



A value-based budget impact model for dronedarone compared with other rhythm control strategies

Journal of **Comparative Effectiveness Research**

Jennifer Ken-Opurum^{*1}, Sessa SS Srinivas¹, Pratyusha Vadagam¹, Lang Faith¹, Seojin Park², Scott Charland², Andrew Revel² & Ronald Preblich²

¹Axtria Inc., Decision Science, Health Economics and Outcomes Research / Real-World Evidence, Berkley Heights, NJ 07922, USA

²Sanofi US, US General Medicines, Bridgewater, NJ 08807, USA

*Author for correspondence: Jennifer.Kenopurum@Axtria.com

Aim: The budgetary consequences of increasing dronedarone utilization for treatment of atrial fibrillation were evaluated from a US payer perspective. **Materials & methods:** A budget impact model over a 5-year time horizon was developed, including drug-related costs and risks for long-term clinical outcomes (LTCOs). Treatments included antiarrhythmic drugs (AADs; dronedarone, amiodarone, sotalol, propafenone, dofetilide, flecainide), rate control medications, and ablation. Direct comparisons and temporal and non-temporal combination scenarios investigating treatment order were analyzed as costs per patient per month (PPPM). **Results:** By projected year 5, costs PPPM for dronedarone versus other AADs decreased by \$37.69 due to fewer LTCOs, treatment with dronedarone versus ablation or rate control medications + ablation resulted in cost savings (\$359.94 and \$370.54, respectively), and AADs placed before ablation decreased PPPM costs by \$242 compared with ablation before AADs. **Conclusion** Increased dronedarone utilization demonstrated incremental cost reductions over time.

Plain language summary

What is this article about? Atrial fibrillation (AFib) is a common type of irregular heartbeat called arrhythmia, which may present with heart palpitations, shortness of breath, extreme fatigue, chest pain, and weakness. Guideline recommended treatment of AFib may include reducing the risk for stroke with anticoagulants, improving heartbeat irregularities with rate control medications or anti-arrhythmic drugs (AADs), and a minimally invasive surgery called ablation.

This study assesses the budgetary consequences (costs) of increasing utilization of a specific AAD, dronedarone, in the treatment of AFib from a US payer's perspective. Comparative analysis explored different possible scenarios, including replacement of other AADs with dronedarone, dronedarone taken alone or in combination with ablation and/or rate control medications, and placing AADs earlier in the treatment sequence compared with ablation and rate control medications.

What were the results? In the scenario replacing other AADs with dronedarone, there was a reduction in costs per patient per month (PPPM), largely related to lower risk for stroke with dronedarone. AADs placed before ablation in the treatment sequence also decreased PPPM costs compared with ablation placed before AADs. Use of AADs, individual or in combination with ablation, resulted in comparable clinical outcomes; however, there were overall cost savings because of the high procedural costs of ablation.

What do the results mean? These findings can help payers make decisions about the most cost-effective treatment strategies for better results.

First draft submitted: 23 November 2022; Accepted for publication: 30 January 2023; Published online: 14 March 2023

Keywords: cardiology/cardiovascular • comparative effectiveness research • health economics

Atrial fibrillation (AFib) is an irregular and often rapid heart rate in which the heart's two upper chambers (the atria) beat chaotically, irregularly, and out of coordination with the two lower chambers (the ventricles) of the



heart. Symptoms can include heart palpitations, shortness of breath, fainting, and weakness. In addition, AFib can increase the risk of stroke, heart failure (HF), and other heart-related complications [1].

Worldwide, AFib is the most common sustained cardiac arrhythmia in adults [2]. As of 2010, AFib affected approximately 5.1 million Americans. Prevalence is projected to double between 2010 and 2030 [3]. With increasing prevalence comes the eventual reality of increasing costs and healthcare spending, with current estimates for the economic burden of AFib on the US healthcare system at \$6.5 billion annually, distributed among AFib-related hospitalizations (44%), inpatients costs (29%), outpatient costs (23%) and pharmaceutical costs (4%) [4].

Management of AFib is broadly captured by the ABC pathway, which is “*Avoid stroke (with Anticoagulants); Better symptom management, with patient-centered decisions on rate or rhythm control; Cardiovascular and comorbidity risk optimization*” [5]. Thus, stroke prevention via oral anticoagulants is offered as an initial step when risk factors for stroke are present. Rate control is preferred as first choice therapy for symptom management when the patient has not demonstrated rhythm control issues. Treatment approaches for rhythm control include cardioversion, anti-arrhythmic drugs (AADs), and cardiac ablation [2].

In the EAST-AFNET 4 study, the cohort undergoing early rhythm control via AADs had a lower likelihood of cardiovascular death and stroke (hazard ratios 0.72 [0.52–0.98] and 0.65 [0.44–0.97], respectively), compared with the cohort of patients undergoing usual care [6]. Based on findings from multiple RCTs, ablation is generally recommended as a second-line therapy after failure (or intolerance) of class I or class III AADs, and is effective in maintaining sinus rhythm in patients with paroxysmal and persistent AFib [2]. For some patients, ablation may be considered as first-line therapy [7].

Multiple AADs are available in the market. Amiodarone is recommended for long-term rhythm control; however, owing to its extracardiac toxicities (pulmonary toxicity, hypothyroidism, hepatic toxicity, corneal deposits, optic neuropathy, and skin discoloration) [8], other AADs should be considered first whenever possible. Dronedarone is a benzofuran derivative with an electro-pharmacologic profile closely resembling that of amiodarone, but with structural differences intended to be efficacious without causing the extracardiac toxicities associated with amiodarone [9]. Based on findings from ATHENA [10], a large outcomes trial in patients with AFib/ atrial flutter (AFL), dronedarone was approved to reduce hospitalizations due to AFib in patients with paroxysmal and persistent AFib in the US [11]. Based on the 2020 European Society of Cardiology (ESC) guidelines, dronedarone was shown to have a favorable safety profile in terms of lower risk for cardiovascular hospitalization and incident comorbidities as well as atrioventricular nodal-slowness properties in patients with paroxysmal or persistent AFib, thus making it the likely first choice among these patients [2]. Despite proven clinical benefits, the long-term use of AADs is complicated by various long-term clinical outcomes (LTCOs), including all-cause mortality, withdrawal due to adverse events (AEs), proarrhythmia, stroke, and recurrence of AFib [12].

For AFib patients eligible for treatment with dronedarone, economic consequences are driven by clinical outcomes (drug utilization, outpatient visits, and hospitalization). However, the cost savings of dronedarone’s use in rhythm control therapy has yet to be comprehensively explored. Moreover, an investigation of the optimal sequencing of treatments in AFib is warranted. The primary objective of this analysis was to assess the budgetary consequences of increasing the utilization of dronedarone from the US payer perspective via a value-based budget impact model (BIM). Scenarios included replacement of other AADs with dronedarone, dronedarone versus ablation or rate control medications, and placing AADs earlier in the treatment sequence. Findings from this study will allow payers to make more informed pricing and formulary decisions for dronedarone.

