Cost Implications of Anticoagulation Strategies After Percutaneous Coronary Intervention Among Patients With Atrial Fibrillation (A PIONEER-AF PCI Analysis)

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The PIONEER AF-PCI trial demonstrated that in atrial fibrillation patients who underwent intracoronary stenting, either rivaroxaban 15 mg daily plus $P2Y_{12}$ inhibitor monotherapy (Group 1) or 2.5 mg rivaroxaban twice daily plus dual antiplatelet therapy (DAPT) (Group 2) was associated with fewer recurrent hospitalizations, primarily for bleeding and cardiovascular events, compared with standard-of-care vitamin K antagonist and DAPT (Group 3). Associated costs are unknown. This study estimates costs associated with rivaroxaban strategies compared with vitamin K antagonist and DAPT. Medication costs were estimated using wholesale acquisition costs, medication discontinuation rates, and costs of monitoring. Using a large US healthcare claims database, the mean adjusted increase in 1-year cost of care for individuals with atrial fibrillation and percutaneous coronary intervention (PCI) rehospitalized for bleeding, cardiovascular, and other events was compared with those not rehospitalized. Using adjudicated rehospitalization rates from PIONEER AF-PCI, cost differences were estimated. Rates of rehospitalization for bleeding were 6.5%, 5.4%, 10.5%, and 20.3%, 20.3%, 28.4% for cardiovascular events in Groups 1, 2, and 3. Medication and monitoring costs were $3,942, $4,115, and $1,703. One-year costs for all recurrent hospitalization costs and/or patient for the groups were $24,535, $20,205, and $29,756. One-year cost increase associated with bleeding rehospitalizations and/or patient was $4,160, $3,212, and $6,876 and was $13,264, $11,545, and $17,220 for cardiovascular rehospitalizations and/or patient. Overall estimated cost per patient was $28,476, $24,320, and $31,458. Compared with warfarin, both rivaroxaban treatment strategies had higher medication costs, but these were more than accounted for by fewer hospitalizations. **(Am J Cardiol 2019;123:355−360)**

The optimal treatment strategy for patients with atrial fibrillation (AF) who have received stents has been difficult to determine given that dual antiplatelet therapy (DAPT) is preferred for prevention of stent thrombosis in patients undergoing percutaneous coronary intervention (PCI),[1] and oral anticoagulation with a vitamin K antagonist (VKA) is superior to DAPT in reducing the risk of ischemic stroke in patients with AF.[2] All 3 drugs are often combined in a strategy known as triple therapy consistent with consensus guidelines[3]; however, this approach results in excessive major bleeding, with rates of 2.2% within the first month and 4% to 12% within the first year of treatment.[4] PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) provided the first randomized data comparing triple therapy with warfarin with 2 regimens that included the factor Xa inhibitor, rivaroxaban, in combination with either a $P2Y_{12}$ inhibitor alone or DAPT.[5] The study demonstrated a significantly lower rate of clinically significant bleeding in the 2 groups receiving rivaroxaban compared with the group receiving standard triple therapy, with similar rates of death from cardiovascular causes, myocardial infarction, or stroke.[5] Furthermore, rivaroxaban based therapy was associated with a reduction in the end point of all-cause death

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and rehospitalization, when the latter resulted from bleeding.[6] We hypothesized the increased medication cost of rivaroxaban-based strategies would be offset by the cost savings associated with reductions in rehospitalization and bleeding events compared with warfarin and DAPT. This study evaluates the costs of care and the economic implications of clinical events in the PIONEER AF-PCI population.

Methods

The design and primary results of the PIONEER AF-PCI study have been previously published.[5] In brief, a total of 2,124 adult patients with nonvalvular AF who underwent PCI with stent placement were randomized 1:1:1 to administration of either rivaroxaban 15 mg daily plus a $P2Y_{12}$ inhibitor for 12 months (Group 1), rivaroxaban 2.5 mg twice daily with stratification to a prespecified duration of DAPT of 1, 6, or 12 months (Group 2), or dose-adjusted VKA daily with a similar DAPT stratification (Group 3). Patients in Group 2 who received the treatment for 1 or 6 months then received rivaroxaban at a dose of 15 mg once daily plus single antiplatelet therapy with aspirin (75 mg once daily) for the remainder of the 12-month treatment period. Patients in Group 3 who received the treatment for 1 or 6 months then received warfarin once daily plus single antiplatelet therapy with aspirin for the remainder of the 12-month treatment period.

