

SUPPLEMENTAL MATERIAL

Data S1. Cost Details and Background Event Rates

Costs provided in 2018 Canadian dollars based on publicly available Alberta costing data.

A. Detailed Cost Breakdowns

Catheter ablation	Item	Subtotals / Totals	Notes
Procedure HSC (SOMB)	49.98AB Complex ablation of arrhythmic substrate	\$2,222.50	
	49.98Y cardioversion with EPS HSC	\$66.50	
	49.99AA, intra-operative TEE	\$135.92	\$2,424.92
Provider fee	03.08A Cardiologist (EP) Consultation	\$175.00	
	CMXC30 Complex modifier > 30 min	\$31.43	
	03.08I Prolonged by 15 minutes	\$12.45	\$218.88
Ambulatory facility costs	CACS C209 – Other Cardiac Intervention	\$6,519.71	\$6,519.71
Hospital admission	For routine observation (no adverse events), overnight / single day		
	Average AB cost of a hospital stay	\$7,983.00	CIHI
	Average AB length of stay 7.8 days - cost per day	\$1,023.46	
	Cardiologist consultation and rounding x 1 day for admission	\$319.53	
	Expected cost per day given 35% risk of overnight observation	\$470.05	\$470.05
Total		\$9,633.56	

Tamponade	Item	Subtotals / Totals	Notes
CMG+ hospital cost	173 Minor cardiothoracic intervention	\$30,921.59	\$30,921.59
Procedure	49.0 Pericardiocentesis	\$218.04	\$218.04
Provider fee	03.08A Cardiology consultation for admission	\$175.00	
	03.03D Daily rounding, regular cardiology ward	\$104.12	
	COINPT	\$40.41	
	Total daily rounding given average length of stay 10.87 days	\$1,571.04	\$1,746.04
Formal TTE	X306A - Complex complete echocardiogram	\$250.25	
Limited TTE to re-assess	X307 - Ultrasound heart, echo, limited	\$59.99	\$310.24
Total		\$33,195.91	

Effusion	Item	Subtotals / Totals	Notes
CMG+ hospital cost	209 - Other / Miscellaneous cardiac disorder	\$13,007.23	\$13,007.23
Provider fee	03.08A Cardiology consultation for admission	\$175.00	
	03.03D Daily rounding, regular cardiology ward	\$104.12	
	COINPT	\$40.41	
	Total daily rounding given average length of stay 7.31 days	\$1,056.51	\$1,231.51
Formal TTE	X306A - Complex complete echocardiogram	\$250.25	
Limited TTE to re-assess	X307 - Ultrasound heart, echo, limited	\$59.99	\$310.24
Total		\$14,548.98	

Pneumonia	Item	Subtotals / Totals	Notes
CMG+ hospital cost	138 Viral / Unspecified pneumonia	\$10,942.11	\$10,942.11
Provider fee	03.08A Internal medicine consultation	\$198.70	
	03.03D Daily rounding, regular medicine ward	\$55.64	
	COINPT	\$40.41	
	Total daily rounding given average length of stay 7.58 days	\$728.06	\$926.76
ED costs	CACS B211 Disease or disorder Resp system with acute admission without	\$973.25	\$973.25
ED provider fee	03.04F Comprehensive visit in ED	\$99.19	
	CMXC30 Complex patient requiring > 30 minutes	\$31.43	\$130.62
Total		\$12,972.74	

Pulmonary vein stenosis	Item	Subtotals / Totals	Notes
CMG+ hospital cost	195 Heart Failure without coronary angiogram	\$12,639.07	\$12,639.07
Imaging	CT pulmonary veins*	\$850.00	\$850.00
Provider fee	03.08A Cardiology consultation for admission	\$175.00	
	03.03D Daily rounding, cardiologist	\$104.12	
	COINPT	\$40.41	
	Total daily rounding given average length of stay 11.51 days	\$1,663.54	\$1,838.54
ED costs	CACS B212 Disease/Disorder Cardiovascular System with Acute Admissio	\$1,065.89	\$1,065.89
ED provider fee	03.04F Comprehensive visit in ED	\$99.19	
	CMXC30 Complex patient requiring > 30 minutes	\$31.43	\$130.62
Total		\$16,524.12	

* Imputed from a private provider's CT coronary angiogram fee (MIC, <https://x-ray.ca/services/computed-tomography/angiogram-ct/>, accessed Jul 03, 2020).