Methods

Model overview

The economic impact of increasing the market share of dronedarone while reducing the market shares of other AADs was calculated using a BIM developed in Microsoft Excel 2010 (Microsoft Corp, WA). The budget impact was calculated by comparing annual healthcare costs assuming dronedarone was available for use in the market but in lower demand versus in higher demand among patients in the target population compared with other AADs (sotalolol, flecainide, amiodarone, propafenone and dofetilide). The expected budget impact of dronedarone was calculated as the difference in costs between these two scenarios (Figure 1). An incident-based modeling approach was employed, in which patients were only included in the study if they were not previously using AADs (i.e., incident patients). Accordingly, total healthcare costs were calculated on an annual basis for all incident patients in the target population during each year of the projection period.

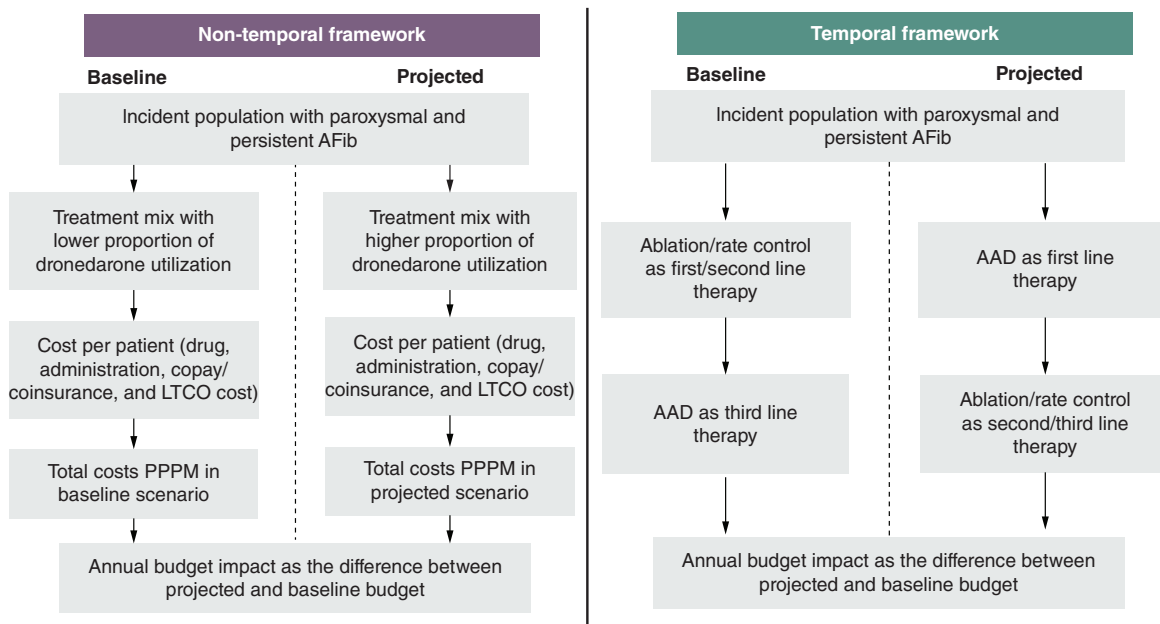


Figure 1. Determination framework.

AAD: Anti-arrhythmic drug; AFib: Atrial fibrillation; LTCO: Long-term clinical outcome.

The analysis was conducted from a US payer perspective over a time horizon of 5 years. The BIM considered direct medical costs to the payer including medication costs, treatment administration costs, and LTCO costs, reported in 2021 USD. The model did not consider monitoring costs for usage and administration of AADs and for the post-procedural period following ablation. Discount rates over time were not included in the budget impact calculations.

The base case scenario was the comparison of dronedarone versus other AADs. This BIM also included non-temporal scenarios, in which the order of treatments (individual AADs, ablation, rate control medication) was not considered, as well as temporal scenarios, in which the order of treatments (e.g., AADs as a class followed by ablation followed by rate control medication, or ablation followed by AADs as a class followed by rate control medication) was considered.

Results were reported as costs per patient in the target population per month (PPPM) and per year (PPPY).

Study population & data source

Model inputs included a mix of data available from the literature, data on file, and results generated from a retrospective database analysis of US Merative (previously Truven MarketScan) data among a reference AFib population of patients meeting the following inclusion criteria:

- Patients with ≥ 1 inpatient or ≥ 2 outpatient claims with a primary or secondary diagnosis of paroxysmal (International Classification of Diseases, 10th Revision [ICD-10] I48.0) or persistent (ICD-10 I48.1) AFib occurring on different days during the identification period (January 2016 to December 2019)
 - The index date is the date of the first qualifying claim for AFib
- ≥ 18 years of age at the beginning of the baseline period (12 months pre-index)
- Had continuous health plan eligibility during the 12-month baseline period
- Had no diagnosis of AFib during the baseline period
- Had no diagnosis of AFL during the baseline period
- Had no hospitalization for HF during the baseline period

The target population was assumed to be all treated patients with AFib (paroxysmal and persistent) in a hypothetical health plan of 1,000,000 members. The yearly growth rate for the incident AFib population was assumed to be 4.6% [3].

Table 1. Utilization of antiarrhythmic drugs in non-temporal scenarios.

Therapy	Baseline	AAD + RC	AAD + ablation	AAD + RC + ablation
Dronedarone	8.4%	7.6%	12.7%	11.7%
Sotalol	21.6%	17.3%	14.8%	16.9%
Flecainide	21.1%	24.3%	32.4%	32.0%
Amiodarone	36.5%	41.5%	27.1%	27.1%
Propafenone	6.3%	6.7%	8.2%	7.6%
Dofetilide	6.2%	2.7%	4.8%	4.8%

AAD: Antiarrhythmic drug; RC: Rate control medication.

Table 2. Utilization of interventions in temporal scenarios.

Scenario	Reference therapy at baseline	Utilization	Projected therapy at baseline	Utilization
Scenario 1	Ablation → RC → AAD	0.21%	AAD → Ablation → RC	0.21%
Scenario 2	RC → Ablation → AAD	0.66%	AAD → RC → Ablation	0.66%
Scenario 3	RC → AAD	17.57%	AAD → RC	17.57%
Scenario 4	Ablation → AAD	0.39%	AAD → Ablation	0.39%
Scenario 5	RC → Ablation	2.28%	AAD → RC → Ablation or RC → Ablation → AAD	2.28%
Scenario 6	Ablation → RC	0.68%	AAD → Ablation → RC or Ablation → RC → AAD	0.68%

AAD: Antiarrhythmic drug; RC: Rate control medication.