A cost comparison model was constructed to compare the differences in total direct healthcare costs in the 3 treatment arms from a US managed care payer's perspective. Total healthcare costs, involving total drug costs and total clinical event costs, were assessed over a 1-year time period. Cost for a given drug was calculated as the product of the drug price and duration of treatment (DOT) for that drug. In Group 3, patients on warfarin were required to have routine international normalized ratio (INR) monitoring, and thus, the cost for INR monitoring was considered as the part of drug cost for patients receiving warfarin.

Clinical event cost was calculated as the product of annual incremental cost of care associated with a clinical event (vs absence of a clinical event) and the number of events observed over the 1-year time period, based on Kaplan-Meier event estimates. Three types of clinical events were considered: rehospitalization for bleeding, rehospitalization for a cardiovascular cause, and rehospitalization for all other causes. All costs were adjusted to 2016 US dollars using Consumer Price Index medical services data from the Bureau of Labor Statistics. Based on PIONEER trial results, the overall 1-year Kaplan-Meier rates for clinical events in Groups 1, 2, and 3 were 34.1%, 31.2% and 41.5%, respectively. The event rates for rehospitalization in Groups 1, 2, and 3 due to bleeding were 6.5%, 5.4%, and 10.5%, respectively; due to a cardiovascular cause were 20.3%, 20.3%, and 28.4%, respectively; and due to other causes were 14.8%, 11.7%, and 14.3%, respectively.[6]

Duration of treatment used in the cost comparison analysis was determined based on the PIONEER trial. Since patients in the PIONEER trial were assigned to receive varied durations of treatments, for each treatment, a weighted average of the assigned DOT was calculated with weights equal to the proportions of patients receiving alternative assigned DOTs. The weighted average of the assigned DOT was further adjusted to account for discontinuation rates (21.0%, 21.1%, and 29.4%[5] of patients discontinued treatments in Groups 1, 2, and 3, respectively). Specifically, patients who discontinued a treatment were assumed to have been on the treatment for only half the period of the assigned DOT. The adjusted weighted average DOT was then used to calculate the drug cost for each treatment in each group.

Unit cost of treatment was estimated based on the wholesale acquisition cost 2016 drug prices from Redbook.[7] The unit cost for rivaroxaban was estimated at $359.61 for a 30-pill package at a dose of 15 mg. Since there is no wholesale acquisition cost price available for rivaroxaban 2.5 mg in US, we assumed that the price for a 56-pill package at a dose of 2.5 mg was also $359.61. This assumption was made given European pricing. The unit cost for warfarin was estimated at $29.96 for 100 tablets at a dose of 5 mg. Aspirin 81 mg was estimated at $3.67 for 90 tablets, and clopidogrel was estimated at $7.39 for a 30-pill package of 75 mg tablets. Finally, the unit cost for 1 INR monitoring was estimated at $69.76 based on previous analyses.[6]

Due to limited information in the literature about the annual incremental costs of care for each type of rehospitalization in AF patients who underwent PCI, a claims analysis using the IQVIA Real-World Data Adjudicated Claims—US database (January 2011 to September 2015) was conducted to develop the average costs associated with various types of rehospitalizations and subsequent care. These were then applied these costs to the specific type of rehospitalizations in PIONEER AF-PCI to estimate the annual costs of care. Patients without a rehospitalization during the 1-year follow-up period served as a reference group. Patients with rehospitalizations were classified into multiple groups based on the cause of rehospitalization as assigned by the Percutaneous/Pharmacologic Endoluminal Revascularization For Unstable Syndromes Evaluation core laboratory, determined using the primary diagnosis recorded at the first day of the first rehospitalization after the index date. For example, rehospitalizations due to bleeding events were subdivided into 6 groups (gastrointestinal bleeding [GI], cerebral bleeding, anemia, genitourinary bleeding, hematoma and/or postprocedure bleeding, or other bleeding events), and rehospitalizations due to cardiovascular causes were subdivided into 12 subgroups (e.g., heart failure, atrial arrhythmia, unstable coronary disease, stroke and/or transient ischemic attack, etc.).

