ORIGINAL RESEARCH

Leveraging Real-World Evidence in Disease-Management Decision-Making with a Total Cost of Care Estimator

Thanh-Nghia Nguyen, DrPH, MPH, MBA; Jeffrey Trocio, MPH; Stacey Kowal, MS; Cheryl P. Ferrufino; Julie Munakata, MS; Dell South, PharmD

BACKGROUND: Health management is becoming increasingly complex, given a range of care options and the need to balance costs and quality. The ability to measure and understand drivers of costs is critical for healthcare organizations to effectively manage their patient populations. Healthcare decision makers can leverage real-world evidence to explore the value of disease-management interventions in shifting total cost trends.

OBJECTIVE: To develop a real-world, evidence-based estimator that examines the impact of disease-management interventions on the total cost of care (TCoC) for a patient population with nonvalvular atrial fibrillation (NVAF).

METHODS: Data were collected from a patient-level real-world evidence data set that uses the IMS PharMetrics Health Plan Claims Database. Pharmacy and medical claims for patients meeting the inclusion or exclusion criteria were combined in longitudinal cohorts with a 180-day preindex and 360-day follow-up period. Descriptive statistics, such as mean and median patient costs and event rates, were derived from a real-world evidence analysis and were used to populate the base-case estimates within the TCoC estimator, an exploratory economic model that was designed to estimate the potential impact of several disease-management activities on the TCoC for a patient population with NVAF. Using Microsoft Excel, the estimator is designed to compare current direct costs of medical care to projected costs by varying assumptions on the impact of disease-management activities and applying the associated changes in cost trends to the affected populations. Disease-management levers are derived from literature-based concepts affecting costs along the NVAF disease continuum. The use of the estimator supports analyses across 4 US geographic regions, age, cost types, and care settings during 1 year.

RESULTS: All patients included in the study were continuously enrolled in their health plan (within the IMS PharMetrics Health Plan Claims Database) between July 1, 2010, and June 30, 2012. Patients were included in the final analytic file and were indexed based on (1) the service date of the first claim within the selection window (December 28, 2010-July 11, 2011) with a diagnosis of NVAF, or (2) the service date of the second claim for an NVAF medication of interest during the same selection window. The model estimates the current trends in national benchmark data for a hypothetical health plan with 1 million covered lives. The annual total direct healthcare costs (allowable and patient out-of-pocket costs) of managing patients with NVAF in this hypothetical plan are estimated at $184,981,245 ($25,754 per patient, for 7183 patients). A potential 25% improvement from the base-case disease burden and disease management could translate into TCoC savings from reducing the excess costs related to hypertension (–5.3%) and supporting the use of an appropriate antithrombotic treatment that prevents ischemic stroke (–0.7%) and reduces bleeding events (–0.1%).

CONCLUSIONS: The use of the TCoC estimator supports population health management by providing real-world evidence benchmark data on NVAF disease burden and by quantifying the potential value of disease-management activities in shifting cost trends.

KEY WORDS: cost drivers, disease-management levers, health management, healthcare costs, healthcare decision-making, nonvalvular atrial fibrillation, population health, real-world evidence, total cost of care estimator

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Am Health Drug Benefits.
2016;9(9):475-485
www.AHDBonline.com

Manuscript received Mar. 10, 2016
Accepted in final form Aug. 15, 2016

Disclosures are at end of text

Dr Nguyen is Director, Payer Channel Access, Pfizer Innovative Health, New York, NY; Mr Trocio is Director, Global Health & Value-Health Outcomes and Evidence, Pfizer Innovative Health; Ms Kowal is Principal, Health Economics & Outcomes Research, IMS Health, Fairfax, VA; Ms Ferrufino is Senior Consultant, Health Economics & Outcomes Research, IMS Health; Ms Munakata is Senior Principal, Health Economics & Outcomes Research, IMS Health; Dr South is Executive Director, Medical Affairs, Pfizer Innovative Health.

KEY POINTS

- Real-world evidence is increasingly used as a business and analytic tool to measure the value of disease-management interventions.
- A real-world evidence data set was used to develop a total cost of care (TCoC) estimator for patients with nonvalvular atrial fibrillation (NVAF).
- This exploratory economic tool can estimate the potential impact of disease-management activities on the TCoC for a patient population.
- Current and projected costs of treatment are compared by varying assumptions on the impact of disease management, applying the associated cost trend changes to the affected populations.
- The TCoC estimator demonstrates how stakeholders can quantify the burden of untreated or inappropriately managed patients across healthcare conditions.
- This novel decision tool leverages patient-level real-world evidence and published disease-management evidence to examine cost trends at a more holistic level.
- The TCoC estimator can inform healthcare program development in support of population health management and to meet the Triple Aim goals of healthcare.

The healthcare system in the United States is evolving as a result of the increasing availability of real-world data and the influence of value-based policy and quality initiatives. Policy initiatives, such as the Patient Protection and Affordable Care Act, stress the importance of demonstrating value in terms of the Triple Aim of healthcare—improving the quality and satisfaction of care, improving population health outcomes, and lowering costs—which, when merged, emphasize the total cost of care (TCoC) as a value metric.[1] The cost burden of chronic diseases has been well-established, and a number of studies have identified successful individual disease-management and treatment strategies.[2-5] However, there is a dearth of real-world studies that quantify the potential impact of multiple disease-management strategies on the TCoC to support a more holistic view of population health and cost trends.