Baseline utilization rates for the base case scenario were 8.4% for dronedarone, 21.6% for sotalol, 21.1% for flecainide, 36.5% for amiodarone, 6.3% for propafenone, and 6.2% for dofetilide (data on file from a Medicare population in Prime Therapeutics data). Baseline utilization rates for all other non-temporal scenarios are shown in [Table 1](#) (derived from the reference AFib population). Utilizations for the temporal scenarios are shown in [Table 2](#). Projected utilization for dronedarone was 10%, 12%, 15%, 18%, and 20% in years 1 through 5, respectively; projected utilizations across the remaining AADs in years 1 through 5 were calculated by subtracting a proportion of the deficit caused in the market by dronedarone relative to each AAD's market share such that total utilization remained at 100%.

Model inputs

LTCOs in the model included proarrhythmia, stroke, AFib recurrence, and withdrawal due to AEs (operationally defined herein as an interval >100 days between two consecutive AAD prescriptions in which an AE occurred). These LTCOs were selected in alignment with outcomes reported in a 2019 Cochrane review of AADs used to maintain sinus rhythm after cardioversion for AFib, in which the outcomes most commonly reported across the literature were included in analysis (all but two trials reported AFib recurrence, all but three reported proarrhythmia or withdrawal due to AEs, and eleven reported stroke; other cardiovascular outcomes such as HF were reported less frequently in the literature, and thus not included in analysis) [12]. For the base case scenario, treated risk was calculated by multiplying risk ratios obtained from a meta-analysis of clinical trials reporting LTCOs associated with use of AADs [12–13] by the risk of LTCOs observed in the reference AFib population ([Supplementary Table 2](#)). For all other scenarios, the risk of LTCOs was derived directly from the retrospective database analysis ([Supplementary Tables 3–9](#)). LTCO costs were obtained from the literature and adjusted to 2021 costs utilizing medical inflation rates [14]: withdrawal due to AEs (\$6389) [15], proarrhythmia (\$10,952) [16], stroke (\$28,008) [17], and AFib recurrence (\$10,288) ([Table 3](#)) [18]. Total costs of LTCOs for each treatment option were calculated as the sum of each LTCO's treated risk multiplied by its cost ([Table 4](#)).

Wholesale acquisition costs (WAC) for AADs were obtained from drugs.com in October 2021 ([Table 5](#)) [19–24]. Annual costs associated with each AAD for rate control medications and ablation are shown in [Supplementary Table 1](#). The daily frequency of AAD intake was considered from product dosage information [25–29]. For all AADs, the cost of outpatient administration was assumed to be \$131.20, based on an office visit of an established patient (Current Procedural Terminology [CPT] 99214) [30]. Outpatient administration proportions were informed by dosing and administration guidelines in the package inserts [31–36]. Accordingly, administration proportions were reflected in administration costs, and considered to be 0% and \$0 in sotalol and dofetilide which are administered

Table 3. Costs of long-term clinical outcomes.

LTCOs	Cost of LTCOs, \$	Ref.
Withdrawal due to AE	6389	[15]
Proarrhythmia	10,952	[16]
Stroke	28,008	[17]
AFib recurrence	10,288	[18]

All costs for LTCOs are inflated to 2021 prices using the United States Bureau of Labor Statistics Consumer Price Index Inflation Calculator [14].
AE: Adverse event; AFib: Atrial fibrillation; LTCO: Long-term clinical outcome.

Table 4. Event risks associated with individual antiarrhythmic drugs.

Therapy	LTCOs	Risk of LTCOs	LTCO costs for each treatment
Dronedarone	Withdrawal due to AE	0.1183	\$755.82
	Proarrhythmia	0.3560	\$3898.91
	Stroke	0.0389	\$1089.51
	AFib Recurrence	0.4537	\$4667.67
Amiodarone	Withdrawal due to AE	0.5016	\$3204.72
	Proarrhythmia	0.4052	\$4437.75
	Stroke	0.0678	\$1898.94
	AFib recurrence	0.2776	\$2855.95
Sotalol	Withdrawal due to AE	0.1460	\$932.79
	Proarrhythmia	0.6480	\$7096.90
	Stroke	0.0866	\$2425.49
	AFib recurrence	0.4430	\$4557.58
Flecainide	Withdrawal due to AE	1.1538	\$7371.63
	Proarrhythmia	0.8762	\$9596.14
	Stroke	0.1202	\$3366.56
	AFib recurrence	0.3469	\$3568.91
Propafenone	Withdrawal due to AE	0.1213	\$774.99
	Proarrhythmia	0.2410	\$2639.43
	Stroke	0.0204	\$571.36
	AFib recurrence	0.3576	\$3678.99
Dofetilide	Withdrawal due to AE	0.1325	\$846.54
	Proarrhythmia	1.0040	\$10,995.81
	Stroke	0.0644	\$1803.72
	AFib recurrence	0.3843	\$3953.68

LTCO costs for each treatment were calculated by multiplying risk with costs.
AE: Adverse event; AFib: Atrial fibrillation; LTCO: Long-term clinical outcome.

Table 5. Unit costs of antiarrhythmic drugs and daily frequency of antiarrhythmic drugs.

Treatment	Unit cost, \$	Frequency per day	Average daily cost, \$	Ref.
Dronedarone	12.19	2	24.38	[19,25]
Amiodarone	0.31	2	0.62	[20,26]
Sotalol	0.26	2	0.52	[21,27]
Flecainide	0.57	1	0.57	[22,28]
Propafenone	0.77	3	2.31	[23,29]
Dofetilide	3.99	2	7.98	[24,30]

Average daily cost of treatment arms is considered by multiplying unit costs with daily drug intake frequency.

100% in the inpatient setting, 50% and \$65.60 for AADs administered 50% in the inpatient setting and 50% in the outpatient setting (amiodarone, propafenone, and flecainide), and 100% and \$131.20 for dronedarone which is administered entirely in the outpatient setting. The inpatient costs of dronedarone, amiodarone, propafenone, and flecainide were assumed to be the average of the inpatient costs of sotalol and dofetilide [37].

Table 6. Annual costs of antiarrhythmic drugs.

