PAH-related therapies (calcium channel blockers, diuretics, anticoagulants, cardiac glycosides, and oxygen), or PAH-related procedures. Reimbursed amounts were used as a proxy for costs and were computed as the combined amounts paid by health plans and patients (e.g., copays and coinsurance).

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TABLE 2 Characteristics of PAH Patients Using ≥ 1 Prostacyclin, by Year

Characteristic	Year					
	2010	2011	2012	2013	2014	2015 ^a
Number	905	1,119	1,109	960	1,038	667
Age, years						
Mean (SD)	55.0 (14.0)	56.8 (13.9)	56.3 (13.9)	56.4 (14.1)	56.5 (14.2)	55.8 (14.7)
Median (IQR)	56 (46-64)	58 (48-66)	57 (48-65)	57 (47-66)	58 (48-66)	57 (47-65)
Range	(18-89)	(18-90)	(18-90)	(18-92)	(18-93)	(18-94)
Duration of study enrollment in calendar year, months						
Mean (SD)	10.7 (2.7)	10.8 (2.8)	10.9 (2.5)	10.8 (2.7)	10.7 (2.7)	8.2 (2.1)
Median (IQR)	12 (12-12)	12 (12-12)	12 (12-12)	12 (12-12)	12 (11-12)	9 (7-10)
Gender, n (%)						
Male	221 (24.4)	314 (28.1)	290 (26.1)	232 (24.2)	255 (24.6)	165 (24.7)
Female	684 (75.6)	805 (71.9)	819 (73.9)	728 (75.8)	783 (75.4)	502 (75.3)
Geographic region, n (%)						
Northeast	166 (18.3)	235 (21.0)	206 (18.6)	191 (19.9)	208 (20.0)	133 (19.9)
North Central	261 (28.8)	303 (27.1)	276 (24.9)	245 (25.5)	248 (23.9)	170 (25.5)
South	322 (35.6)	368 (32.9)	400 (36.1)	304 (31.7)	360 (34.7)	277 (41.5)
West	145 (16.0)	188 (16.8)	202 (18.2)	191 (19.9)	201 (19.4)	86 (12.9)
Unknown/missing	11 (1.2)	25 (2.2)	25 (2.3)	29 (3.0)	21 (2.0)	1 (0.1)
Payer type, n (%)						
Commercial	694 (76.7)	790 (70.6)	791 (71.3)	679 (70.7)	734 (70.7)	487 (73.0)
Medicare	211 (23.3)	329 (29.4)	318 (28.7)	281 (29.3)	304 (29.3)	180 (27.0)
Charlson Comorbidity Index						
Mean (SD)	3.0 (2.2)	3.0 (2.2)	3.0 (2.2)	3.1 (2.3)	3.0 (2.2)	2.8 (2.0)
Median (IQR)	2 (1-4)	2 (2-4)	2 (1-4)	2 (2-4)	2 (2-4)	2 (1-4)
Comorbidities, n (%)						
Depressive disorders	132 (14.6)	139 (12.4)	171 (15.4)	161 (16.8)	174 (16.8)	84 (12.6)
Anxiety disorders	97 (10.7)	97 (8.7)	124 (11.2)	129 (13.4)	150 (14.5)	67 (10.0)
Sleep disorders	125 (13.8)	177 (15.8)	187 (16.9)	144 (15.0)	155 (14.9)	100 (15.0)
Cerebrovascular disease	76 (8.4)	108 (9.7)	96 (8.7)	80 (8.3)	92 (8.9)	48 (7.2)
Peripheral vascular disease	48 (5.3)	87 (7.8)	75 (6.8)	62 (6.5)	61 (5.9)	28 (4.2)
Coronary heart disease	232 (25.6)	298 (26.6)	280 (25.2)	226 (23.5)	271 (26.1)	161 (24.1)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Raynaud's syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hematological conditions	7 (0.8)	7 (0.6)	4 (0.4)	9 (0.9)	11 (1.1)	9 (1.3)
Liver disease	137 (15.1)	143 (12.8)	149 (13.4)	131 (13.6)	135 (13.0)	66 (9.9)
Renal disease	390 (43.1)	458 (40.9)	469 (42.3)	410 (42.7)	458 (44.1)	263 (39.4)
Diabetes	204 (22.5)	289 (25.8)	281 (25.3)	241 (25.1)	271 (26.1)	170 (25.5)
Neoplasms	158 (17.5)	210 (18.8)	196 (17.7)	171 (17.8)	206 (19.8)	92 (13.8)

^aThrough October 31, 2015, only.

IQR=interquartile range; PAH=pulmonary arterial hypertension; SD=standard deviation.

All costs were adjusted to 2015 U.S. dollars using the medical care component of the Consumer Price Index.²⁴ In the incident prostacyclin new-start cohort, patterns of health care resource utilization and costs were compared between the 6-month periods before and after initiation of prostacyclin therapy, using paired t-tests for continuous variables and McNemar's test for binary data. In these analyses, patients served as their own controls (i.e., were compared against themselves) over relatively short time periods, and thus there was no need to further account for potential confounding.

Results

Prevalence-Based Analyses

PAH-Specific Medication Prescribing Patterns. A total of 14,430 patients had evidence of PAH during the study period, of whom 13,633 were at least 18 years of age and were included in the prevalent PAH cohort. Of these, only 3,006 (22.0%) patients received a prostacyclin (Table 1). The most commonly prescribed drug class was PDE-5i, used by 74.2% of patients; fewer than half (41.6%) received an ERA.