The TCoC represents the total cost, in dollars, spent by healthcare purchasers for healthcare services rendered to an individual or a group.[6] The most common application of the TCoC as a composite measure of healthcare costs typically consists of direct healthcare expenditures (including inpatient and outpatient hospital care), professional physician and clinical services, prescription drugs, durable medical equipment, skilled nursing care, home healthcare services, and healthcare administration costs (eg, health insurance costs, overhead for structures, equipment, and training).[7,8]

A number of factors influence the TCoC, including population composition and characteristics, disease prevalence rates, provider and patient behaviors, the availability of primary and specialty care, geographic variation in service utilization, and negotiated prices. The ability to measure and understand drivers of costs is critical for healthcare organizations to effectively manage costs and improve healthcare quality. As such, TCoC decision tools can provide insights on quality of care, population health, and healthcare costs.[9,10]

Large patient data sets are increasingly used to provide real-world evidence to assess the value of treatments and healthcare services.[11] Derived from patient-level data, such as healthcare claims data and electronic medical records, real-world evidence has become a driving force in decision analysis and is increasingly used to shape patient care. Although randomized controlled trials are the gold standard in measuring clinical efficacy, real-world evidence provides a snapshot of how the broader healthcare environment, including patient and provider behaviors, can influence outcomes across disease areas.[11]

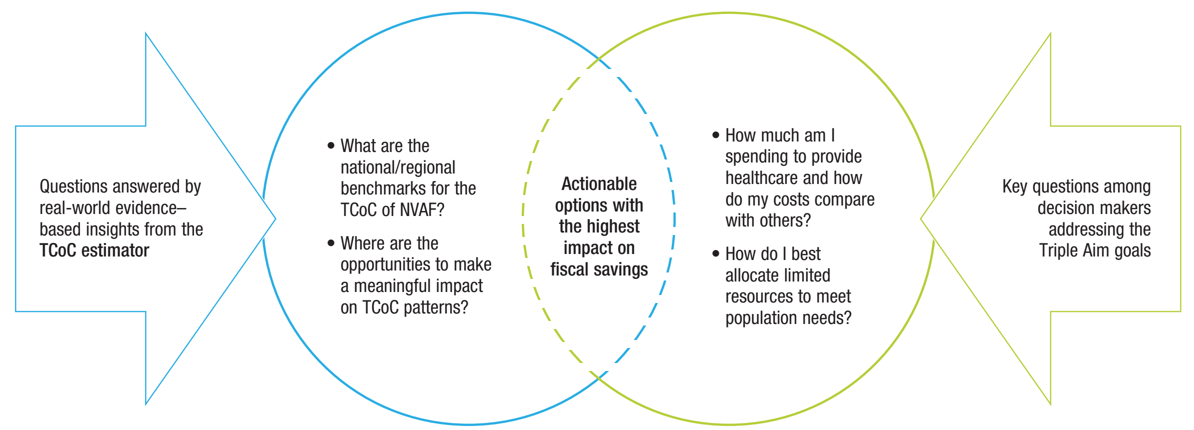
The need to balance quality of care, health outcomes, and costs, coupled with observations from real-world evidence, creates an opportunity to improve population health through the use of empirical decision support tools.

The aim of this study was to develop a TCoC estimator that measures the potential impact of disease or care management interventions for patients with nonvalvular atrial fibrillation (NVAF) on TCoC (**Figure 1**) using inputs based on real-world evidence claims data.

Although theoretical results are presented for a handful of disease-management levers, the model results are not the core focus of the article. Instead, we aim to present how readily available descriptive statistics from real-world evidence data sets can be combined with a user-friendly hypothesis-generating tool to help understand cost trends and to assess the relative value of potential interventions. As such, theoretical analyses are presented in this study for a small selection of levers for illustration purposes. The true impact of disease-management activities to any healthcare decision maker would be dependent on their population and their cost trends.

It is estimated that approximately 2.3 million adults in the United States have NVAF, and it is projected that this number will increase to a range of 5.6 million to 15.9 million individuals by 2050.[12] Thus, it is vital to identify opportunities for NVAF disease management to help

Figure 1 TCoC Estimator: Spheres of Influence



NVAF indicates nonvalvular atrial fibrillation; TCoC, total cost of care.

contain spending growth, while simultaneously working to maintain high-quality care.

Methods

We developed a TCoC estimator using Microsoft Office Excel (Microsoft Corporation; Redmond, WA) to compare the current, real-world, evidence-based costs of healthcare to the projected costs after adjusting inputs for specific levers. Levers are defined as potential disease-management activities that could influence the TCoC within a group of patients. A real-world evidence analysis was used to identify a cohort of patients with NVAF and to estimate the true annual cost per patient (based on medical and pharmacy claims data) and the rates for a series of defined events (eg, ischemic stroke) or patient characteristics (eg, prevalence of hypertension or diabetes).

The results of the real-world evidence analysis were then used to populate the base-case estimates for the TCoC estimator. Powered by real-world data, the TCoC estimator provides the ability to stratify costs by age-groups (all, aged <65 years, aged ≥65 years), US regions (all, Midwest, Northeast, South, West), type of cost (allowed, out-of-pocket, or total), and the point of care (inpatient, outpatient, pharmacy, or all). The results presented in this article focus solely on the overall costs as an illustration of the estimator's function and output.

Model Inputs and Description of Data Sources

The TCoC estimator leverages data from a custom real-world evidence platform for the cost inputs and peer-reviewed published studies to determine how costs may change based on selected disease-specific levers. Cost and utilization estimates used to populate the TCoC estimator were obtained from the IMS PharMetrics Health Plan Claims Database. The aggregated IMS PharMetrics database is comprised of adjudicated claims for more than 150 million unique enrollees across the United States. Enrollees with medical and pharmacy coverage in 2011 represent 40 million active lives. The data are also longitudinal, with more than 30 million patients who have medical and pharmacy coverage with 3 or more years of continuous enrollment.