The adjusted annual cost differences between each rehospitalization subgroup and patients without rehospitalization were estimated using multivariate linear regression models adjusted for the following baseline variables: age, gender, insurance plan, year of index date, Quan-Charlson comorbidity index,[8] CHA_2DS_2-VASc score,[9] HAS-BLED score,[10] inpatient costs, emergency department costs, outpatient costs, and pharmacy costs. The annual incremental costs of care for rehospitalization due to bleeding, cardiovascular, or other causes were then calculated as weighted averages of costs of care associated with subgroups of each rehospitalization type. The proportions of rehospitalizations for each subgroup, calculated using the PIONEER trial line

listing of all adverse events requiring hospitalization, were used as the weights.

Based on the event rates and durations of treatment obtained from PIONEER previously reported,[6] as well as the unit costs assumed above, total healthcare costs were calculated for each treatment arm as the sum of total drug costs (i.e., costs associated with all treatments and treatment administration if applicable over the treatment period) and total clinical event costs (i.e., costs associated with rehospitalization over the 1-year period). To account for the uncertainties surrounding the model inputs, probabilistic sensitivity analysis (PSA) based on Monte Carlo methods was conducted to obtain 95% confidence intervals of cost estimates associated with treatments. The Monte Carlo simulation was conducted based on 1,000 iterations. In each iteration, model inputs were sampled at random from their respective assumed probability distributions. Total drug costs, total clinical event costs, and total healthcare costs were then calculated using these randomly generated model inputs for each treatment group. Finally, the 95% confidence intervals of the cost estimates corresponding to the 2.5th and 97.5th percentiles of 1,000 cost estimates were obtained from the 1000 iterations. The base-case value and probability distributions for each model input used in the PSA (i.e., treatment and 3 clinical events) are listed in Appendix Table 1.

Results

Average 1-year cost of care for rehospitalization for bleeding events estimated using the claim analysis was $63,318 and for cardiovascular events was $61,439. The majority of rehospitalizations for bleeding events (40.2%) observed in the PIONEER study were due to GI with a 1-year cost of care of approximately $60,258. The most common reason for cardiovascular rehospitalization was congestive heart failure with a 1-year cost of care of approximately $84,665.

The 1-year medication cost for VKA + DAPT compared with Riva + $P2Y_{12}$ was approximately $2,200 less and $2,400 less than Riva + DAPT (Table 1). Costs associated with rehospitalization due to bleeding events and cardiovascular events were higher with VKA + DAPT (Table 2). The 1-year cost of care for rehospitalization due to bleeding events for VKA + DAPT compared with Riva + $P2Y_{12}$ was approximately $2,600 greater and $3,600 greater than Riva + DAPT. The 1-year cost of care for rehospitalization due to cardiovascular events for VKA + DAPT compared with Riva + $P2Y_{12}$ was approximately $3,900 greater and $5,700 greater than with Riva + DAPT. Overall 1-year costs including medication costs were $2,982 greater for VKA + DAPT compared with Riva + $P2Y_{12}$ and $7,138 greater than with Riva + DAPT (Figure 1). Results of the PSA are shown in Table 3 indicating that the cost differences for the 2 rivaroxaban arms versus the VKA + DAPT arm were significant.

Discussion

Our analyses demonstrate that a medication strategy of either rivaroxaban 15 mg daily with a $P2Y_{12}$ inhibitor or rivaroxaban 2.5 mg twice daily with DAPT in patients with AF who undergo PCI had both superior outcomes and was cost saving relative to standard triple therapy including VKA and DAPT. Although medication costs were higher with either rivaroxaban strategy, lower costs of rehospitalization more than made up for these differences and resulted in approximately $3,000 to $7,000 per year cost savings. These data suggest a cumulative cost saving is associated with both rivaroxaban-based strategies compared with standard warfarin.