Stroke	Item	Subtotals / Totals	Notes
CMG+ hospital cost	026 Ischemic event of central nervous system	\$17,988.43	\$17,988.43
Provider fee	03.08A Neurology consultation	\$197.86	
	03.08A Cardiology consultation for admission	\$175.00	
	03.03D Daily rounding, stroke neurology consultant	\$59.36	
	COINPT	\$40.41	
	03.03D Daily rounding, cardiologist	\$104.12	
	COINPT	\$40.41	
	Total daily rounding given average length of stay 15.1 days	\$3,688.93	\$4,061.79
Total		\$22,050.22	

Bleeding post-catheter ablation	Item	Subtotals / Totals	Notes
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Bleeding, no vascular intervention required (85% of cases) - 10.82 days				
			Subtotals / Totals	Notes
Blood transfusion x1	Lagerquist et al., 2017 costing study {Lagerquist, 2017}	\$666.10	\$666.10	
Hospital admission	For routine observation (no adverse events), overnight / single day			CIHI
	Average AB cost of a hospital stay	\$7,983.00		
	Average AB length of stay 7.8 days - cost per day	\$1,023.46		
	Cardiologist consultation and rounding x 1 day for admission	\$319.53		
	Expected cost per day including cardiologist fees	\$1,342.99	\$1,342.99	
Ultrasound peripheral arteries	X332	\$161.47	\$161.47	
Total			\$2,170.56	
Bleeding, vascular intervention required (15% of cases) - Assumed 1 day				
			Subtotals / Totals	Notes
CMG+ hospital cost	185 Other/miscellaneous vascular intervention	\$27,470.28	\$27,470.28	
Procedures	51.3B Repair to peripheral vessels, traumatic injury	\$755.22		
	Blood transfusion x1, as above {Lagerquist, 2017}	\$666.10		
	Anesthesia (51.3B ANES)	\$287.78	\$1,709.10	
Provider fee	03.08A Vascular surgery consultation	\$160.56		
	03.08A Cardiology consultation	\$175.00		
	03.03D Daily rounding, regular cardiology ward	\$104.12		
	COINPT	\$40.41		
	Total daily rounding given average length of stay 10.82 days	\$1,563.81	\$1,899.37	
Ultrasound peripheral arteries	X332	\$161.47	\$161.47	
Total			\$31,240.22	
Weighted average of all bleeding cases				
Total	(Weighted average duration 2.47 days)		\$6,531.01	
HF admission				
	Item		Subtotals / Totals	Notes
CMG+ hospital cost	196 – HF without coronary angiogram	\$12,639.07	\$12,639.07	
Provider fee	03.08A Cardiology consultation	\$175.00		
	03.03D Daily rounding, regular cardiology ward	\$104.12		
	COINPT	\$40.41		
	Total daily rounding given average length of stay 11.35 days	\$1,640.42	\$1,815.42	
ED costs	CACS B212 Disease/Disorder Cardiovascular System with Acute Admissioi	\$1,065.89	\$1,065.89	
ED provider fee	03.04F Comprehensive visit in ED	\$99.19		
	CMXC30 Complex patient requiring > 30 minutes	\$31.43	\$130.62	
Total			\$15,651.00	
Non-HF admission				
	Item		Subtotals / Totals	Notes
CMG+ hospital cost	All combined CMG+ groupers	\$12,169.11	\$12,169.11	
Provider fee	03.08A Internal medicine consultation	\$198.70		
	03.03D Daily rounding, regular medicine ward	\$55.64		
	COINPT	\$40.41		
	Total daily rounding given average length of stay 8.52 days	\$818.35	\$1,017.05	
ED costs	CACS B218 Other condition with acute admission without high resource int	\$907.71	\$907.71	
ED provider fee	03.04F Comprehensive visit in ED	\$99.19		
	CMXC30 Complex patient requiring > 30 minutes	\$31.43	\$130.62	
Total			\$14,224.49	
Amiodarone pulmonary toxicity				
	Item		Subtotals / Totals	Notes
CMG+ hospital cost	142 Other lung disorder	\$23,637.38	\$23,637.38	
Provider fee	03.08A Pulmonary medicine consultation	\$207.31		
	03.03D Daily rounding, regular pulmonary ward	\$52.30		
	COINPT	\$40.41		
	Total daily rounding given average length of stay 11.13 days	\$1,031.86	\$1,239.17	
ED costs	CACS B211 Disease or disorder respiratory system with acute admission wi	\$973.25	\$973.25	
ED provider fee	03.04F Comprehensive visit in ED	\$99.19		
	CMXC30 Complex patient requiring > 30 minutes	\$31.43	\$130.62	
Total			\$25,980.42	