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TABLE 3 Utilization of PAH-Related Therapies by Patients Using ≥ 1 Prostacyclins, by Year

Medication, n patients (%)	Year						P Value
	2010	2011	2012	2013	2014	2015 ^a	
Prostacyclins	905 (100.0)	1,119 (100.0)	1,109 (100.0)	960 (100.0)	1,038 (100.0)	667 (100.0)	
Epoprostenol	283 (31.3)	290 (25.9)	268 (24.2)	237 (24.7)	247 (23.8)	129 (19.3)	<0.001
Flolan	5 (0.6)	5 (0.4)	5 (0.5)	4 (0.4)	4 (0.4)	1 (0.1)	0.269
Veletri	1 (0.1)	6 (0.5)	4 (0.4)	11 (1.1)	24 (2.3)	19 (2.8)	<0.001
Generic	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0.454
Iloprost (Ventavis)	239 (26.4)	205 (18.3)	156 (14.1)	116 (12.1)	96 (9.2)	49 (7.3)	<0.001
Treprostinil	456 (50.4)	692 (61.8)	742 (66.9)	660 (68.8)	744 (71.7)	514 (77.1)	<0.001
Remodulin (IV and SC)	329 (36.4)	359 (32.1)	372 (33.5)	313 (32.6)	331 (31.9)	201 (30.1)	0.023
Tyvaso (inhaled)	132 (14.6)	359 (32.1)	395 (35.6)	366 (38.1)	388 (37.4)	256 (38.4)	<0.001
Orenitram (oral)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	58 (5.6)	85 (12.7)	<0.001
Parenteral prostacyclin	572 (63.2)	613 (54.8)	611 (55.1)	522 (54.4)	550 (53.0)	310 (46.5)	<0.001
Nonparenteral prostacyclin	359 (39.7)	549 (49.1)	543 (49.0)	474 (49.4)	518 (49.9)	375 (56.2)	<0.001
Parenteral and nonparenteral prostacyclin	26 (2.9)	43 (3.8)	45 (4.1)	36 (3.8)	30 (2.9)	18 (2.7)	0.446
Other PAH medications	562 (62.1)	733 (65.5)	741 (66.8)	663 (69.1)	706 (68.0)	528 (79.2)	<0.001
ERA	385 (42.5)	493 (44.1)	486 (43.8)	443 (46.1)	481 (46.3)	366 (54.9)	<0.001
Ambrisentan	126 (13.9)	192 (17.2)	229 (20.6)	210 (21.9)	217 (20.9)	172 (25.8)	<0.001
Bosentan	264 (29.2)	312 (27.9)	266 (24.0)	232 (24.2)	199 (19.2)	97 (14.5)	<0.001
Macitentan	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.7)	119 (11.5)	117 (17.5)	<0.001
PDE-5i	423 (46.7)	562 (50.2)	599 (54.0)	542 (56.5)	568 (54.7)	413 (61.9)	<0.001
Sildenafil	334 (36.9)	380 (34.0)	339 (30.6)	269 (28.0)	267 (25.7)	189 (28.3)	<0.001
Revatio	334 (36.9)	380 (34.0)	333 (30.0)	76 (7.9)	50 (4.8)	17 (2.5)	<0.001
Generic	0 (0.0)	0 (0.0)	117 (10.6)	225 (23.4)	230 (22.2)	174 (26.1)	<0.001
Tadalafil (Adcirca)	118 (13.0)	213 (19.0)	284 (25.6)	289 (30.1)	314 (30.3)	234 (35.1)	<0.001
sGC	0 (0.0)	0 (0.0)	0 (0.0)	12 (1.3)	45 (4.3)	38 (5.7)	<0.001
Exactly 1 of the above 3 categories	316 (34.9)	411 (36.7)	397 (35.8)	333 (34.7)	330 (31.8)	246 (36.9)	0.383
≥ 2 of the above 3 categories	246 (27.2)	322 (28.8)	344 (31.0)	330 (34.4)	376 (36.2)	282 (42.3)	<0.001

^aThrough October 31, 2015 only.

ERA = endothelin receptor antagonist; IV = intravenous; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; SC = subcutaneous; sGC = soluble guanylate cyclase.

Prostacyclin use was relatively constant from 2010 to 2015, ranging between 19.9% in 2015 and 22.6% in 2014 ($P=0.637$ for comparison across all calendar-year cohorts). Although the trend was not linear, there was an overall increase in prescribing of PDE-5i's from 65.8% in 2010 to 72.8% in 2015 ($P<0.001$). Conversely, ERA prescribing decreased from 47.0% in 2010 to 41.6% in 2014 (it rose again to 46.4% in 2015; $P=0.002$).

Characteristics of Prostacyclin Users. Demographic and clinical characteristics of the subset of the cohort who were prostacyclin users are reported in Table 2. The average patient was middle-aged, with both mean and median age in the mid-to-late 50s across calendar years. Approximately three quarters of PAH patients using prostacyclins were female. A high level of comorbid conditions was observed, with similar high CCI values across years. The most common comorbidities across calendar years were renal disease (39.4%-44.1%), diabetes (22.5%-26.1%), and coronary heart disease (23.5%-26.6%).

Prescribing Patterns in Patients Receiving Prostacyclin. Among patients who were prostacyclin users, there was a decrease of nearly 10% in parenteral prostacyclin use and a

corresponding 10% increase in nonparenteral prostacyclin use from 2010 to 2011, followed by relatively consistent distributions of parenteral versus nonparenteral prostacyclin use from 2011 through 2014, with an additional decrease in parenteral prostacyclin (and corresponding increase in nonparenteral prostacyclin) use from 2014 to 2015 (Table 3). The trend for decreasing parenteral and increasing nonparenteral prostacyclin use was statistically significant ($P<0.001$).

In every year, the most commonly used prostacyclin was treprostinil, and there was a trend for increasing use of its inhaled formulation over time; in contrast, use of IV and subcutaneous treprostinil declined over time (all $P<0.001$). The first prescriptions for oral treprostinil were seen in 2014; it was used by 5.6% of patients who received a prostacyclin in that year and by 12.7% in 2015.