PharMetrics data have a diverse representation of geography, employers, payers, providers, and therapy areas. The patients in each 3-digit zip code and every metropolitan statistical area of the United States are represented, with coverage of data from 90% of US hospitals, 80% of all US physicians, and representation from 85% of the Fortune 100 companies. As a result of the broad reach of the data, records in the PharMetrics database are representative of the national, commercially insured population in terms of age and sex for individuals aged <65 years. Patients aged ≥65 years with commercial supplemental Medicare coverage are also included in these data; however, traditional Medicare or Medicaid claims are not included.

The NVAF cohort was identified using fully adjudicated pharmacy and medical claims for patients meeting key inclusion and exclusion criteria to create a longitudinal cohort with a preindex period of 180 days and a follow-up period of 360 days. The NVAF cohort included patients with a diagnosis of NVAF who were candidates for treatment with oral anticoagulants. The patients were grouped into individuals currently receiving an oral anticoagulant or an antiplatelet medication, or patients who were untreated but were eligible for treatment. The initial cohort of patients with NVAF includ-

Table 1 NVAF Inclusion and Exclusion Criteria

Inclusion codes: antithrombotic medications of interest			
Drug group	**Generic name**	**Brand name**	**GPI/HCPCS codes**
Anticoagulant	Warfarin	Coumadin	83200030[a] or 4300F, 99363, 99364, G8183
Anticoagulant	Dabigatran	Pradaxa	83337030[a]
Anticoagulant	Rivaroxaban	Xarelto	83370060[a]
Anticoagulant	Apixaban	Eliquis	83370010[a]
Antiplatelet	Clopidogrel	Plavix	85158020[a]
Antiplatelet	Ticlopidine	Ticlid	85158080[a]

Exclusion codes: procedures	
Procedure	***ICD-9* procedure code/ *CPT* code**
Diseases of the mitral valve	394.xx
Diseases of mitral and aortic valves	396.xx
Valvotomy, mitral valve; closed heart	33420
Valvotomy, mitral valve; open heart, with cardiopulmonary bypass	33422
Valvuloplasty, mitral valve, with cardiopulmonary bypass	33425
Valvuloplasty, mitral valve, with prosthetic ring	33426
Valvuloplasty, mitral valve, with cardiopulmonary bypass; radical reconstruction, with or without ring	33427
Replacement, mitral valve, with cardiopulmonary bypass	33430
Closure of atrioventricular valve (mitral or tricuspid) by suture or patch	33600
Repair of cor triatriatum or supravalvular mitral ring by resection of left atrial membrane	33732
Percutaneous balloon valvuloplasty; mitral valve	92987
Valvotomy, mitral valve; open heart, with cardiopulmonary bypass	33422

[a]Denotes a wildcard search for strength and form, using generic product indicator codes that were truncated at 8 digits to query each drug by name (thereby gathering information across all available strengths and forms).
CPT indicates *Current Procedural Terminology*; GPI, Generic Product Identifier; HCPCS, Healthcare Common Procedure Coding System; *ICD-9*, *International Classification of Diseases, Ninth Revision*; NVAF, nonvalvular atrial fibrillation.

Table 2 NVAF Disease-Management Levers

Lever	Disease-management lever
Levers relevant to all patients with NVAF	
1	*Disease prevalence*: changing prevalence of NVAF over time to reflect the impact of the aging population[13,14]
2-5	*Comorbidities*: managing and/or preventing key comorbidities (ie, hypertension, diabetes, congestive heart failure, and coronary artery disease) associated with increased cost of care[15]
6	*Treatment patterns*: changing the number of treatment-eligible patients receiving antithrombotic medications to close the treatment gap[16,17]
7	*Multiple hospitalizations*: changing the likelihood of inpatient readmissions among patients with NVAF who are hospitalized for care[18]
Levers relevant only to patients receiving anticoagulants	
8	*Preventing stroke*: new treatment approaches and/or more effective disease management to decrease the risk for ischemic stroke[18,19]
9-12	*Preventing bleeding*: new treatment approaches and/or more effective disease management to decrease the risk for key bleeding events (ie, gastrointestinal bleeds, hemorrhagic stroke, other major bleeds, any bleeding)[20]
13	*Treatment adherence*: changing patient adherence patterns for antithrombotic medications[19]

NVAF indicates nonvalvular atrial fibrillation.

ed patients who had at least 2 medical claims with an *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis code of NVAF (fibrillation, 427.31 or fibrillation and flutter, 427.3). Patients were excluded if they had a diagnosis or procedure codes for specific valvular conditions (**Table 1**).