Previous data from the PIONEER AF-PCI trial demonstrated a significant reduction in the risk of rehospitalization in patients in both rivaroxaban treatment arms compared with standard-of-care triple therapy.[6] This reduction largely drove the observed difference in costs between the treatment arms in this analysis. It is known that therapy with VKA and DAPT is associated with increased risk of bleeding,[11] but this strategy was consistent with guideline recommendations.[12] The duration of triple therapy kept as short as possible, a prerandomization decision by the treating physician, and that triple therapy was of the same duration in the rivaroxaban 2.5 mg twice daily with DAPT and VKA and DAPT arms. Interestingly, cost differences were not only driven by the reduction in bleeding rehospitalizations which may be expected in the rivaroxaban-based treatment groups. There also appeared to be a more significant cost difference related to nonbleeding, cardiovascular events. It is possible that bleeding events, some not requiring medical attention, may result in patients discontinuing medical therapy with a subsequent increase in cardiovascular events. Although data on adherence to nonstudy drugs was not available, patients in the PIONEER VKA + DAPT treatment arm were more likely to discontinue their antithrombotic agents. These findings are also supported by previous data in patients with AF which shows that the most significant contributor to total healthcare costs in this population is from hospital admissions (44%).[13] Furthermore, between the 2 rivaroxaban strategies, patients randomized to the rivaroxaban 2.5 mg BID + DAPT arm had a greater cost difference when compared with VKA + DAPT. Despite a similar rate of rehospitalizations for cardiovascular causes, rivaroxaban 2.5 mg BID + DAPT was associated with lower incidence of rehospitalizations for either bleeding or other causes, when compared with rivaroxaban 15 mg with a $P2Y_{12}$ inhibitor. Furthermore, patients in this treatment group had a lower proportion of hospitalizations from GI bleeding and heart failure which are associated with higher costs.

This study has a number of limitations. First, unit costs for clinical events estimated using a claims analysis may be biased due to residual confounding as well as the inherent limitations of an administrative claims database, such as potential miscoding, billing inaccuracies, and missing data though we would not expect a differential bias based on treatment assignment. Second, given the cost assumptions are based on a claims analysis, they may only apply to patients in the United States. Moreover, this study evaluated the impact treatment only on direct medical costs, but did not assess the potential impact on indirect costs. It may be possible that avoidance of rehospitalization improves productivity and quality of life, which in turn would further

Table 1
Medication costs by treatment assignment

Variable	Riva 15 mg + $P2Y_{12}$	Riva 2.5 mg + DAPT		VKA + DAPT
Anticoagulant daily dose (mg)	15	5	15	Adjustable
Number of pills per day	1	2	1	1
Adjusted duration of treament[3] (months)	10.7	7.3	3.4	10.2
Intended duration of treatment (months)	12.0	8.2	3.8	12.0
1	0.0%	15.4%	0.0%	0.0%
6	0.0%	35.0%	35.0%	0.0%
11	0.0%	0.0%	15.4%	0.0%
12	100.0%	49.6%	0.0%	100.0%
Proportion of discontinuation	21.0%	21.1%	21.1%	29.4%
Drug cost per package (WAC), 2016 US$	359.61	359.61	359.61	29.96
Strength per pill (mg)	15	2.5	15	5
Number of pills per package	30	56	30	100
Total anticoagulant cost (per patient)	***$3,862***	***$4,049***		***$92***
$P2Y_{12}$ daily dose (mg)	75	75		75
Number of pills per day	1	1		1
Adjusted duration of treatment (months)	10.7	7.3		6.9
Intended duration of treatment (months)	12.0	8.1		8.1
1	0.0%	15.4%		16.3%
6	0.0%	35.0%		34.8%
12	100.0%	49.6%		48.9%
Proportion of discontinuation	21.0%	21.1%		29.4%
Drug cost per package (WAC), 2016 US$	7.39	7.39		7.39
Strength per pill (mg)	75	75		75
Number of pills per package	30	30		30
Total $P2Y_{12}$ cost (per patient)	***$79***	***$54***		***$51***
Aspirin daily dose (mg)	0	75 - 100		75 - 100
Number of pills per day	0	1		1
Adjusted duration of treatment (months)	0.0	10.7		10.2
Intended duration of treatment (months)	0.0	12.0		12.0
12	0.0%	100.0%		100.0%
Proportion of discontinuation	21.0%	21.1%		29.4%
Drug cost per package (WAC), 2016 US$	3.67	3.67		3.67
Strength per pill (mg)	81	81		81
Number of pills per package	90	90		90
Total aspirin cost (per patient)	***$0***	***$13***		***$13***
Total medication cost (per patient)	**$3,942**	**$4,115**		**$156**
Other treatment cost				
INR monitoring per visit, 2016 US$	0	0	0	69.76
Adjusted number of INR, per year	0	0		22.2
Number of INR control, per year (at least every 2 weeks)	0	0	0	26
Proportion discontinuation	21.0%	21.1%		29.4%
Total other treatment cost (per patient)	***$0***	***$0***		***$1,547***
Total drug cost (per patient)	**$3,942**	**$4,115**		**$1,703**