Patients receiving prostacyclins also demonstrated increased use of PAH-specific agents of all other drug classes from 62.1% in 2010 to 79.2% in 2015 ($P<0.001$). The first use of sGC in patients receiving prostacyclins was observed in 2013, and increased from 1.3% in that year to 5.7% in 2015 ($P<0.001$).

Incidence-Based Analyses

Demographic characteristics of prostacyclin new-starts were similar to those of the prevalent PAH cohort in that these patients were middle-aged, predominantly female, and had a high level of comorbidities, with a mean CCI of 2.4 (Table 4).

In the 3 months before the index date, 39.6% of prostacyclin new-starts had been hospitalized, 34.1% had visited an emergency room (ER), and nearly all (96.4%) had at least 1 office visit. A high proportion of these hospitalizations and office visits, and one half of ER visits, were PAH-related. Fifty-three percent of new-starts had received at least 1 PAH-specific medication other than a prostacyclin in the 3 months before initiating prostacyclin.

Demographic and clinical characteristics of the patients in the pre- versus post-index analysis are reported in Appendix B (available in online article). Relative to pre-index, the number of inpatient admissions decreased in the postinitiation period for both parenteral ($P<0.001$) and nonparenteral new-starts ($P=0.041$; Table 5). Among patients newly started on nonparenteral prostacyclins, all-cause ER visits decreased in the postinitiation period ($P=0.003$). In contrast, ER visits were relatively consistent from the pre- to post-index period among parenteral prostacyclin users ($P=0.251$).

Across prostacyclin new-starts, mean 6-month aggregate health care costs nearly doubled from \$61,243 during the pre-index period to \$119,283 following therapy initiation ($P<0.001$), nearly exclusively attributable to an increase for PAH-related health care costs, which rose from \$58,815 to \$116,661 ($P<0.001$). This increase in PAH-related health care costs was driven mainly by increased drug costs, which more than doubled their share of total costs from the pre-index period (27.0%) to the post-index period (64.0%). Since the costs of nondrug PAH-related health care decreased following prostacyclin initiation, the additional \$58,804 spent on PAH-related medications exceeded the overall increase of \$57,846 in total PAH-related health care costs.

Among subgroups of new-starts characterized by formulation of prostacyclin received on the index date, the mean overall and PAH-related health care costs more than doubled (pre- to post-index) among nonparenteral prostacyclin recipients, but increased by a factor of only 1.5 among parenteral prostacyclin recipients. The proportion of total PAH-related health care costs accounted for by drugs was higher in both the pre- and post-index periods for nonparenteral prostacyclin new-starts (38.1% and 73.4%, respectively) than for parenteral prostacyclin new-starts (11.7% and 45.9%, respectively). However, the relative difference in spending on PAH-related drugs for parenteral versus nonparenteral new-starts decreased from a factor of 2.8 in the pre-index period (\$7,515 vs. \$21,164, respectively) to a factor of 2.0 in the post-index period (\$47,031 vs. \$92,086, respectively).

Discussion

Drugs for PH ranked in the top 10 specialty therapy classes by spending per member per year for both commercially insured and Medicare enrollees in 2015, with total spending on these agents increasing by 18.1% and 21.4%, respectively, compared with the previous year.²⁵ Given these rising costs and the relatively large number of agents currently available (of which only IV epoprostenol included overall survival as one of the trial endpoints on which FDA approval was based), it is essential to determine how these agents are currently being used in clinical practice.

The main finding of the present study was that use of prostacyclins among patients with PAH has been relatively constant from 2010 to 2015, suggesting that the availability of nonparenteral formulations has not led clinicians to prescribe these agents to patients for whom they would previously have chosen an ERA or a PDE-5i. Indeed, rates of prostacyclin use were within the range reported in previous retrospective database studies by Copher et al. (2012), Said et al. (2012), Kirson et al. (2011), and Johnson et al. (2013).^{10,17,21,26}

It is important to point out that the finding that fewer than one quarter of patients in this study used prostacyclins does not necessarily represent underprescribing. Recent guidelines recommend ERAs, PDE-5i's, or sGC, but not prostacyclins, for initial or second-line therapy of patients with PAH in FC II.^{2,3} Since it is impossible to determine the FC of PAH patients from retrospective claims data,²⁷ there was no way to evaluate observed prescribing patterns relative to different FC subgroups among the study cohort.

Characteristics of our ascertained PAH cohort (i.e., average age, sex ratio, and comorbidity burden) were similar to those of patients with definitive PAH diagnoses (confirmed by RHC) enrolled in the REVEAL registry.²⁸ If the FC distribution in our sample also mirrored that of REVEAL enrollees, 40.4% of whom were in FC I or II at enrollment, this may explain (at least in part) the high levels of use of nonprostacyclin PAH-specific therapies. Even if FC is known, there are additional factors that determine whether or not patients are appropriate candidates for prostacyclins.¹⁵ Indeed, in retrospective cohort studies, most patients not receiving parenteral prostacyclin at death (despite recommendations for use of IV epoprostenol in the most severe cases) died of non-PAH causes²⁹ or were unsuitable candidates for parenteral prostacyclin.^{30,31} Lastly, the use of PDE-5i's in patients not in group 1 PAH or with mixed pre- and postcapillary PH cannot be excluded.