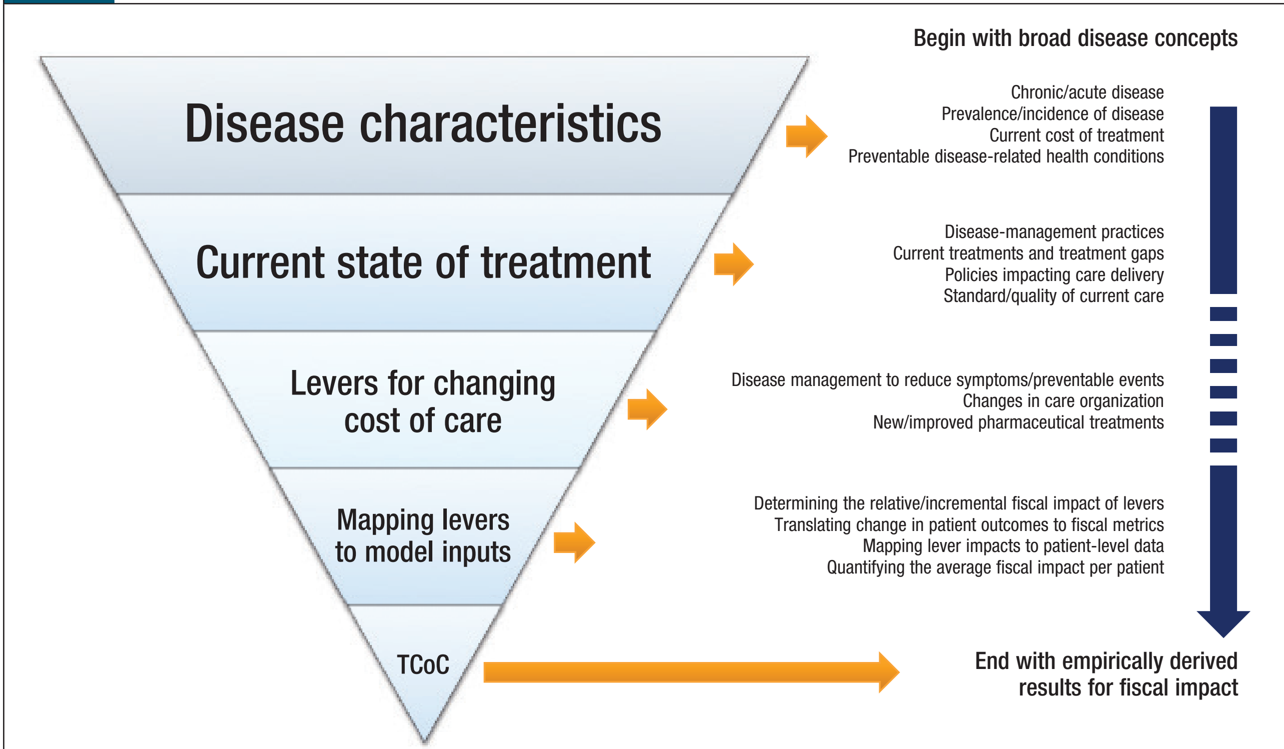
All patients included in the study were continuously enrolled in their respective health plan between July 1, 2010, and June 30, 2012. The patients were included in the final analytic file and were indexed based on (1) the service date of the first claim within the selection window (December 28, 2010-July 11, 2011) with a diagnosis of NVAF, or (2) the service date of the second claim for an NVAF medication of interest during the same selection window. Deidentified patient-level data from the custom real-world evidence platform included information on patient characteristics (age, sex, region), disease characteristics (eg, newly diagnosed flag, previously treated flag, CHADS2 risk level, comorbid conditions diagnosis flags based on the presence of *ICD-9* diagnosis codes) obtained during the 180-day preindex period, and prescription, inpatient, and outpatient utilization and costs (allowed and patient out-of-pocket) obtained from the 360-day follow-up period. Using this aggregate real-world evidence data, the national and regional benchmark values for annual per-patient costs (mean and median) and patient characteristics (prevalence rates) were estimated.

Identification of Disease-Management Levers for the TCoC Estimator

The total costs for managing patients with NVAF are driven by a range of factors given the variation in treatment practices and heterogeneity in patient characteristics. We conducted a targeted literature review to identify disease-management activities influencing the TCoC in patients with NVAF across the continuum of care. The goal of the targeted search was to gather information on potential disease-management concepts for investigation in the real-world evidence data set.

Using the National Library of Medicine's PubMed database, the review involved English language articles published after 2008 that contained atrial fibrillation (using Medical Subject Heading [MeSH] with all subheadings selected) in combination with any of the following search words (using MeSH terms), including epidemiology, incidence, prevalence, comorbidity, risk factors, treatment, manage, outcome, practice guideline (as topic), treatment outcome, diagnosis, costs and cost analysis, economics/hospital, economics/pharmaceutical, economics/medical, cost-benefit analysis, cost of illness, cost-savings, healthcare costs, direct service costs, hospital costs, employer health costs, drug costs, fees and charges, health resources, illness burden, and utilization

Figure 2 Lever Identification Process



TCoC indicates total cost of care.

review. Grey literature searches were performed using these keywords in Google Scholar, and ancestral searches were conducted where relevant.

Disease-management activities identified in the literature were subsequently distilled into potential levers that could affect the TCoC, including disease-management programs, treatment efficacy, healthcare policy, risk reduction, and treatment adherence. Levers were included in the estimator based on several criteria, including (1) established relationship between disease-management activity and cost impact, (2) focus on key patient populations or classes of treatments (ie, no individual treatment levers), and (3) available data in the custom real-world evidence platform for empirical cost or prevalence analysis.

A total of 13 levers for NVAF were chosen for inclusion in the TCoC estimator (**Table 2**).[13-20] Seven levers evaluate concepts that relate to the TCoC for the general population with NVAF (levers 1-7); the remaining 6 levers evaluate concepts that can be applied only to patients with NVAF who received an anticoagulant. The included literature-based levers were then mapped to the real-world evidence cost estimates, so that the impact of each lever on the TCoC could be isolated and investigated via data analysis and modeling. For each lever, patient-level data from the real-world evidence analysis were used to estimate empirically the current annual costs of care per patient diagnosed with NVAF, and by patient characteristics, such as age, sex, and comorbidity profile (**Figure 2**).

TCoC Estimator Approach

Patient-level data were used to estimate the current benchmark cost and utilization data for all levers. A summary of inputs estimated through a real-world evidence analysis for selected levers are presented in **Table 3**.

Current baseline cost estimates were calculated from patient-level data using SAS (SAS Institute; Cary, NC). Descriptive statistics, such as mean and median costs, were calculated for all patients, and then by patient characteristics and identified lever-related events (eg, cost per patient with stroke).