Treatment	Days per dispense	Discount, %	Annual cost before copayment or coinsurance, \$	Tier placement	Patient cost share (coinsurance)%	Annual copayment or coinsurance cost, \$	Annual cost after copayment or coinsurance, \$	Ref.
Dronedarone	30	20	7118.96	3	35	2491.64	4627.32	[38, 39]
Amiodarone	50	0	226.30	1	20	45.26	181.04	[38]
Sotalol	50	0	189.80	1	20	37.96	151.84	[38]
Flecainide	100	0	208.05	1	20	41.61	166.44	[38]
Propafenone	33.33	0	843.15	1	20	168.63	674.52	[38]
Dofetilide	30	0	2912.70	1	20	582.54	2330.16	[38]

Copay and coinsurance were taken from Kaiser's employer health benefits – 2021 annual survey [38] based on each drug's tier placement (Table 6). Tier placement for dronedarone was considered as tier 3, while the other AADs were assumed to be tier 1 because they are available in the market as generics. A 20% discount was applied to the WAC price of dronedarone, which was approximated from savings providing through the Multaq® savings card program [39].

Model assumptions

Drug adherence and persistence were not accounted for in this analysis. LTCO costs related to each therapy were estimated on an annual basis rather than reported at the event level. In non-temporal scenarios, the baseline analysis at year 0 is the reference point for calculating budget impact. Due to limited availability of data, there was no distinction between different AADs in the temporal scenarios.

Sensitivity analysis

A one-way sensitivity analysis (OWSA) was conducted to evaluate how individual parameters impacted the model results. The variables included in the OWSA were target population, utilization mix, and cost, which were varied by $\pm 20\%$ from baseline.

Results

Non-temporal base case scenario: dronedarone versus other AADs

In the base case scenario, the formulary inclusion of dronedarone over other AADs (amiodarone, dofetilide, flecainide, propafenone, and sotalol) resulted in a budget reduction of \$37.69 PPPM, over a 5-year time horizon with a projected utilization of 20%. This translates to a PPPY budget reduction of -\$452.30 when dronedarone replaces other AADs. Despite higher drug acquisition costs for dronedarone compared with other AADs, cost reductions in projected scenarios were driven by lower LTCO costs (primarily stroke, the costliest LTCO to treat) with dronedarone. Cost savings were likewise demonstrated in projected years 1–5 with incremental increases in utilization of dronedarone (Figure 2).

Non-temporal scenario: dronedarone versus ablation & rate control medications

Due to lower LTCO costs associated with dronedarone and higher cost of ablation treatment, dronedarone yielded substantial cost savings over ablation alone and rate control medication in conjunction with ablation. The LTCO costs of dronedarone were comparable to the LTCO costs associated with other AADs and rate control medication, which makes dronedarone a clinically and economically more suitable treatment from a patient perspective. The budget impact of non-temporal scenarios is presented in Table 7.

Temporal scenario analysis

In the reference scenario, the inclusion of AADs as first-line therapy followed by ablation as second-line therapy and rate control medication as third-line therapy demonstrated cost-savings in the majority of temporal scenarios (Table 8). In addition, ablation as first-line therapy followed by AADs as second-line therapy and rate control medication as third-line therapy also demonstrated cost benefits. Rate control medication used as first- or second-line therapy resulted in less cost-savings as compared with when used as third-line therapy (Table 8). AADs showed cost benefits when used before rate control medication; however, ablation considered before AADs demonstrated better value. Additionally, a marginal cost difference was seen when AADs and ablation were compared in the

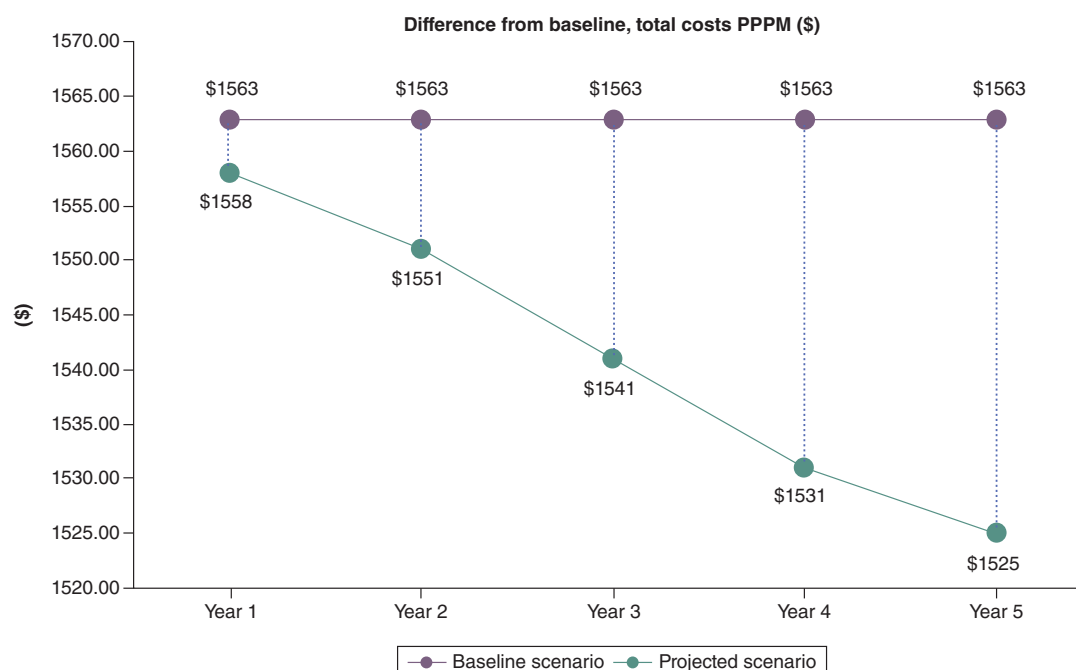


Figure 2. Base case analysis – per patient in target population per month results.

Table 7. Non-temporal scenario analysis.

Treatment comparisons	Utilization mix/cost savings	1st year	2nd year	3rd year	4th year	5th year
Dronedarone vs other AADs	Projected utilization	10%	12%	15%	18%	20%
	Savings (in PPPM)	-\$5.09	-\$11.61	-\$21.39	-\$31.17	-\$37.69
Dronedarone vs RC + Ablation	Projected utilization	30%	35%	40%	45%	50%
	Savings (in PPPM)	-\$28.07	-\$113.69	-\$199.31	-\$284.93	-\$370.54
Dronedarone vs Ablation	Projected utilization	25%	30%	35%	40%	45%
	Savings (in PPPM)	-\$31.57	-\$113.67	-\$195.76	-\$277.85	-\$359.94
Dronedarone + RC vs AADs + Rate Control	Projected utilization	10%	13%	17%	22%	28%
	Savings (in PPPM)	\$3.95	\$8.82	\$15.30	\$23.41	\$33.14
Dronedarone vs RC	Projected utilization	3%	4%	5%	6%	8%
	Savings (in PPPM)	\$1.33	\$3.01	\$4.69	\$6.37	\$9.74
Dronedarone + Ablation vs other AADs + Ablation	Projected utilization	15%	20%	25%	30%	35%
	Savings (in PPPM)	\$4.65	\$14.96	\$25.26	\$35.57	\$45.88
Dronedarone + RC + Ablation vs AADs + Rate Control + Ablation	Projected utilization	15%	20%	25%	30%	35%
	Savings (in PPPM)	\$6.41	\$16.11	\$25.81	\$35.51	\$45.21
Dronedarone vs RC vs Ablation	Projected utilization	3%	4%	5%	6%	8%
	Savings (in PPPM)	\$0.39	\$0.80	\$1.21	\$1.63	\$2.45