DAPT = dual antiplatelet therapy; INR = international normalized ratio; Riva = Rivaroxaban; US = United States; VKA = vitamin K antagonist; WAC = wholesale acquisition cost.

Table 2
Clinical events and costs by treatment assignment

	Event rate			Event cost/patient		
	Riva 15 mg + $P2Y_{12}$	Riva 2.5 mg + DAPT	VKA + DAPT	Riva 15 mg + $P2Y_{12}$	Riva 2.5 mg + DAPT	VKA + DAPT
Total	34.1%	31.2%	41.5%	-	-	-
Bleeding or Cardiovascular	24.7%	24.0%	35.7%	-	-	-
Bleeding	6.5%	5.4%	10.5%	$4,160	$3,212	$6,786
Cardiovascular	20.3%	20.3%	28.4%	$13,264	$11,545	$17,220
Other	14.8%	11.7%	14.3%	$7,111	$5,447	$5,750
Total clinical event cost (2016 US$)	-	-	-	**$24,535**	**$20,205**	**$29,756**

DAPT = dual antiplatelet therapy; Riva = Rivaroxaban; VKA = vitamin K antagonist.

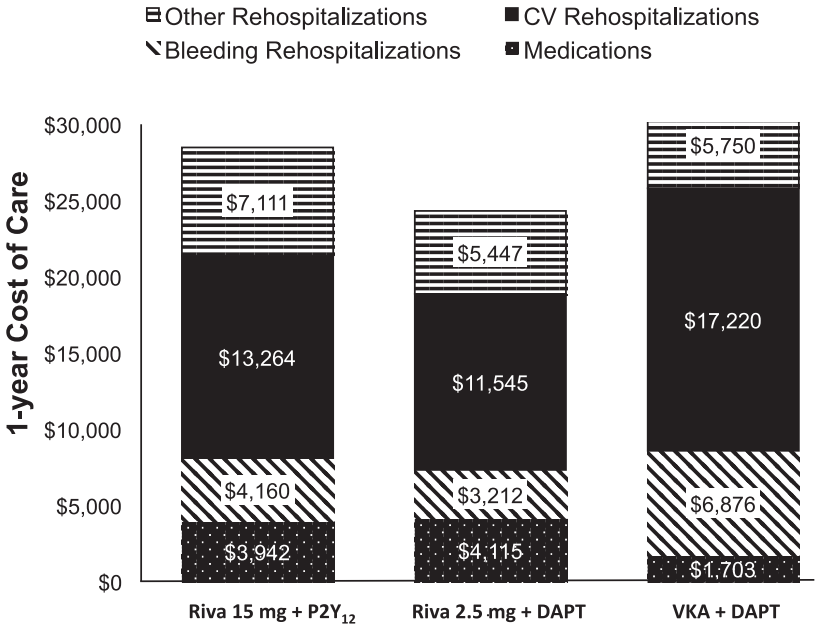

Figure 1. Total healthcare cost per patient per year by treatment assignment.