The prevalence of select comorbid conditions (eg, diabetes, hypertension, congestive heart failure, coronary artery disease), or disease-related event rates (eg, frequency of stroke among patients with NVAF), were also calculated. The costs and event rates derived from the real-world evidence analysis were used as base-case inputs in the TCoC estimator. The patients were attributed to relevant subpopulations, such as patients receiving an anticoagu-

Table 3 NVAF Model Inputs Derived from Real-World Evidence Analysis

Real-world evidence claims-based cost per patient	Mean, $	Median, $
With hypertension[a]	26,805	10,977
Without hypertension[a]	20,292	7718
With ischemic stroke event[a]	40,740	17,469
Without ischemic stroke event[a]	24,932	10,111
With GI bleeding, hemorrhagic stroke, or other bleeding event[a]	45,962	19,051
Without GI bleeding, hemorrhagic stroke, or other bleeding event[a]	24,588	10,068
Real-world evidence claims-based prevalence rates	**Value, %**	
Proportion of patients with hypertension[b]	83.9	
Proportion of patients with ischemic stroke event[b]	4.5	
Proportion of patients with GI bleeding, hemorrhagic stroke, or other bleeding event[b]	4.9	
Proportion of patients receiving an antithrombotic drug[b]	54.1	

[a]All costs are annual total healthcare costs.
[b]Percent of patients with the reported characteristic among patients diagnosed with NVAF.
GI indicates gastrointestinal; NVAF, nonvalvular atrial fibrillation.

Table 4 Total Cost of Care Analytic Framework, by Disease-Management Lever

Example lever	Input	Population	Incremental cost	Estimating TCoC
Managing comorbidities associated with increased cost of care	Comorbidity prevalence in patients diagnosed with NVAF (%)	Change in the prevalence of comorbid conditions among all patients with NVAF	Annual cost of a patient with NVAF and a comorbidity minus the cost of a patient with NVAF without a comorbidity	Among all patients diagnosed with NVAF, change in comorbid cases times incremental cost
Effective disease management to change the risk for ischemic stroke	Prevalence of stroke in the treated population	Change in number of patients with stroke events	Annual cost of a patient with a stroke event minus the cost of a patient without a stroke event	Among patients receiving an antithrombotic drug, change in number of bleeding cases times the incremental cost
Effective disease management to change the risk for a bleeding event[a]	Prevalence of bleeding events in the treated population	Change in number of patients with a bleeding event	Annual cost of a patient with a bleeding event minus the cost of a patient without a bleeding event	Among patients receiving an antithrombotic drug, change in number of bleeding cases times the incremental cost

[a]Bleeding events include gastrointestinal bleeding; hemorrhagic stroke; acute posthemorrhagic anemia; vascular injury; intraocular or periocular bleeding; intraspinal, hemarthrosis, hemoperitoneum, liver, spleen, and kidney bleeding; and blood transfusions.
NVAF indicates nonvalvular atrial fibrillation; TCoC, total cost of care.

Table 5 Population Estimate for Cohort of Patients with NVAF

	NVAF inputs		Source
Hypothetical population	1 million	1 million	Assumption
Proportion of adults	75.5%	755,273	US Census Bureau[21]
Prevalence of NVAF	1.0%	7183	Go et al[22]
Proportion of patients receiving an antithrombotic drug[a]	54.1%	3886	PharMetrics

[a]Percentage reflects percent of patients among patients diagnosed with NVAF.
NVAF indicates nonvalvular atrial fibrillation.

lant or all patients with NVAF, to ensure levers were appropriately applied to eligible patient populations. The TCoC was estimated based on user selection of lever settings, the range of which has the effect of moving patients from one risk cohort to another (**Table 4**).

TCoC Estimator Base-Case

The results reflect national-level benchmark costs for a hypothetical health plan with 1 million members. For the analyses, all diagnosed patients (treated and untreated) of every age were considered; the costs include all points of care and a total of the allowed costs plus out-of-pocket costs. All costs and associated results in the estimator are reported in 2015 US dollars. The results of the cohort analyses represent the 1-year total direct healthcare costs, and can be interpreted as the cost of care to a fiscal risk-bearing stakeholder in the United States.

The numbers of patients affected by each lever were estimated based on US population and epidemiologic studies (**Table 5**).[21,22] A benchmark for each lever was found in the medical literature. A theoretical 25% improvement, from the established benchmark, was modeled for each lever to evaluate and illustrate the relative ability of each disease-management activity (or "lever") to shift the total cost trends. Maximum precision was maintained for all calculations in the model. For the purposes of this article, rounded values are presented for the interim (ie, cost per patient) and final (ie, TCoC) results.

Results

Of the 13 disease-management levers, 3 NVAF levers were selected to illustrate the function and output of the TCoC estimator. The 3 NVAF levers include the management of hypertension as a comorbidity, as well as the use of appropriate treatments or disease-management activities to modify ischemic strokes and bleeding risks (eg, gastrointestinal bleeding, hemorrhagic stroke, or other bleeding).

The direct annual TCoC (allowable and patient out-of-pocket cost) of managing patients diagnosed with NVAF was estimated to be $184,981,245. This represents an annual per-patient cost of $25,754 for 7183 patients with NVAF in the hypothetical 1-million-member health plan population. Patients diagnosed with NVAF who have comorbidities (eg, hypertension) have excess healthcare costs compared with patients with NVAF without hypertension ($26,805 vs $20,292, respectively) based on real-world evidence analysis. Therefore, managing the risk for comorbidities and reducing avoidable comorbidity-related costs can affect the TCoC. By reducing the number of patients with hypertension by 25% (a proxy for reduced comorbidity cost burden), a potential reduction of $9.81 million (5.3%) in TCoC was observed.