PPPM positive cost results favor the reference scenario, while negative PPPM cost results favor the projected scenario.
AADs: Antiarrhythmic drug; PPPM: Per patient in the target population per month; RC: Rate control medication.

temporal analysis, i.e., placing AADs either before or after ablation had minimal impact on the overall cost. Similarly, a marginal difference was observed which favored AADs placed before rate control medication in the treatment sequence.

Sensitivity analysis (non-temporal analysis)

The market share (over projected years 5, 4, and 3) and annual cost of dronedarone had the greatest influence on PPPM cost. A 20% increase in the market share of dronedarone at year 5 over other AADs increased PPPM savings by \$13.04 from its base value (\$37.69). Other key variables influencing OWSA results were the market share of

Table 8. Temporal scenario analysis.

Reference scenario (1st line → 2nd line → 3rd line treatment)	Projected scenario (1st line → 2nd line → 3rd line treatment)	Cost savings for reference scenario (PPPM), \$ [†]
AAD → Ablation → RC	RC → Ablation → AAD	\$0.23
	RC → AAD → Ablation	\$0.23
	AAD → RC → Ablation	\$0.17
	Ablation → RC → AAD	\$0.04
	Ablation → AAD → RC	-\$0.04
AAD → RC → Ablation	Ablation → RC → AAD	-\$0.79
	AAD → Ablation → RC	-\$1.02
	Ablation → AAD → RC	-\$1.25
	RC → Ablation → AAD	\$0.38
	RC → AAD → Ablation	\$0.39
Ablation → AAD → RC	RC → Ablation → AAD	\$0.35
	RC → AAD → Ablation	\$0.35
	AAD → RC → Ablation	\$0.27
	Ablation → RC → AAD	\$0.10
	AAD → Ablation → RC	\$0.05
Ablation → RC → AAD	RC → Ablation → AAD	\$0.21
	RC → AAD → Ablation	\$0.21
	AAD → RC → Ablation	\$0.14
	Ablation → AAD → RC	-\$0.08
	AAD → Ablation → RC	-\$0.04
RC → Ablation → AAD	Ablation → AAD → RC	-\$0.93
	AAD → Ablation → RC	-\$0.80
	Ablation → RC → AAD	-\$0.66
	AAD → RC → Ablation	-\$0.22
	RC → AAD → Ablation	\$0.01
RC → AAD → Ablation	Ablation → AAD → RC	-\$2.93
	AAD → Ablation → RC	-\$2.52
	Ablation → RC → AAD	-\$2.10
	AAD → RC → Ablation	-\$0.69
	RC → Ablation → AAD	-\$0.02
AAD → Ablation	Ablation → AAD	-\$0.22
Ablation → AAD	AAD → Ablation	\$0.15
AAD → RC	RC → AAD	\$5.73
RC → AAD	AAD → RC	-\$7.80

[†]Positive cost results favor the reference scenario, while negative cost results favor the projected scenario.
AADs: Antiarrhythmic drug; PPPM: Per patient in the target population per month; RC: Rate control medication.

dronedarone (over projected years 2 and 1), cost of proarrhythmia, cost of withdrawal due to AEs, cost of stroke, cost of AFib recurrence, and discount on dronedarone (Figure 3).

Sensitivity analysis (temporal analysis)

An OWSA was also conducted to test the impact of factors influencing the temporal analysis results. Position of the treatments only had an impact on risk of LTCOs and costs associated with LTCOs (Figure 4).

Discussion

In this study, a BIM assessed the anticipated costs of adopting dronedarone in the treatment journey of patients with AFib, where economic consequences were driven by clinical outcomes. In the base case analysis, despite higher WAC of dronedarone compared with other AADs, lower risk for LTCOs combined with lower administration costs among patients resulted in cost savings. Moreover, cost savings in the projected years were observed with incremental utilization of dronedarone. From the perspective of providers, payers, and patients, the lower LTCO

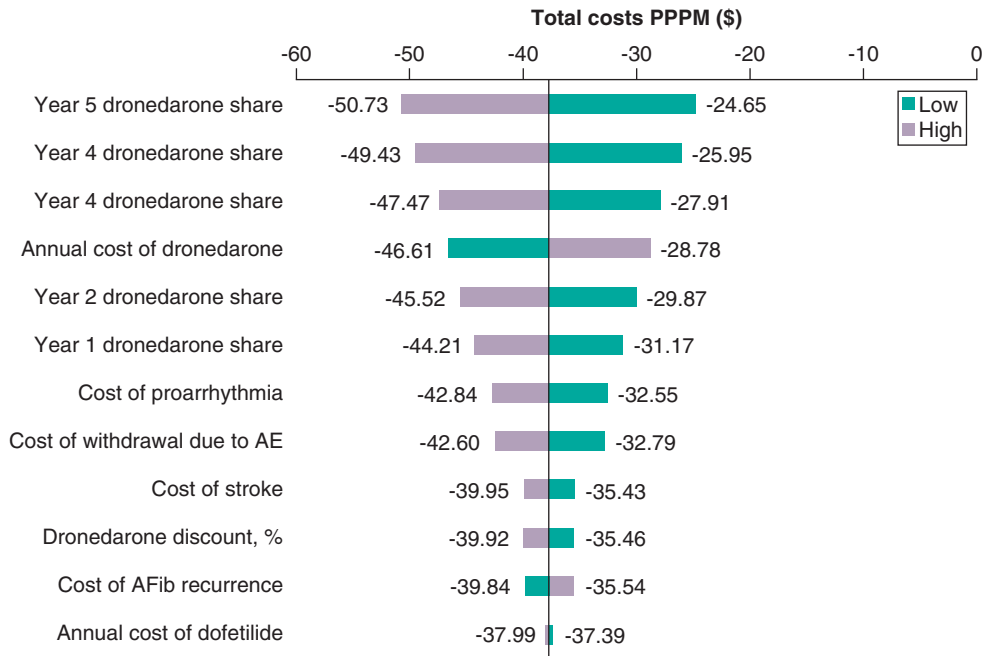


Figure 3. Tornado diagram presenting sensitivity analysis results (base case analysis: dronedarone vs other AADs). AE: Adverse event; AFib: Atrial fibrillation; PPPM: Per patient in the target population per month.