Table 3
Probabilistic sensitivity analysis by treatment assignment

	Riva 15 mg + $P2Y_{12}$	Riva 2.5 mg + DAPT	VKA + DAPT	Cost difference	Cost difference
Group	1	2	3	1−3	2−3
Annual drug costs per patient (2016 US$ [95%CI])	3,942 [3,215, 4,649]	4,115 [3,357, 4,854]	1,703 [1,389, 2,008]	2,239 [1,826, 2,640]	2,413 [1,968, 2,846]
Annual clinical event costs per patient (2016 US$ [95%CI])	24,535 [13,780, 43,521]	20,205 [11,830, 35,108]	29,756 [18,402, 49,465]	−5,221 [−5,945, −4,622]	−9,551 [−14,358, −6,573]
Annual total costs per patient (2016 US$ [95%CI])	28,476 [17,527, 47,801]	24,320 [15,741, 39,577]	31,458 [20,021, 51,315]	−2,982 [−3,607, −2,494]	−7,138 [−11,738, −4,280]

DAPT = dual antiplatelet therapy; Riva = Rivaroxaban; VKA = vitamin K antagonist.

Probabilistic sensitivity analysis based on Monte Carlo method was conducted to obtain the 95% CI for all the cost estimates. In each iteration of Monte Carlo simulation, model inputs were sampled at random from probability distributions that were assumed for each model input and costs associated with treatments and clinical events were then calculated using these randomly generated model inputs for each treatment group. The 95% CIs of cost estimates then took the values of 2.5th and 97.5th percentiles of the 1,000 cost estimates obtained from 1000 iterations.

magnify the cost savings associated with rivaroxaban. Finally, since this analysis used the data from the PIONEER trial, in which patients received continuous care and close monitoring, application to a less selected group of patients may be limited.

In patients with AF undergoing stenting, a medication strategy of either rivaroxaban 15 mg daily with a $P2Y_{12}$ inhibitor or rivaroxaban 2.5 mg twice daily with DAPT was more economic compared with standard triple therapy. This evidence demonstrates triple therapy is not only associated with increased bleeding and adverse outcomes, but also a subsequent increase in total healthcare costs.

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Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.10.033.

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter Aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–1607.
2. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903–1912.
3. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey J-Y, Ponikowski P, Rutten FH, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Vardas PE, Agladze V, Aliot E, Balabanski T, Blomstrom-Lundqvist C, Capucci A, Crijns H, Dahlöf B, Folliguet T, Glikson M, Goethals M, Gulba DC, Ho SY, Klautz RJM, Kose S, McMurray J, Perrone Filardi P, Raatikainen P, Salvador MJ, Schalij MJ, Shpektor A, Sousa J, Stepinska J, Uuetoa H, Zamorano JL, Zupan I. Guidelines for the management of atrial fibrillation the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *EP Europace* 2010;12:1360–1420.
4. Paikin JS, Wright DS, Crowther MA, Mehta SR, Eikelboom JW. Triple antithrombotic therapy in patients with atrial fibrillation and coronary artery stents. *Circulation* 2010;121:2067–2070.
5. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GYH, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med* 2016;375:2423–2434.
6. Gibson CM, Pinto DS, Chi G, Arbetter D, Yee M, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Burton P, van Eickels M, Korjian S, Daaboul Y, Jain P, Lip GY, Cohen M, Peterson ED, Fox KA. Recurrent hospitalization among patients with atrial fibrillation undergoing intracoronary stenting treated with 2 treatment strategies of rivaroxaban or a dose-adjusted oral vitamin k antagonist treatment strategy. *Circulation* 2017;135:323–333.
7. Truven Health Analytics. Micromedex solution: red book online search results. Available at: http://www.micromedexsolutions.com/. Published 2016. Accessed on September 2, 2016.
8. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–1139.
9. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263–272.
10. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093–1100.
11. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen JG, van 't Hof AW, ten Berg JM. WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;381:1107–1115.
12. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, Haeusler KG, Boriani G, Capodanno D, Gilard M, Zeymer U, Lane D, Document R, Storey RF, Bueno H, Collet JP, Fauchier L, Halvorsen S, Lettino M, Morais J, Mueller C, Potpara TS, Rasmussen LH, Rubboli A, Tamargo J, Valgimigli M, Zamorano JL. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J* 2014;35:3155–3179.
13. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health* 2006;9:348–356.