Table 6 NVAF Total Cost of Care Results—Reduce Benchmark Prevalence or Event Rates by 25%[a]

			Current scenario		Projected scenario		
Lever	Target population	Cost per patient	Lever value	TCoC	Lever value	TCoC	Relative change in TCoC
Management of comorbidities: hypertension							
Mean $	All patients diagnosed with NVAF	Δ = $6513	N = 7183	$184,997,786	N = 7183	$175,186,173	–5.3%
	Patients with hypertension	$26,805	83.9% (N = 6026)	$161,531,821	62.9% (N = 4520)	$121,148,866	
	Patients without hypertension	$20,292	16.1% (N = 1156)	$23,465,965	37.1% (N = 2663)	$54,037,307	
Median $	All patients diagnosed with NVAF	Δ = $3259	N = 7183	$75,073,409	N = 7183	$70,164,144	–6.5%
	Patients with hypertension	$10,977	83.9% (N = 6026)	$66,148,157	62.9% (N = 4520)	$49,611,118	
	Patients without hypertension	$7718	16.1% (N = 1156)	$8,925,252	37.1% (N = 2663)	$20,553,027	
Risk for ischemic stroke							
Mean $	Patients receiving antithrombotic drugs	Δ = $15,808	N = 3886	$99,645,956	N = 3886	$98,954,900	–0.7%
	Patients with ischemic stroke	$40,740	4.5% (N = 175)	$7,123,903	3.4% (N = 131)	$5,342,927	
	Patients without ischemic stroke	$24,932	95.5% (N = 3711)	$92,522,053	96.6% (N = 3755)	$93,611,972	
Median $	Patients receiving antithrombotic drugs	Δ = $7358	N = 3886	$40,575,528	N = 3886	$40,253,854	–0.8%
	Patients with ischemic stroke	$17,469	4.5% (N = 175)	$3,054,696	3.4% (N = 131)	$2,291,022	
	Patients without ischemic stroke	$10,111	95.5% (N = 3711)	$37,520,832	96.6% (N = 3755)	$37,962,831	
Likelihood of any bleeding							
Mean $	Patients receiving antithrombotic drugs	Δ = $21,374	N = 3886	$99,616,323	N = 3886	$98,598,894	–1.0%
	Patients with any bleeding	$45,962	4.9% (N = 190)	$8,751,501	3.7% (N = 143)	$6,563,625	
	Patients without any bleeding	$24,588	95.1% (N = 3695)	$90,864,823	96.3% (N = 3743)	$92,035,269	
Median $	Patients receiving antithrombotic drugs	Δ = $8983	N = 3886	$40,833,693	N = 3886	$40,406,101	–1.0%
	Patients with any bleeding	$19,051	4.9% (N = 190)	$3,627,412	3.7% (N = 143)	$2,720,559	
	Patients without any bleeding	$10,068	95.1% (N = 3695)	$37,206,281	96.3% (N = 3743)	$37,685,542	

[a]Maximum precision was maintained for all calculations; however, for the purposes of this article, rounded values are presented.
NOTE: Δ indicates change (ie, cost change per patient associated with the lever of interest).
NVAF indicates nonvalvular atrial fibrillation; TCoC, total cost of care.

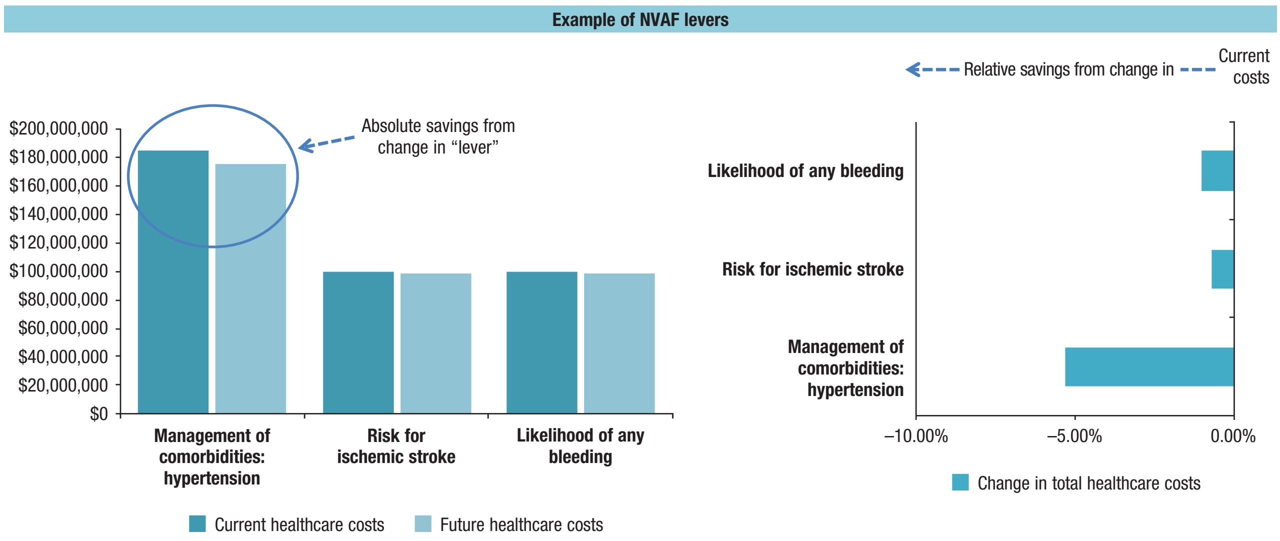
Among patients currently receiving antithrombotic drugs, the TCoC estimator demonstrated that patients with NVAF who had an ischemic stroke or any bleeding event had higher annual costs compared with patients with NVAF who did not have an ischemic stroke ($40,740 vs $24,932, respectively) or a bleeding event ($45,962 vs $24,588, respectively). A theoretical 25% decrease in the risk for ischemic stroke per treated patient resulted in a potential reduction of $691,056 (0.7%) in the TCoC. Furthermore, a $1,017,429 (1.0%) reduction in the TCoC was seen for a similar risk reduction in patients with any bleeding event (**Table 6, Figure 3**).