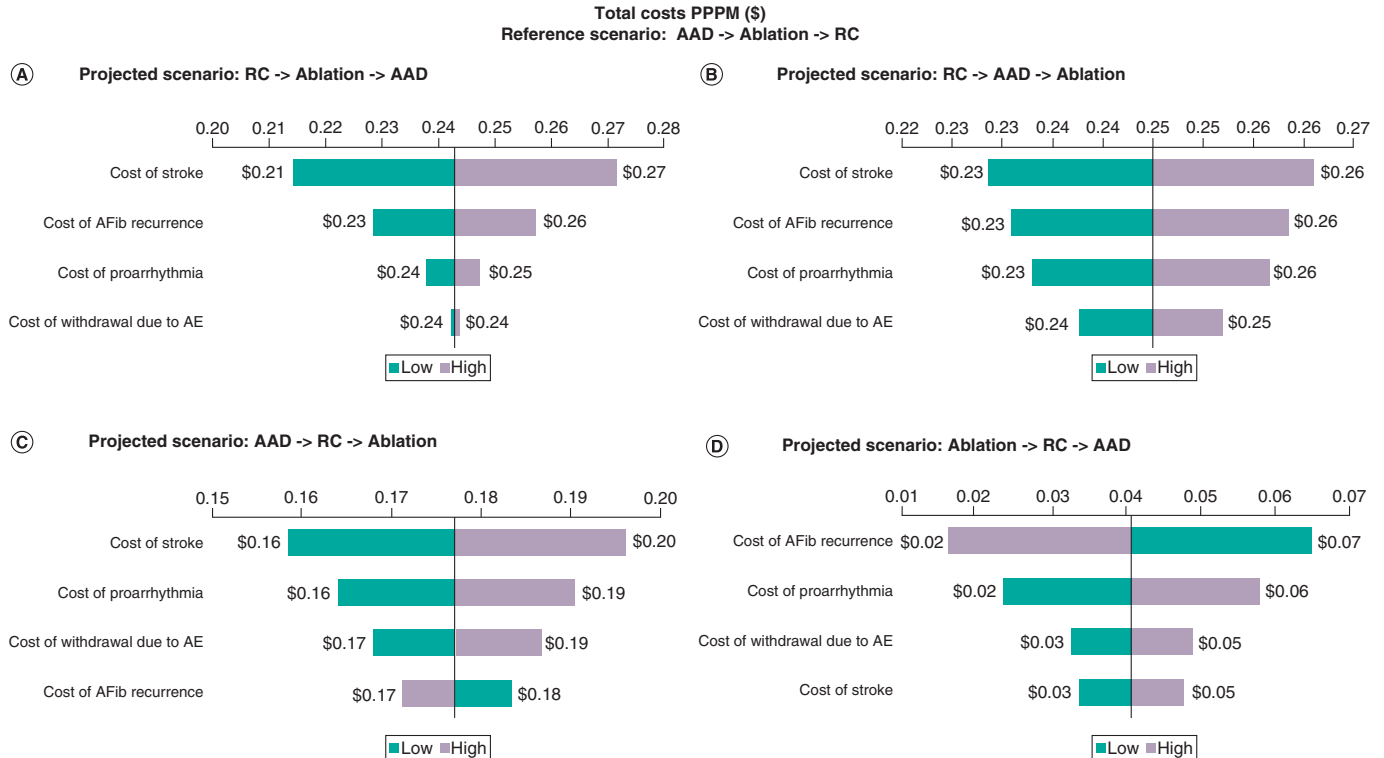


Figure 4. Tornado diagram presenting sensitivity analysis results for temporal scenarios. (A) Projected scenario: RC → ablation → AAD. (B) Projected scenario: RC → AAD → ablation. (C) Projected scenario: AAD → RC → ablation. (D) Projected scenario: Ablation → RC → AAD. AAD: Antiarrhythmic drug; AE: Adverse event; AFib: Atrial fibrillation; RC: rate control medication.

costs associated with dronedarone along with high cost of ablation makes dronedarone the preferred treatment option.

There is also evidence suggesting clinical benefits of adjunctive therapies. For example, findings from the CABANA trial indicated 47% of patients with HF who underwent catheter ablation were taking AADs during the post-blanking follow-up period [40]. Calkins *et al.* found that patients undergoing multiple ablations had a 77% success rate when also taking AADs as compared with a 71% success rate when not taking AADs [41]. Despite only a 6%-point benefit of taking AADs over placebo, this difference is likely to have substantial cost benefits, as ablation failure has been associated with higher rates of emergency room visits and hospitalizations, resulting in total higher medical costs (\$52,821 vs \$13,412; $p < 0.001$) [42]. Likewise, Gunawardena *et al.* found that majority (73%) of patients routinely took AADs prior to undergoing ablation [43]. In the EAST-AFNET 4 study, the cohort undergoing early rhythm control via AADs had a lower likelihood of cardiovascular death and stroke (hazard ratios 0.72 [0.52–0.98] and 0.65 [0.44–0.97], respectively), compared with the cohort of patients undergoing usual care [6].

In a post-hoc analysis of the ATHENA study, safety and efficacy outcomes were assessed among patients with paroxysmal or persistent AFib/AFL treated with dronedarone post-ablation. Findings suggest that treatment post-ablation significantly reduced the risk of AFib/AFL recurrence compared with placebo. Rates of cardiovascular hospitalizations or all-cause mortality were also lower, but not statistically significant [44]. In the present study, placing AADs as first-line therapy ahead of rate control medication and ablation (in any order) resulted in greater cost benefits as compared with when prescribed as second- or third-line. Due to a lack of data, we were only able to investigate AADs as a group, and not dronedarone specifically, in temporal scenario analyses. To the best of our knowledge, no previous research has reported outcomes associated with the use of dronedarone pre-ablation. This remains a gap in the literature and an area for future research. However, the ESC guidelines corroborate the above points, given that dronedarone may be preferred as first antiarrhythmic treatment due to better safety and potential outcome benefit, while patients with coronary artery disease should be treated with dronedarone as first-line therapy over other AADs [45].

Although the WAC of dronedarone is higher relative to other AADs, evidence suggests that various dimensions of quality of life of patients with AFib were improved on dronedarone [46]. Evidence from the ATHENA trial also showed that dronedarone significantly reduced the incidence rate and total duration of hospital stays among patients with AFib/AFL [47]. Hence, payers may consider the impact of dronedarone on hospitalizations, length of stay, and non-tangible events such as quality of life and other patient outcomes, while making formulary decisions.