There was, however, a pronounced and significant shift from parenteral to nonparenteral formulations, primarily attributable to increased uptake of inhaled treprostinil, which was introduced in 2009. The shift may reflect the improved convenience and safety of nonparenteral formulations in comparison with parenteral prostanoids, which are associated with burdensome administration protocols, the risk for bloodstream

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TABLE 4 Characteristics of Patients During 3 Months Before Initiating Prostacyclin Use, by Form of Prostacyclin Initiated

Characteristic	Parenteral Prostacyclin New-Starts	Nonparenteral Prostacyclin New-Starts	Any Prostacyclin New-Starts (Fully Naive)
Number	674	977	1,651
Age, years			
Mean (SD)	54.0 (13.5)	60.7 (13.8)	57.9 (14.1)
Median (IQR)	55 (46-63)	61 (52-71)	59 (49-68)
Range	18-90	18-90	18-90
Gender, n (%)			
Male	187 (27.7)	307 (31.4)	494 (29.9)
Female	487 (72.3)	670 (68.6)	1,157 (70.1)
Payer type, n (%)			
Commercial	541 (80.3)	585 (59.9)	1,126 (68.2)
Medicare	133 (19.7)	392 (40.1)	525 (31.8)
Charlson Comorbidity Index			
Mean (SD)	2.5 (1.7)	2.3 (1.8)	2.4 (1.8)
Median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)
Comorbidities, n (%)			
Depressive disorders	61 (9.1)	60 (6.1)	121 (7.3)
Anxiety disorders	48 (7.1)	38 (3.9)	86 (5.2)
Sleep disorders	71 (10.5)	101 (10.3)	172 (10.4)
Cerebrovascular disease	31 (4.6)	41 (4.2)	72 (4.4)
Peripheral vascular disease	22 (3.3)	37 (3.8)	59 (3.6)
Coronary heart disease	172 (25.5)	214 (21.9)	386 (23.4)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)
Raynaud's syndrome	0 (0.0)	0 (0.0)	0 (0.0)
Hematological conditions	12 (1.8)	7 (0.7)	19 (1.2)
Liver disease	64 (9.5)	79 (8.1)	143 (8.7)
Renal disease	239 (35.5)	229 (23.4)	468 (28.3)
Diabetes	147 (21.8)	229 (23.4)	376 (22.8)
Neoplasms	66 (9.8)	116 (11.9)	182 (11.0)
Inpatient admissions			
Any, n (%)	403 (59.8)	250 (25.6)	653 (39.6)
Number of visits			
Mean (SD)	0.9 (0.9)	0.3 (0.6)	0.5 (0.8)
Median (IQR)	1 (0-1)	0 (0-1)	0 (0-1)
Length of stay, days			
Mean (SD)	5.5 (7.6)	2.0 (7.4)	3.4 (7.7)
Median (IQR)	3 (0-8)	0 (0-1)	0 (0-5)
PAH-related, n (%)	377 (55.9)	214 (21.9)	591 (35.8)
Number of visits			
Mean (SD)	0.7 (0.8)	0.3 (0.6)	0.5 (0.7)
Median (IQR)	1 (0-1)	0 (0-0)	0 (0-1)
Length of stay, days			
Mean (SD)	5.4 (7.6)	1.8 (7.4)	3.3 (7.7)
Median (IQR)	2 (0-9)	0 (0-0)	0 (0-4)
Emergency room visits			
Any, n (%)	273 (40.5)	290 (29.7)	563 (34.1)
Number of visits			
Mean (SD)	0.7 (1.1)	0.5 (0.9)	0.6 (1.0)
Median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)

Characteristic	Parenteral Prostacyclin New-Starts	Nonparenteral Prostacyclin New-Starts	Any Prostacyclin New-Starts (Fully Naive)
PAH-related, n (%)	145 (21.5)	135 (13.8)	280 (17.0)
Number of visits			
Mean (SD)	0.3 (0.6)	0.2 (0.5)	0.2 (0.5)
Median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)
Office visits			
Any, n (%)	645 (95.7)	946 (96.8)	1,591 (96.4)
Number of visits			
Mean (SD)	8.5 (6.9)	8.1 (5.8)	8.3 (6.3)
Median (IQR)	7 (4-11)	7 (4-11)	7 (4-11)
PAH-related, n (%)	542 (80.4)	854 (87.4)	1,396 (84.6)
Number of visits			
Mean (SD)	3.2 (4.6)	2.9 (2.4)	3.0 (3.5)
Median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)
Health care costs, \$			
PAH-related medications			
Mean (SD)	4,156 (8,165)	10,174 (10,980)	7,717 (10,357)
Median (IQR)	0 (0-3,820)	5,432 (0-20,105)	1,492 (0-16,222)
PAH-related medical care			
Mean (SD)	39,252 (71,550)	17,326 (59,715)	26,277 (65,678)
Median (IQR)	16,907 (2,707-44,966)	3,873 (778-15,800)	7,319 (1,136-28,161)
Total PAH-related costs			
Mean (SD)	43,408 (72,038)	27,500 (60,115)	33,994 (65,692)
Median (IQR)	23,197 (6,158-51,349)	19,345 (5,577-32,005)	20,858 (5,605-37,480)
All other health care costs			
Mean (SD)	7,643 (27,944)	5,954 (14,071)	6,643 (20,888)
Median (IQR)	2,538 (739-5,909)	2,547 (939-5,381)	2,539 (848-5,667)
Total health care costs			
Mean (SD)	51,051 (79,070)	33,453 (62,449)	40,637 (70,227)
Median (IQR)	29,180 (11,885-58,717)	23,310 (9,957-38,334)	24,997 (10,516-44,776)
Prostacyclins, n (%)			
Any, n (%)	NA	NA	NA
Other PAH medications, n (%)			
ERA	120 (17.8)	425 (43.5)	545 (33.0)
Ambrisentan	44 (6.5)	183 (18.7)	227 (13.7)
Bosentan	71 (10.5)	209 (21.4)	280 (17.0)
Macitentan	6 (0.9)	37 (3.8)	43 (2.6)
PDE-5i	172 (25.5)	475 (48.6)	647 (39.2)
Sildenafil	100 (14.8)	253 (25.9)	353 (21.4)
Revatio	78 (11.6)	178 (18.2)	256 (15.5)
Generic	23 (3.4)	76 (7.8)	99 (6.0)
Tadalafil (Adcirca)	74 (11.0)	228 (23.3)	302 (18.3)
sGC	7 (1.0)	12 (1.2)	19 (1.2)
Any of the above 3 categories (i.e., ERA, PDE-5i, sGC)	230 (34.1)	649 (66.4)	879 (53.2)
Exactly 1 of the 3 categories	161 (23.9)	386 (39.5)	547 (33.1)
≥ 2 of the 3 categories	69 (10.2)	263 (26.9)	332 (20.1)