Discussion

The availability of healthcare claims and other patient-level data provides healthcare decision makers with the key insights needed to estimate the cost burden of disease. The TCoC estimator integrates the use of dynamic disease-management levers with empirically based real-world evidence costs to highlight the potential value of disease-management activities on the TCoC in a cohort of patients with NVAF. By examining the TCoC trends at a more comprehensive level, decision makers can explore the potential impact of different levers across patient subpopulations, disease-management options, geographic regions, and cost components. Real-world evidence-based tools such as the TCoC estimator can assist healthcare stakeholders by providing useful national and regional benchmark information on the current disease trends and costs. In addition, the financial impact of implementing disease-management programs, such as care coordination and patient education programs, to support appropriate use of treatments, can be estimated and evaluated in terms of broader healthcare resource utilization and costs.

The TCoC estimator demonstrates how stakeholders can quantify the burden of untreated or inappropriately managed patients across healthcare conditions and the additional costs incurred from inadequate adherence to clinical guidelines and recommendations. Gaps in effective patient management have the potential to drive patient costs up as a result of poor symptom management, insufficient treatment, and suboptimal outcomes.

Figure 3 Nonvalvular Atrial Fibrillation Results



NVAF indicates nonvalvular atrial fibrillation.

Table 7 Examples of Actionable Interventions Associated with Each Lever

Disease-management activity	Potential actionable interventions
Management of comorbidities: hypertension	Careful management of patients with hypertension may reduce the onset of NVAF in at-risk patients through diet and lifestyle changes or the pharmacologic management of hypertension
Risk for ischemic stroke	Because NVAF is a risk factor for stroke and is associated with higher costs and mortality, a patient's risk for stroke should be evaluated on diagnosis of NVAF and antithrombotic therapy should be considered in those indicated
Likelihood of any bleed	The risk for stroke prevention and the risk for hemorrhagic bleeding must be weighed carefully when establishing a management strategy for patients with NVAF

NVAF indicates nonvalvular atrial fibrillation.

Because ischemic stroke is a preventable outcome for patients with NVAF, effective treatment and disease-management protocols could potentially reduce the risk for ischemic stroke and stroke-related costs. Also, among the same subpopulation of anticoagulant-treated patients, appropriate drug therapy management is necessary to reduce the frequency of bleeding events in this high-risk population to contain or minimize costs.

As such, the TCoC estimator provides empirical evidence of the relationship between undertreated or untreated patients and preventable outcomes, highlighting trends in event rates and patient costs. This type of evidence can assist healthcare decision makers in prioritizing and identifying effective population health and cost-management strategies.

Data-driven insights are increasingly required to inform treatment choices and resource allocation for patient care. The TCoC estimator allows stakeholders to quantify relationships between high-cost comorbid conditions and the resulting excess financial burden in a patient population. In practice, TCoC tools can assess whether disease-management or wellness programs result in improved patient health and cost-savings.[23] The TCoC estimator quantifies the excess costs attributed to patients with key comorbid conditions, highlighting the magnitude of opportunity for shifting cost trends through initiatives that prevent the incidence of comorbid conditions or reduce the excess costs associated with the treatment and care of patients with comorbidities.

The TCoC estimator is a novel decision tool that leverages patient-level real-world evidence and published disease-management evidence to examine cost trends at a more holistic level. Although real-world evidence analytics are currently being used to evaluate a broad range of individual disease-management activities, housing real-world evidence insights in a user-friendly tool enhances the ability for decision makers to conduct quick investigations across a spectrum of population health management topics to prioritize interventions, identify areas for future research, and to pinpoint differences between their populations and benchmark trends.

The use of levers in the TCoC estimator provides an example of the breadth of disease-management activities that can be translated into potential interventions to improve population health. Once decision makers identify the high-priority levers for action, they can use a range of available solutions to affect change in cost trends (**Table 7**).

A directly comparable tool was not identified through a review of content in the public domain. A related tool is the Chronic Disease Cost Calculator developed by the Centers for Disease Control and Prevention, which estimates state-level medical costs, absenteeism costs, and 10-year medical cost projections for arthritis, asthma, cancer, congestive heart failure, coronary heart disease, hypertension, stroke, other heart diseases, depression, and diabetes. The major differences between the TCoC estimator and the Chronic Disease Cost Calculator are the calculation methods and functionality. Although both tools offer benchmark estimates of total cost, the TCoC estimator takes its estimates from commercial claims data, whereas the Chronic Disease Cost Calculator uses a population survey for commercial payers and Medicare and Medicaid statistics for government programs. The TCoC estimator does not cover Medicare or Medicaid patient populations, which may have different utilization and cost patterns. In addition, the TCoC estimator has the functionality of identifying and quantifying the impact of potential disease-management strategies (or levers) to "bend the cost curve." Finally, the 2 tools cover different disease areas and examine different time horizons for costs.

Limitations

The TCoC estimator does not explicitly account for any differences in treatment performance through estimates of efficacy or safety. All unit costs in the estimator represent the total allowable costs and the total patient out-of-pocket costs from medical or pharmacy claims recorded in a database comprised predominantly of US commercial payers. As with all claims-based analyses, claims are collected for payment purposes rather than for research purposes; this points to the potential for coding errors and undercoding contained in claims.