Limitations

Where available, inputs coming from the literature were prioritized over data on file and results from analysis of RWD (real-world data). When RWD was used, classification of patients into study groups and measures derived for inputs relied on inferences based upon information appearing from claims data; thus, as with any analysis of claims data, there was the potential for medical coding inaccuracies leading to misclassification bias. The model did not account for drug adherence nor drug persistence and utilizations of different treatment combinations were not mutually exclusive. To accommodate increased utilization of dronedarone, market shares were distributed proportionally among comparators, which may not accurately reflect real-world changes in demand in response to changes in supply. Furthermore, monitoring costs were not included in the model, which could contribute to higher costs for comparators, thus yielding potentially conservative results. In temporal scenarios, the model did not differentiate between different AADs due to a lack of available data, which precludes differentiation between dronedarone and other AADs as a first-line therapy/early treatment. All cost inputs were held constant over the 5-year time horizon and the LTCO costs were taken as yearly costs of a single patient. Thus, usual inflation, as well as potential significant shifts in the economy, were not accounted for. Finally, while the model was developed using robust evidence from the literature and an analysis of RWD, some model inputs were informed by clinical opinion; namely, inpatient/outpatient administration proportions and the discount applied to dronedarone [39].

Conclusion

A BIM was developed to understand the value of dronedarone from a US payer perspective over a 5-year time horizon. This was achieved by performing a non-temporal analysis in which the value of dronedarone versus other AADs was assessed in combination or compared with rate control medication and ablation as individual therapies without considering the order in which treatments were given and a temporal analysis in which AADs were assessed

in combination with or compared with rate control medication and ablation as individual therapies when given in different orders (i.e., AADs in first-, second-, or third-line). Increasing the utilization of dronedarone and decreasing the utilization for other AADs resulted in PPPM cost savings of ~\$38 over the 5-year time horizon due to lower LTCO costs (primarily stroke, the costliest LTCO to treat). AADs placed prior to rate control medication and ablation in the treatment sequence resulted in incremental PPPM cost savings (\$0.23–\$0.39) in the projected scenario when compared with reference scenarios having rate control medication as first-line therapy. However, the magnitude of the incremental costs was lower compared with when AADs were given as a third-line therapy after rate control medication and ablation (rate control medication and ablation in any order). Taken together, results of the BIM suggest that AADs as first-line therapy for patients with AFib is a cost-effective treatment option, with potentially greater savings compared with alternative ordering of treatments. Results from this study can be used to help guide decision-makers in terms of formulary placement and utilization controls.

Summary points

- Atrial Fibrillation (AFib) is the most common sustained cardiac arrhythmia in adults, affecting approximately five million people in the US.
- Rate and rhythm control are therapeutic targets for managing symptoms of AFib. Rate control medications aim to prevent thromboembolic events, while rhythm control treatments (cardioversion, anti-arrhythmic drugs (AADs), and cardiac ablation) aim to restore the heart to sinus rhythm.
- Among AADs, dronedarone is considered to be a relatively safer option for patients with paroxysmal and persistent AFib compared with amiodarone.
- This study aimed to utilize budget impact analysis to estimate changes in costs associated with increasing utilization of dronedarone compared with other AADs in a hypothetical plan population of one million US adults. In addition to direct comparisons of AADs, treatment combinations of AADs, rate control medication, and ablation, both with and without considering the order of treatments, were included in analysis.
- Results from the base case suggest that increasing utilization of dronedarone while decreasing utilization of other AADs will provide cost savings (\$37.69 PPPM) over a 5-year time horizon.
- In non-temporal analysis of combination therapies, treatment with dronedarone versus ablation or rate control medication $\pm$ ablation resulted in cost savings (\$359.94 and \$370.54, respectively) by projected year 5.
- In temporal analysis of combination therapies, AADs showed cost benefits when used before rate control medication; however, ablation considered before AADs demonstrated better value.
- Overall, dronedarone demonstrated cost savings in direct comparisons and non-temporal analysis of combination therapies, while placement of AADs earlier in the treatment sequence had comparable favorable outcomes.
- Study findings may inform formulary placement and utilization controls.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2022-0196>

Financial & competing interests disclosure

This study was funded by Sanofi and conducted by Sanofi & Atria. S Park, S Charland, A Revel and R Preblich are employed by and may hold stock and/or stock options at Sanofi (NJ, USA). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors thank JKO & SSSS of Atria Inc. (NJ, USA) for medical writing and editorial assistance.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Mayo Clinic. Atrial fibrillation. <https://www.mayoclinic.org/diseases-conditions/atrial-fibrillation/symptoms-causes/syc-20350624> (Accessed 7 July 2021).