B. Background Mortality Rates

From Canada Chronic Disease Surveillance System for Heart Failure Patients (CDSS)

Age band	From CDSS				Calculated		
	Mortality		Standard error		CV	Mortality	Standard error
	Male	Female	Male	Female	Average	Average	Average
40-54	0.034	0.038	0.001	0.002	0.041	0.036	0.001
55-64	0.048	0.048	0.001	0.001	0.021	0.048	0.001
65-74	0.074	0.068	0.001	0.001	0.014	0.071	0.001
75-84	0.127	0.105	0.001	0.001	0.009	0.116	0.001
85+	0.224	0.198	0.002	0.001	0.007	0.211	0.001

CV = Coefficient of Variation

Inflated for comorbid AF using OR = 1.14 factor (Mamas et al., Eur J Heart Fail, 2009;11:676-683)

Age band	Calculated		Inflated for comorbid AF			Age band mid-point for linear interpolation
	Mortality	Standard error	Mortality	Post-AF Odds	Risk	
	Average	Average	Odds	Post-AF Odds	Risk	
40-54	0.036	0.001	0.038	0.043	0.041	47.5
55-64	0.048	0.001	0.050	0.057	0.054	60
65-74	0.071	0.001	0.077	0.087	0.080	70
75-84	0.116	0.001	0.131	0.149	0.130	80
85+	0.211	0.001	0.267	0.304	0.233	85

C. Yearly Event Rates from CASTLE-AF - Approximate Calculations Based on Supplemental Data

Yearly outcome rates in CASTLE-AF - interpolated from published Kaplan-Meier cumulative survival data

What is the HF admission rate per year in the control arm of CASTLE-HF?

Calculation step	Time point (months)						
	0	12m	24m	36m	48m	60m	
1		0.142		0.358		0.463	KM cumulative event rates from Supplement table S6
2		0.858		0.642		0.537	Complement taken to calculate cumulative survival
3		0.858		0.748		0.836	Period specific survival - $S[\text{period}](t) = S[\text{cumulative}](t) / S[\text{cumulative}](t-1)$
4		0.858	0.865	0.865	0.915	0.915	Interpolated per year - See note.
5		0.142	0.135	0.135	0.085	0.085	Event rate taken as complement of period-specific survival rate. Average yearly event rate = 0.117

Note: Interpolation of survival rates per year using the following formula:

$S[\text{cumulative}]$ at 36 = $S[\text{cumulative } 0-12m] * S[\text{period } 12-24m] * S[\text{period } 24-36m]$, assume $S[\text{period } 12-24m]$ and $S[\text{period } 24-36m]$ are equal = x, solve for x.

What is the all-cause admission rate per year in the control arm of CASTLE-HF?

Calculation step	Time point (months)						
	0.000	12m	24m	36m	48m	60m	
1		0.369		0.699		0.815	KM cumulative event rates from Supplement table S6
2		0.631		0.301		0.185	Complement taken to calculate cumulative survival
3		0.631		0.477		0.615	Period specific survival
4		0.631	0.691	0.691	0.784	0.784	Interpolated per year - See above note.
5		0.369	0.309	0.309	0.216	0.216	Event rate taken as complement of period-specific survival rate. Average yearly event rate = 0.284 It turns out these figures are very similar to those of Roy et al. (AF-CHF).

Provided for interest only

What is the all-cause mortality rate per year in the control arm of CASTLE-HF?