Inclusion or exclusion criteria for the database analysis were designed to isolate cohorts of patients who were diagnosed and/or treated to support the resource use and cost analysis. However, inputs may be influenced by other underlying diseases or conditions, or by additional patient characteristics unrelated to their diagnosis.

Inpatient, outpatient, and pharmacy costs are inclusive of all healthcare utilization among patients and should not be interpreted as exclusive or limited to NVAF-related medical costs.

The TCoC estimator's data are derived from a custom real-world evidence analysis. Therefore, baseline costs, disease and comorbidity prevalence rates, patient characteristics, and geographic differences in treatment patterns may vary from other published sources. The estimates that were derived from claims data are dependent on accurate *ICD-9* coding and billing for all visits.

Also, any assumed changes in costs or utilization trends only apply to insured populations. Given the nature and intent of the estimator to look at "real-world" benchmark costs derived from claims analyses, the costs were not adjusted for potential confounders. Therefore, the results should be interpreted as hypothesis-generating insights for further, more detailed investigation.

Conclusions

Real-world evidence is gaining traction as an important business and analytic tool in population health management. The TCoC estimator leverages real-world evidence to estimate the population burden of NVAF via national and regional benchmarks. It further identifies and quantifies the potential fiscal impact of disease-management and treatment strategies that are demonstrated to be successful in managing patients with NVAF. As such, the TCoC estimator can help inform healthcare program development and resource allocation to support efficient population health management and meet the goals of the Triple Aim. ■

Acknowledgments

The authors gratefully acknowledge Fifi Klein, of P.D. Sherman Associates, and Linh B. ter Riet, PharmD, BCPS, CPEHR, of Pfizer, for providing editorial support during the development of the manuscript.

Source of Funding

This study was funded by Pfizer.

Author Disclosure Statement

Dr Nguyen, Mr Trocio, and Dr South hold stocks of Pfizer. Ms Kowal, Ms Ferrufino, and Ms Munakata are employees of IMS Health, which is a consultant to Pfizer.

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STAKEHOLDER PERSPECTIVE

Hypothesis Generation: An Essential Component of Informed Healthcare Management

By Michael F. Murphy, MD, PhD
Chief Medical and Scientific Officer, Worldwide Clinical Trials

In an era in which integrated healthcare delivery attempts to optimize efficiency and quality, Nguyen and colleagues provide a superb example of an accessible method for hypothesis generation through the creation of a total cost of care (TCoC) estimator within a comprehensive health plan claims database.[1] As an illustrative example, a longitudinal cohort of patients with nonvalvular atrial fibrillation (NVAF) who are candidates for treatment with oral anticoagulants is created from commercially insured patients using a preindex (180 days) and follow-up period (360 days) design. Input data include pharmacy and medical costs, as well as information permitting stratification by age, type of costs, point of care, and region. The model attributes permit the comparison of the current costs versus the projected costs by varying assumptions regarding the impact of disease-management activities that target critical outcomes mapped against associated changes in cost trends. Although the applicability of the TCoC estimator in population healthcare management and in program development is intuitive, applications are apparent for other stakeholders given its accessibility, flexibility, and variety of model inputs, accentuating the importance of hypothesis generation as well as testing for therapeutic optimization on a population level.

RESEARCHERS: Observational and interventional research flourishes in data-rich environments, and modifications in patient characteristics, point of care, interventions, measures, and methods of analyses yield meaningful changes in outcome. Although randomized

STAKEHOLDER PERSPECTIVE *Continued*

controlled trials supporting market authorization identify influential parameters, mapping data from controlled settings into real-world healthcare delivery environments is hampered by recognized constraints created by the randomized controlled trials setting.

Contrasting disease-management levers relevant to patients receiving anticoagulants versus all patients with NVAF, the relationships between disease-management options and cost impact are examined within a total cost of care analytic framework to select actionable options with the highest fiscal impact. The TCoC estimator thus complements "gedankenexperiments," by empirically examining the impact of changes in patient eligibility, variations in standards of care, assessments, and durations of exposure on healthcare utilization expressed as a financial metric.[2] As a dynamic, ready accessibility model, the TCoC estimator can inform the design of clinical development and disease-management programs.

PAYERS: The TCoC estimator quantifies the financial burden of untreated or poorly managed patients for outcomes that are preventable. Similar to demands placed on healthcare professionals, payers require "actionable content" to prioritize interventions yielding maximum benefit, and the base-case within the TCoC estimator, which assumed a theoretical 25% improvement from the established benchmark for illustrative purposes, reflects the importance of that concept.

The TCoC estimator does not purport to substitute for a mosaic of other data-informing benefit design, such as electronic medical records, and studies provided by pharmaceutical companies. Indeed, the optimal analyses of patient health status require access to patient-level care and claims data,[3,4] acknowledging that managed care organizations, pharmacy benefit managers, and integrated delivery networks differentially weigh the implication of data based on the focus of their coverage.[5]

Potential applications of the TCoC estimator as a research stratagem also may extend into other databases that sample different demographics, enhancing the statistical power of measurements and implications, particularly if all payer claims databases are realized as a single national standard.[6]

PATIENTS: An efficient healthcare system is predicated on the concept of measuring value, and incorporating the TCoC in producing near-term and longer-term patient outcomes is central to its concept.[7] Although patient satisfaction with plan design may be dissociated from changes in healthcare utilization and expenditures,[8] estimating the TCoC while exploring adjustments for modifiable risk factors and critical inflection points for healthcare delivery can influence organizational dynamics and plan design, thereby ultimately enhancing patient satisfaction. ■

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