Note: Information in this table reflects all patients newly started on prostacyclins, regardless of their duration of enrollment following initiation of prostacyclins. ERA= endothelin receptor antagonist; IQR=interquartile range; NA=not available; PAH=pulmonary arterial hypertension; PDE-5i=phosphodiesterase type-5 inhibitor; SD=standard deviation; sGC=soluble guanylate cyclase.

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TABLE 5 Health Care Resource Utilization and Costs in the 6-Month Periods Before and After Prostacyclin Initiation, by Form of Prostacyclin Initiated

	Parenteral Prostacyclin New-Starts (n = 409)			Nonparenteral Prostacyclin New-Starts (n = 651)			Any Prostacyclin New-Starts (n = 1,060)		
	Pre-index	Post-index	P Value ^a	Pre-index	Post-index	P Value ^a	Pre-index	Post-index	P Value ^a
Health care resource utilization									
Inpatient admissions									
Any, n (%)	280 (68.5)	238 (58.2)	<0.001	230 (35.3)	198 (30.4)	0.041	510 (48.1)	436 (41.1)	<0.001
Number of visits, mean (SD)	1.1 (1.1)	1.0 (1.3)	0.402	0.5 (0.9)	0.4 (0.8)	0.007	0.7 (1.0)	0.7 (1.0)	0.012
Total length of stay, days, mean (SD)	9.0 (13.9)	9.5 (14.8)	0.430	3.8 (11.0)	3.3 (11.8)	0.297	5.8 (12.5)	5.7 (13.4)	0.773
PAH-related, n (%)	252 (61.6)	219 (53.5)	0.004	199 (30.6)	168 (25.8)	0.038	451 (42.5)	387 (36.5)	<0.001
Number of visits, mean (SD)	0.9 (0.9)	0.9 (1.1)	0.634	0.4 (0.7)	0.3 (0.6)	0.029	0.6 (0.8)	0.6 (0.9)	0.247
Total length of stay, days, mean (SD)	7.7 (11.2)	8.6 (14.4)	0.173	3.2 (10.4)	2.5 (8.8)	0.114	4.9 (10.9)	4.9 (11.7)	0.799
Emergency room visits									
Any, n (%)	209 (51.1)	194 (47.4)	0.251	271 (41.6)	223 (34.3)	0.003	480 (45.3)	417 (39.3)	0.002
Number of visits, mean (SD)	1.1 (1.5)	1.0 (1.5)	0.372	0.8 (1.2)	0.7 (1.2)	0.071	0.9 (1.3)	0.8 (1.3)	0.053
PAH-related, n (%)	110 (26.9)	97 (23.7)	0.233	129 (19.8)	105 (16.1)	0.059	239 (22.5)	202 (19.1)	0.027
Number of visits, mean (SD)	0.4 (0.7)	0.4 (0.9)	0.245	0.2 (0.6)	0.2 (0.6)	0.483	0.3 (0.6)	0.3 (0.8)	0.708
Office visits									
Any, n (%)	398 (97.3)	402 (98.3)	0.344	643 (98.8)	647 (99.4)	0.289	1,041 (98.2)	1,049 (99.0)	0.059
Number of visits, mean (SD)	16.0 (13.7)	16.8 (13.2)	0.179	16.1 (10.5)	14.8 (10.4)	0.001	16.0 (11.9)	15.6 (11.6)	0.139
PAH-related, n (%)	340 (83.1)	387 (94.6)	<0.001	607 (93.2)	602 (92.5)	0.522	947 (89.3)	989 (93.3)	<0.001
Number of visits, mean (SD)	4.7 (9.6)	7.0 (8.5)	<0.001	4.7 (3.6)	4.7 (4.4)	0.774	4.7 (6.6)	5.6 (6.4)	<0.001
Total health care contacts									
Any, n (%)	401 (98.0)	403 (98.5)	0.727	643 (98.8)	647 (99.4)	0.289	1,044 (98.5)	1,050 (99.1)	0.134
Number of visits, mean (SD)	18.2 (14.2)	18.8 (13.9)	0.284	17.3 (11.1)	15.9 (11.0)	<0.001	17.7 (12.4)	17.0 (12.3)	0.054
PAH-related, n (%)	372 (91.0)	389 (95.1)	<0.001	618 (94.9)	618 (94.9)	1.000	990 (93.4)	1,007 (95.0)	0.038
Number of visits, mean (SD)	5.9 (9.8)	8.3 (8.9)	<0.001	5.4 (3.8)	5.2 (4.6)	0.423	5.6 (6.8)	6.4 (6.8)	<0.001
Costs, \$, mean (SD)									
Any costs									
Medications									
PAH medications	6,772 (13,954)	46,022 (48,331)	<0.001	20,255 (21,331)	91,098 (48,405)	<0.001	15,053 (19,935)	73,705 (53,104)	<0.001
Ancillary PAH-related therapies	742 (1,403)	1,009 (1,871)	<0.001	910 (1,144)	988 (1,525)	0.130	845 (1,252)	996 (1,667)	<0.001
Other medications	3,995 (12,532)	3,819 (10,024)	0.748	4,019 (9,290)	4,457 (12,585)	0.390	4,009 (10,653)	4,211 (11,663)	0.594
Total medications	11,509 (19,782)	50,850 (49,552)	<0.001	25,181 (23,906)	96,539 (49,770)	<0.001	19,906 (23,364)	78,910 (54,420)	<0.001
Health care contacts									
Inpatient	38,764 (74,605)	31,643 (97,761)	0.222	15,504 (49,340)	18,024 (105,270)	0.567	24,479 (61,375)	23,279 (102,606)	0.733
Emergency room	1,389 (3,820)	1,008 (1,943)	0.053	1,026 (3,766)	932 (3,034)	0.594	1,166 (3,789)	961 (2,665)	0.122
Office visit	11,587 (23,947)	10,090 (17,327)	0.050	9,956 (16,250)	7,207 (17,534)	<0.001	10,585 (19,587)	8,319 (17,503)	<0.001
Total health care contacts	51,405 (80,967)	42,535 (101,255)	0.137	26,089 (53,006)	25,877 (110,107)	0.963	35,857 (66,349)	32,305 (107,038)	0.326
Other costs ^b	3,309 (9,730)	11,345 (14,671)	<0.001	6,845 (23,775)	6,158 (20,423)	0.385	5,480 (19,657)	8,160 (18,582)	<0.001
Total costs	66,224 (84,473)	104,729 (117,666)	<0.001	58,114 (63,594)	128,427 (120,938)	<0.001	61,243 (72,437)	119,283 (120,186)	<0.001