Calculation step	Time point (months)						
	0.000	12m	24m	36m	48m	60m	
1		0.039		0.172		0.375	KM cumulative event rates from Supplement table S6
2		0.961		0.828		0.625	Complement taken to calculate cumulative survival
3		0.961		0.862		0.755	Period specific survival
4		0.961	0.928	0.928	0.869	0.869	Interpolated per year - see above note.
5		0.039	0.072	0.072	0.131	0.131	Event rate taken as complement of period-specific survival rate. Average yearly event rate = 0.089

Table S1. Costs of Treatment Outcomes and On-Going Care (2018 Canadian Dollars).

	Cost, mean (sd) \$ 2018 CAD	Probability Distribution	Sources and Assumptions
Outcomes			
Hospitalizations for HF			
... Costs	\$15,651 (\$1,996)	Gamma, a = 61.466, b = 0.003927	(F)
... Duration	11.4 days	--	(A)
Hospitalizations, non-HF			
... Costs	\$14,224 (\$1,814)	Gamma, a = 61.466, b = 0.004321	(A)
... Duration	8.5 days	--	(A)
Mortality			
... Costs	\$0	--	Assumed.
On-Going Medical Care			
Amiodarone			
... Drug costs	\$136	--	(B), amiodarone 200mg daily.
... Monitoring	\$197	--	(C)
... Hypothyroidism		--	Assumed in 6% of amiodarone users (27).
Levothyroxine	\$41	--	(B)
Additional TSH	\$95	--	(C)
... Pulmonary toxicity			
Risk / year	0.8%	Beta, a= 6.14, b = 731.86	(2, 3)
Hospitalization costs	\$25,980 (\$3,314)	Gamma, a = 61.466, b = 0.002366	(A)
Hospitalization duration	11.1 days	--	(A)
Death	9.1%	Beta, a= 3 b= 30	(2, 4)
Irreversible	25%	Beta alpha 25 beta75	(2, 5)
On-going yearly costs	1: \$10,675 (\$351) 2: \$6,116 (\$562) 3: \$1,256 (\$676)	Gamma, a = 926.486, b = 0.08679 Gamma, a = 118.350, b = 0.01935 Gamma, a = 3.458, b = 0.002752	Annual incremental health care costs in the first, second, and >= third years after diagnosis (31).
... Other complications	\$0	--	(D), assumed.
Other drug costs per year			
... ACEi / ARB	\$77	--	(B), valsartan 320mg daily.
... Beta-blocker	\$91	--	(B), metoprolol 100mg BID.
... CCB	\$211	--	(B), diltiazem, 360mg daily.
... Digoxin	\$110	--	(B), digoxin 0.125mg daily.
... Diuretic	\$113	--	(B), furosemide 60mg and spironolactone 50mg daily.
... OAC	\$1,048	--	(B), rivaroxaban 20mg daily.
Pharmacy fees per year			
... Dispensing fees	\$49	--	(E)
... Stocking fees	+8%	--	I.e.: Of drug costs. Assumed.
Routine clinic follow-up			
... Cost per visit	\$441	--	(A) including basic lab monitoring.
... Visits per year	4	--	Assumed.
Additional Procedures			
Cardioversions	\$983 (\$125)	Gamma, a = 61.466, b = 0.06251	(A)
Catheter ablation	\$9,634 (\$1,228)	Gamma, a = 61.466, b = 0.006380	(A)

HF, heart failure; TSH, thyroid stimulating hormone; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; OAC, oral anticoagulant. (A) Estimated from provider billing fees (Alberta Schedule of Medical Benefits [SOMB]), case-mix based ambulatory (Comprehensive Ambulatory Care Classification System [CACS]), and/or case-mix based inpatient (Canada Institute for Health Information Case Mix Group [CMG+]) average encounter costs in 2017-18. Distribution of costs including standard deviations were unavailable. Standard errors were assumed to be 25% of the mean cost. Gamma distributions for costs were imputed from means and standard deviations. No probabilistic distributions were specified for duration of hospitalizations, since duration was not expected to affect results materially apart from its effects on the average costs of a hospitalization. Specific CACS and CMG+ codes available in Supplementary appendix. (B)

Alberta Blue Cross Drug Benefits List prices, 2019. (C) Alberta SOMB, based on recommended monitoring for amiodarone in (27), including TSH testing every 6 months. Additional TSH twice a year (so overall every 3 months) in patients with hypothyroidism. (D) Other complications of amiodarone use were assumed rare (e.g.: cirrhosis), transient (e.g.: hyperthyroidism), or captured elsewhere (e.g.: bradycardia admission to hospital). (E) Assumed medications refilled every 3 months. Alberta dispensing fee is \$12.25 per fill.