2. Hindricks G, Potpara T, Dagres N *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur. Heart J.* 42(5), 373–498 (2021).
- **This literature is used to provide an insight on the guidelines available to treat atrial fibrillation (AFib).**
3. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am. J. Cardiol.* 112(8), 1142–1147 (2013).
- **This literature is used to calculate the growth rate of AFib population.**
4. 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* 9(5), 348–356 (2006).
5. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat. Rev. Cardiol.* 14(11), 627–628 (2017).
6. Kirchhof P, Camm AJ, Goette A *et al.* Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N. Engl. J. Med.* 383(14), 1305–1316 (2020).
- **This literature is used to provide an insight on the benefits of early rhythm control.**
7. Mayo Clinic. Atrial fibrillation ablation. <https://www.mayoclinic.org/tests-procedures/atrial-fibrillation-ablation/about/pac-20384969> (Accessed 24 March 2022).
8. Dan GA, Martinez-Rubio A, Agewall S *et al.* Antiarrhythmic drugs-clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). *Europace* 20(5), 731–732an (2018).
- **This literature is used to provide an insight on the AAD treatments available to treat AFib.**
9. Laughlin JC, Kowey PR. Dronedronarone: a new treatment for atrial fibrillation. *J. Cardiovasc. Electrophysiol.* 19(11), 1220–1226 (2008).
10. Hohnloser SH, Crijns HJ, Van Eickels M *et al.* Effect of dronedronarone on cardiovascular events in atrial fibrillation. *N. Engl. J. Med.* 360(7), 668–678 (2009).
- **This literature is used to provide an insight on the safety of dronedronarone.**
11. Drugs.com. Multaq. <https://www.drugs.com/pro/multaq.html> (Accessed 26 April 2021).
12. Valembois L, Audureau E, Takeda A, Jarzebowski W, Belmin J, Lafuente-Lafuente C. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst. Rev.* 9, CD005049 (2019).
- **This literature is used to calculate the risk of LTCOs for the AADs which forms the base of our non-temporal dronedronarone vs other AADs scenario.**
13. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedronarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 13(3), 329–345 (2011).
- **This literature is used to calculate the risk of LTCOs for the AADs which forms the base of our non-temporal dronedronarone vs other AADs scenario.**
14. US Bureau of Labor Statistics. CPI Inflation Calculator. <https://www.bls.gov/data/inflation-calculator.htm> (Accessed 26 April 2021).
15. Reynolds MR, Zimetbaum P, Josephson ME, Ellis E, Danilov T, Cohen DJ. Cost-effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal atrial fibrillation. *Circ. Arrhythm Electrophysiol.* 2(4), 362–369 (2009).
16. Podrid PJ, Kowey PR, Frishman WH *et al.* Comparative cost-effectiveness analysis of quinidine, procainamide and mexiletine. *Am. J. Cardiol.* 68(17), 1662–1667 (1991).
17. Anderson LH, Black EJ, Civello KC, Martinson MS, Kress DC. Cost-effectiveness of the convergent procedure and catheter ablation for non-paroxysmal atrial fibrillation. *J. Med. Econ.* 17(7), 481–491 (2014).
18. Bruggenjurgen B, Kohler S, Ezzat N, Reinhold T, Willich SN. Cost effectiveness of antiarrhythmic medications in patients suffering from atrial fibrillation. *Pharmacoeconomics* 31(3), 195–213 (2013).
19. Drugs.com. Multaq Prices, Coupons and Patient Assistance Programs. <https://www.drugs.com/price-guide/multaq> (Accessed 19 October 2021).
20. Drugs.com. Amiodarone Prices, Coupons and Patient Assistance Programs. <https://www.drugs.com/price-guide/amiodarone> (Accessed 19 October 2021).
21. Drugs.com. Sotalol Prices, Coupons and Patient Assistance Programs. <https://www.drugs.com/price-guide/sotalol> (Accessed 19 October 2021).
22. Drugs.com. Flecainide Prices, Coupons and Patient Assistance Programs. <https://www.drugs.com/price-guide/flecainide> (Accessed 19 October 2021).
23. Drugs.com. Propafenone Prices, Coupons and Patient Assistance Programs. <https://www.drugs.com/price-guide/propafenone> (Accessed 19 October 2021).

24. Drugs.com. Dofetilide Prices, Coupons and Patient Assistance Programs. <https://www.drugs.com/price-guide/dofetilide> (Accessed 19 October 2021).
25. Drugs.com. Dronedarone Dosage. <https://www.drugs.com/dosage/dronedarone.html> (Accessed 19 October 2021).
26. Drugs.com. Amiodarone Dosage. <https://www.drugs.com/dosage/amiodarone.html> (Accessed 19 October 2021).
27. Drugs.com. Sotalol Dosage. <https://www.drugs.com/dosage/sotalol.html> (Accessed 19 October 2021).
28. Drugs.com. Flecainide Dosage. <https://www.drugs.com/dosage/flecainide.html> (Accessed 19 October 2021).
29. Drugs.com. Propafenone Dosage. <https://www.drugs.com/dosage/propafenone.html> (Accessed 19 October 2021).
30. Centers for Medicare & Medicaid Services. License for Use of Current Procedural Terminology, Fourth Edition ("CPT®"). <https://www.cms.gov/medicare/physician-fee-schedule/search/license-agreement?destination=/medicare/physician-fee-schedule/search%3FY%3d0%26T%3d4%26HT%3d0%26CT%3d3%26H1%3d99214%26M%3d5> (Accessed 19 October 2021).
31. BETAPACE AF® (sotalol HCl). https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021151s010lbl.pdf (Accessed 26 April 2021).
32. TIKOSYN® (dofetilide) Capsules. <https://labeling.pfizer.com/showlabeling.aspx?id=639> (Accessed 26 April 2021).
33. Multaq (dronedarone) tablets, for oral use. <https://products.sanofi.us/Multaq/Multaq.html> (Accessed 7 July 2021).
34. Amiodarone. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/018972s054lbl.pdf (Accessed 7 July 2021).
35. Drugs.com. Flecainide. <https://www.drugs.com/pro/flecainide.html> (Accessed 7 July 2021).
36. Propafenone. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019151s012lbl.pdf (Accessed 7 July 2021).
37. Kim MH, Klingman D, Lin J, Pathak P, Battleman DS. Cost of hospital admission for antiarrhythmic drug initiation in atrial fibrillation. *Ann. Pharmacother.* 43(5), 840–848 (2009).
38. KFF. Among Covered Workers With Prescription Drug Coverage, Average Copayments and Coinsurance, 2021 9805. <https://www.kff.org/report-section/ehbs-2021-section-9-prescription-drug-benefits/attachment/table-9-6-7/> (Accessed 15 November 2021).
39. Multaq dronedarone 400mg Tablets. Start with savings. <https://www.multaq.com/savings-and-support/multaq-savings-card-program> (Accessed 17 October 2022).
40. Packer DL, Piccini JP, Monahan KH *et al.* Ablation Versus Drug Therapy for Atrial Fibrillation in Heart Failure: Results From the CABANA Trial. *Circulation* 143(14), 1377–1390 (2021).
41. Calkins H, Reynolds MR, Spector P *et al.* Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ. Arrhythm Electrophysiol.* 2(4), 349–361 (2009).
42. Mansour M, Karst E, Heist EK *et al.* The Impact of First Procedure Success Rate on the Economics of Atrial Fibrillation Ablation. *JACC Clin. Electrophysiol.* 3(2), 129–138 (2017).
43. Gunawardena R, Furniss SS, Shepherd E, Santarpia G, Lord SW, Bourke JP. Outcomes following catheter ablation of atrial fibrillation in the UK: a single-centre cohort analysis. *Brit. J. Cardiol.* 17, 271–276 (2010).
44. Vamos M, Calkins H, Kowey PR *et al.* Efficacy and safety of dronedarone in patients with a prior ablation for atrial fibrillation/flutter: insights from the ATHENA study. *Clin. Cardiol.* 43(3), 291–297 (2020).
45. European Heart Rhythm A, European Association for Cardio-Thoracic S. Camm AJ, Kirchhof P, Lip GYH *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur. Heart J.* 31(19), 2369–2429 (2010).
46. Goette A, Benninger G, Pittrow D, Paar WD, Von Stritzky B, Bosch RF. One-year safety and quality of life outcomes in patients with atrial fibrillation on dronedarone: prospective, non-interventional study in German ambulatory care. *Herzschrittmacherther Elektrophysiol.* 26(2), 148–154 (2015).
47. Sanofi. Dronedarone (Multaq®) Reduced the Incidence and Duration of Hospitalization in Patients with Atrial Fibrillation. <https://www.news.sanofi.us/press-releases?item=118276> (Accessed 3 September 2021).