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TABLE 5 Health Care Resource Utilization and Costs in the 6-Month Periods Before and After Prostacyclin Initiation, by Form of Prostacyclin Initiated (*continued*)

	Parenteral Prostacyclin New-Starts (n = 409)			Nonparenteral Prostacyclin New-Starts (n = 651)			Any Prostacyclin New-Starts (n = 1,060)		
	Pre-index	Post-index	P Value ^a	Pre-index	Post-index	P Value ^a	Pre-index	Post-index	P Value ^a
PAH-related costs									
Medications									
PAH medications	6,772 (13,954)	46,022 (48,331)	<0.001	20,255 (21,331)	91,098 (48,405)	<0.001	15,053 (19,935)	73,705 (53,104)	<0.001
Ancillary PAH-related therapies	742 (1,403)	1,009 (1,871)	<0.001	910 (1,144)	988 (1,525)	0.130	845 (1,252)	996 (1,667)	<0.001
Total medications	7,515 (14,176)	47,031 (48,505)	<0.001	21,164 (21,523)	92,086 (48,483)	<0.001	15,897 (20,148)	74,701 (53,205)	<0.001
Health care contacts									
Inpatient	33,058 (59,779)	29,137 (95,787)	0.465	12,273 (42,268)	13,422 (98,773)	0.780	20,293 (50,752)	19,486 (97,886)	0.805
Emergency room	286 (1,348)	363 (1,177)	0.389	130 (565)	196 (1,398)	0.256	190 (949)	260 (1,319)	0.157
Office visit	6,289 (22,061)	6,350 (14,735)	0.921	5,254 (9,004)	2,756 (5,767)	<0.001	5,653 (15,412)	4,143 (10,350)	<0.001
Total health care contacts	39,632 (63,353)	35,849 (97,652)	0.482	17,657 (43,098)	16,375 (101,108)	0.759	26,136 (52,924)	23,889 (100,192)	0.496
Other costs ^b	16,901 (44,403)	19,663 (29,570)	0.243	16,709 (39,932)	17,193 (51,654)	0.817	16,783 (41,694)	18,146 (44,452)	0.387
Total costs	64,048 (83,861)	102,543 (116,977)	<0.001	55,528 (63,115)	125,531 (120,350)	<0.001	58,815 (71,915)	116,661 (119,530)	<0.001

Note: Information in this table reflects subgroup of patients newly started on prostacyclins with at least 6 months of enrollment following initiation of prostacyclins.

^aBased on paired t-tests for continuous data and McNemar's test for binary data.

^bFor example, durable medical equipment.

PAH = pulmonary arterial hypertension; SD = standard deviation.

infection and/or potentially serious administration errors, and pain (notably with subcutaneous infusion).³² We consider it unlikely that these prescribing changes were directly influenced by guideline changes or updates. Comprehensive PH guidelines were published in 2009 (i.e., at the start of the observation period) by subspecialty societies in Europe and the United States.^{1,33} The most specific recommendation was for parenteral prostanoid therapy in patients presenting with FC IV symptoms. All of the then-available FDA-approved prostanoids (IV epoprostenol, IV and subcutaneous treprostinil, inhaled treprostinil, and inhaled iloprost) were included as options for “lower risk” patients.

Following the 5th World Symposium on Pulmonary Hypertension in early 2013, consensus recommendations were published in December 2013,¹⁴ but the treatment algorithm did not change significantly from the 2009 guidelines¹ for prostanoid therapy. In 2014, updated treatment guidelines from the American College of Chest Physicians made specific recommendations for prostacyclin use by FC, including the suggestions that inhaled or parenteral prostanoids not be used as first-line therapy in treatment-naïve patients in FC II, that parenteral prostacyclins be used for patients in FC III with “rapid progression” or “progression” despite use of 1 or 2 classes of oral agents, and that parenteral prostanoids be used for patients in FC IV, with an inhaled formulation suggested for patients who are not candidates for or who refuse parenteral therapy.²

Of note, the most recent PH guidelines from the European Society of Cardiology and the European Respiratory Society

postdated our study.³ Thus, the guideline publications during the time frame of the study did not offer any substantive change in the recommendations for the use of either parenteral or inhaled prostanoids, so they do not explain the observed trend toward inhaled prostanoids and away from parenteral formulations.