Table S2. Health Utilities Associated With Outcomes.

	Health Utility	Probability Distribution	Sources and Assumptions
Survival - Utilities			
AF and HF	0.66 (0.51-0.78)	Beta, a = 30.56, b = 15.74	SR of Dyer et al., 2010 (A)
Decrement associated with previous stroke	-0.187 (-0.281-(-0.093))	Normal, u = -0.187, s = 0.048	Based on moderate vs minor stroke (B)
Irreversible amiodarone-induced pulmonary toxicity	0.60 (0.503-0.693)	Beta, a = 60, b = 40	Previous cost-utility study (C)
Outcomes			
Hospitalization, HF	0.25	--	Assumed, for duration of hospitalization.
Hospitalization, non-HF	0.25	--	Return to previous health utility post-discharge.
Mortality	0	--	

(A) Based on mean EQ-5D values from studies with 0-67% NYHA III/IV patients reported in the systematic review of Dyer et al. 2010 (34). A credible interval was considered the range of mean EQ-5D for these studies, i.e.: 0.58-0.78. (B) From (47). (C) From (29).

Table S3. Base Case Results – CA vs MED – Cost and Events Enumeration.

	CA (\$CAD)	MED (\$CAD)
Cost (discounted)		
Total cost	\$64,960	\$49,865
CA costs	\$12,563	\$815 (A)
CA complications	\$1,312	\$0 (A)
HF admissions	\$13,332	\$13,909
Non-HF admissions	\$20,328	\$18,685
Other medical costs (HF and AF management only)	\$17,425	\$16,456
Effectiveness		
LY (undiscounted)	10.58	9.69
QALY (discounted)	5.63	5.18
Other outcomes (undiscounted)		
HF admissions	1.05	1.07
Non-HF admissions	1.70	1.56
Amiodarone pulmonary toxicity cases	0.02	0.03

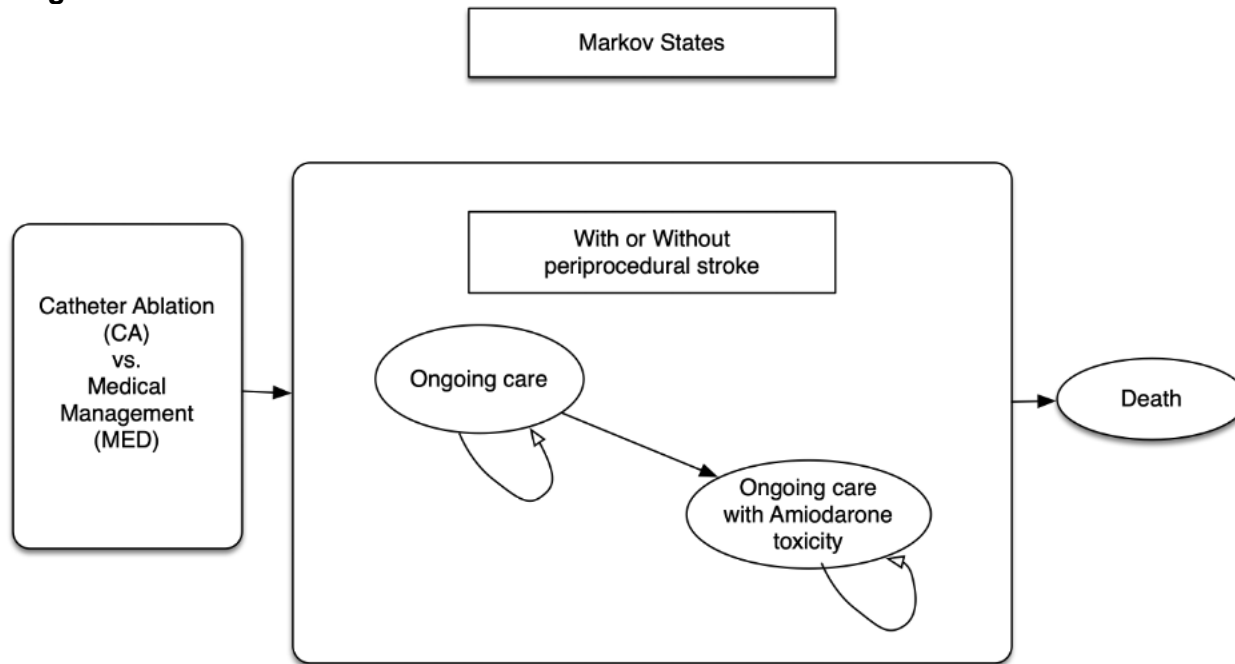
Obtained from expected values of probabilistic analysis. “Other medical costs” taken as the remainder of total costs after subtracting other costs. Costs in 2018 Canadian dollars (Table S3a) denominated in 2018 US dollars (Table S3b) by foreign currency exchange rates. (A) Due to cross-over, where medically managed patients end up getting catheter ablation for refractory symptoms or other reasons. Such an event was considered uncommon enough that peri-procedural complications after a cross-over CA in a MED patient were not modeled.

Table S4. Base Cases Analysis with Discount Rate of 1.5% per Year.

		95% Confidence Interval
Cost (discounted)		
... CA	\$70,059	\$60,084-81,569
... MED	\$54,634	\$46,168-64,556
Effectiveness (QALY, discounted)		
... CA	6.22	4.84-7.47
... MED	5.71	4.47-6.83
Incremental		
... Cost (\$CAD)	\$15,425	\$10,761-20,281
... Effectiveness (QALY)	0.51	0.18-0.78
Incremental Cost-Effectiveness		
... ICER (\$CAD/QALY)	\$31,348	\$19,772-69,326

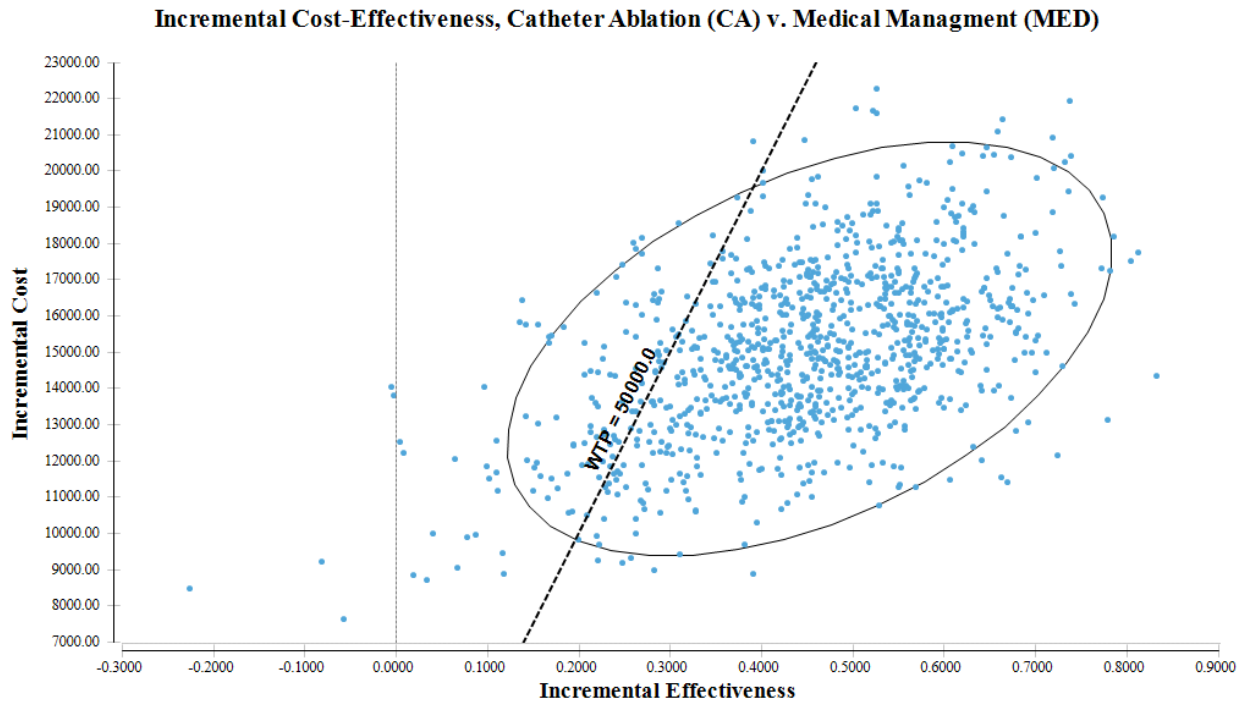
At a willingness-to-pay threshold of \$50,000/QALY, CA was cost-effective in 93% of simulations.