Since the parenteral and inhaled prostanoids that are FDA-approved for use in PAH were available throughout the entire study time frame, the observed shift from parenteral to inhaled formulations mainly reflects a trend toward previously available nonparenteral prostanoids rather than any significant influence of new formulations becoming available during the study period. The oral treprostinil formulation that was approved during the study time frame (in December 2013) had prescription claims only in the last 2 years of the observation period.

It remains to be seen whether the introduction of oral agents targeting the prostacyclin pathway will alter the overall percentage of patients treated with medications in this class in the future. Such change may occur with proven clinical benefit, as shown in the pivotal phase 3 trial for selexipag, which demonstrated a reduced risk for the primary composite endpoint of death or a complication related to PAH compared with placebo.³⁴

Another important finding of this study is that from 2010 to 2015, patients receiving prostacyclins showed increasing use of PAH-specific medications from other drug classes. These observed treatment patterns potentially reflect the increasing focus on combination therapy in clinical practice

guidelines.^{1,6,8,14,33} As the focus of our study was on patients receiving prostacyclins, we did not investigate whether patients initiating therapy with other drug classes had similar levels of augmentation from different classes; however, similar rates of presumed concomitant prostacyclin use among patients receiving ERAs and PDE-5i's were noted by Angalakuditi et al. (2010) and Berger et al. (2012).^{9,11}

The increase we observed in health care costs in the 6 months after initiation of prostacyclin compared with the 6-month period before was largely attributable to nearly 5-fold higher costs for PAH-specific medications. While prostacyclin use may improve patient outcomes, even with the appropriate use of these or other PAH-specific drugs, the risk of hospitalization and death remains elevated in patients with PAH.^{35,36} Owing to inherent limitations of health care claims, our study does not address whether the observed increase in the cost of treatment is accompanied by reduced morbidity and mortality, improved quality of life, and/or lower health care resource utilization and costs after the 6-month post-index period.

Limitations

The main limitation of this study is shared with all other retrospective analyses of PAH based on U.S. claims databases, in that these databases do not contain the clinical findings necessary to definitively establish a diagnosis of PAH (e.g., cardiopulmonary hemodynamics), and the codes used to identify patients with PAH are not specific, due to the lack of a unique ICD-9-CM code for PAH according to the modern classification of PH.¹⁹ Consequently, patients had to be identified based on algorithms that, while logical and consistent with how PAH is diagnosed and treated, may misclassify some in the sample. Although the vast majority of patients (85.5%-93.3%, depending on year) had the ICD-9-CM code 416.0, which maps directly to the most common subgroup of PAH (idiopathic PAH), and the ascertainment algorithms required a PAH-related medication and/or a diagnostic test indicative of PAH, it remains possible that a proportion of patients in our sample may have had forms of PH other than PAH, a potential issue identified in previous studies based on claims data.¹¹

The databases also do not contain measures of disease severity such as FC or the 6-minute walk test, which hindered our ability to fully characterize patients receiving prostacyclins and to assess the observed prescribing patterns of prostacyclins within the framework of current guidelines. Moreover, without additional clinical information, we could not examine the degree to which switching, discontinuation, and/or augmentation occurred as a response to lack of efficacy as opposed to tolerability issues, treatment guidelines, or other concerns.

Health care claims provide information only on medications administered in physicians' offices and prescription drugs dispensed by retail pharmacies, so to the degree that patients

received prostacyclins and other medications of interest while hospitalized, our findings underestimate use of these pharmacotherapies, though any such impact on the present study is likely minimal, since PAH-specific medications are dispensed mainly from specialty pharmacies. We also could not determine the correspondence between prescriptions written versus dispensed, whether medications dispensed were actually taken, and, assuming that they were taken, whether they were taken as directed.

Conclusions

From 2010 to 2015, approximately 1 in 5 PAH patients received prostacyclins. Although overall prostacyclin use was relatively unchanged, there was a shift toward nonparenteral formulations during this period. Prostacyclins were associated with increased total health care costs over the 6-month period following initiation of such therapy, largely due to higher expenditure on medications, as spending on inpatient and outpatient care remained consistent or decreased modestly. Further research is needed to better understand the benefits of prostacyclin therapy for PAH, including positive quality-of-life impacts and the potential for reduced long-term health care costs.

Authors

CHARLES D. BURGER, MD, FCCP, Department of Medicine, Mayo Clinic, Jacksonville, Florida. JANIS A. PRUETT, EdD, MSN, FNP-BC; CASSANDRA A. LICKERT, MD; and WILLIAM DRAKE, III, PharmD, Actelion Pharmaceuticals US, South San Francisco, California. ARIEL BERGER, MPH, and BRIAN MURPHY, MS, Evidera, Waltham, Massachusetts.

AUTHOR CORRESPONDENCE: Charles D. Burger, MD, FCCP, 4500 San Pablo Rd., S., Jacksonville, FL 32224. Tel.: 904.953.2869; E-mail: burger.charles@mayo.edu.

DISCLOSURES

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Pruett, Lickert, Berger, and Drake contributed to study conception and participated with Burger in study design. Lickert and Murphy performed the data analyses. Burger, Pruett, Lickert, Murphy, and Drake interpreted the data. All authors participated in manuscript drafting and/or critical revision, approved the final manuscript, and agree to be accountable for all aspects of the work.

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APPENDIX A Claims Database Codes Used to Ascertain PAH Patients, Procedures, and Drugs

Diagnosis, Procedure, or Drug	Definition
PAH	ICD-9-CM diagnoses 416.0, 416.8, 416.9
Heart catheterization	ICD-9-CM procedures 37.21, 37.23, 89.63, 89.64; CPT procedures 93451, 93453, 93456, 93460, 93501, 93526
Cardiac surgery	ICD-9-CM procedures 35.4, 35.41, 35.42; CPT procedures 33737, 33735, 33736, 92992, 92993
Echocardiogram	ICD-9-CM procedure 88.72; CPT procedures 93350, 93351, 93303, 93304, 93306, 93307, 93308, 93312, 93313, 93314, 93315, 93316, 93317
Transplant	ICD-9-CM procedures 33.5, 33.50, 33.51, 33.52, 33.6; CPT procedures 32851, 32852, 32853, 32854, 33935
Ventilation-perfusion scan	CPT procedures 78580, 78585
Cardiac computed tomography angiography	CPT procedures 75571-75574, 75571, 75572, 75573
Epoprostenol (Veletri, Flolan, Epoprostenol)	HCPCS codes J1325, S0155; NDC numbers 0703-1985, 0703-1995, 66215-401, 66215-402, 66215-403, 0173-0517, 0173-0519
Iloprost (Ventavis)	HCPCS codes Q4080, Q4074; NDC numbers 66215-302, 66215-303
Treprostinil (Remodulin, Tyvaso, Orenitram)	HCPCS codes J3285, Q4077, S0114, J7686; NDC numbers 66302-101, 66302-102, 66302-105, 66302-110, 66302-206, 66302-300, 66302-302, 66302-310, 66302-325
Bosentan (Tracleer)	NDC numbers 66215-101, 66215-102
Ambrisentan (Letairis)	NDC numbers 61958-0801, 61958-0802
Macitentan (Opsumit)	NDC numbers 66215-501
Sildenafil (Revatio, Viagra)	HCPCS codes J3490, S0090; NDC numbers 63629-5029, 65162-351, 67544-355, 67544-356, 68001-176, 68084-622, 16714-338, 21695-157, 21695-158, 33342-121, 0069-0336, 0069-0338, 0069-4190, 0069-4200, 0069-4210, 0069-4220, 0093-5517, 0179-0160, 0378-1657, 0591-3780, 13668-185, 42291-730, 43063-256, 43063-550, 43353-764, 49999-316, 51655-131, 52125-494, 52125-710, 54868-4084, 54868-4706, 54868-4784, 55111-372, 55154-2727, 55154-2729, 55154-2736, 55289-524, 55289-577, 59762-0033, 60505-3404, 63539-421, 63539-422, 63629-1792, 63629-2640
Tadalafil (Adcirca, Cialis)	NDC numbers 16590-905, 21695-028, 21695-029, 0002-4462, 0002-4463, 0002-4464, 0002-4465, 43063-236, 43353-857, 54868-4665, 54868-4968, 54868-5956, 55154-1830, 63629-2734, 63629-4145, 63629-4601, 66302-467, 66336-566
Vardenafil (Levitra, Staxyn ODT)	NDC numbers 0179-0102, 43353-323, 43353-741, 43353-744, 43353-748, 54868-4967, 54868-4984, 54868-6333, 55289-193, 55289-194, 67544-507, 67544-512, 0173-0822, 0173-0828, 0173-0829, 0173-0830, 0173-0831, 63629-3372
Riociguat (Adempas)	NDC numbers 50419-250, 50419-251, 50419-252, 50419-253, 50419-254

CPT-4 = Current Procedural Terminology-4; HCPCS = Healthcare Common Procedure Coding System; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NDC = National Drug Code; PAH = pulmonary arterial hypertension.

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APPENDIX B Characteristics of Patients in the Pre-Post Analysis Cohort Before the Index Date, by Form of Prostacyclin Initiated

Characteristic	Parenteral Prostacyclin New-Starts		Nonparenteral Prostacyclin New-Starts		Any Prostacyclin New-Starts (Fully Naive)	
Number	409		651		1,060	
Age, years						
Mean (SD)	54.3	(13.4)	61.1	(13.5)	58.5	(13.8)
Median (IQR)	55	(46-62)	62	(52-71)	59	(50-68)
Range	18-90		18-90		18-90	
Gender, n (%)						
Male	110	(26.9)	203	(31.2)	313	(29.5)
Female	299	(73.1)	448	(68.8)	747	(70.5)
Payer type, n (%)						
Commercial	324	(79.2)	380	(58.4)	704	(66.4)
Medicare	85	(20.8)	271	(41.6)	356	(33.6)
Charlson Comorbidity Index						
Mean (SD)	2.8	(1.8)	2.7	(2.0)	2.7	(1.9)
Median (IQR)	2	(2-4)	2	(1-4)	2	(1-4)
Comorbidities, n (%)						
Depressive disorders	46	(11.2)	62	(9.5)	108	(10.2)
Anxiety disorders	37	(9.0)	34	(5.2)	71	(6.7)
Sleep disorders	62	(15.2)	97	(14.9)	159	(15.0)
Cerebrovascular disease	27	(6.6)	50	(7.7)	77	(7.3)
Peripheral vascular disease	28	(6.8)	34	(5.2)	62	(5.8)
Coronary heart disease	124	(30.3)	197	(30.3)	321	(30.3)
Atrial fibrillation	0	(0.0)	0	(0.0)	0	(0.0)
Raynaud's syndrome	0	(0.0)	0	(0.0)	0	(0.0)
Hematological conditions	6	(1.5)	5	(0.8)	11	(1.0)
Liver disease	54	(13.2)	71	(10.9)	125	(11.8)
Renal disease	150	(36.7)	185	(28.4)	335	(31.6)
Diabetes	102	(24.9)	181	(27.8)	283	(26.7)
Neoplasms	59	(14.4)	97	(14.9)	156	(14.7)

IQR = interquartile range; SD = standard deviation.