Figure S1. Cost-Utility Model Comparing CA versus Medical Therapy for AF in patients with HF as a state transition diagram.



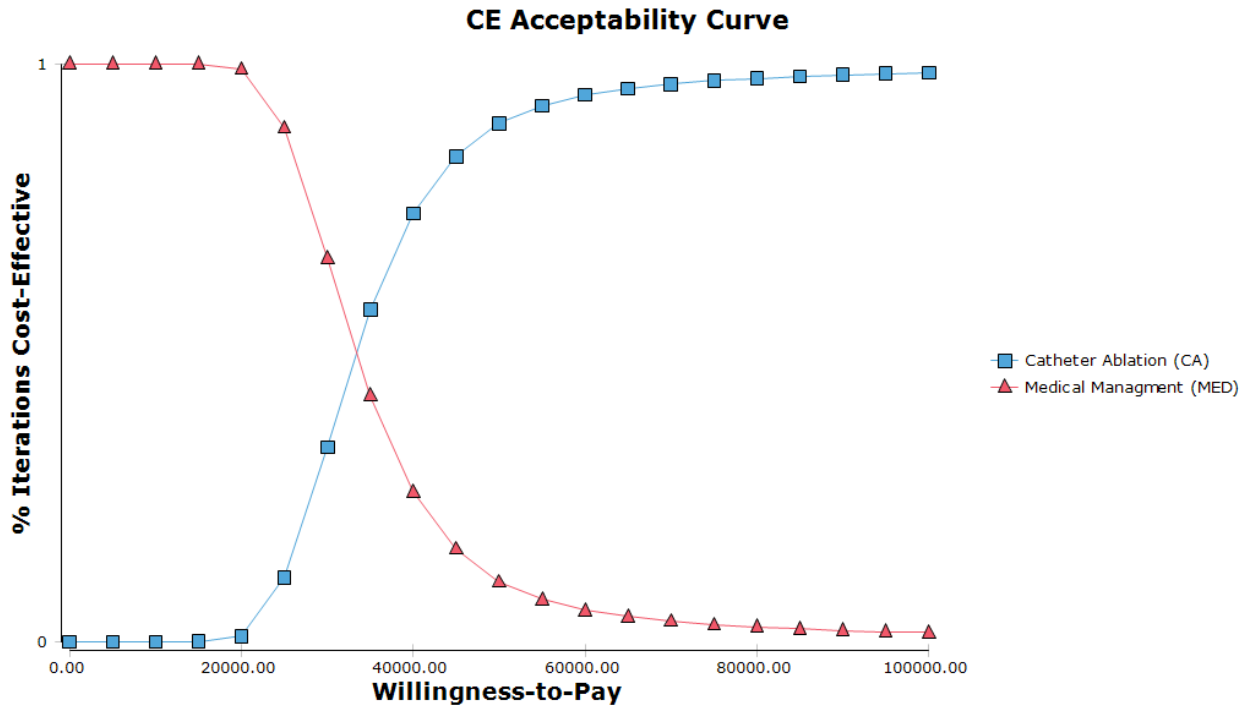
As rendered in TreeAge Pro 2019 (TreeAge Software, LLC, Williamstown, MA).

Figure S2. Scatterplot of Incremental Cost-Effectiveness Outcomes From Probabilistic Analysis (10000 Monte Carlo Resamplings).



Incremental cost and WTP denominated in 2018 Canadian dollars. WTP line drawn at \$50,000 CAD/QALY.

Figure S3. Cost-Effectiveness Acceptability Curve – CA vs MED for Patients with HF and Symptomatic AF.



Willingness-to-Pay (WTP) denominated in 2018 Canadian dollars (CAD). At WTP threshold of \$50,000/QALY, in 90% of simulations CA was cost-effective compared to MED. CA remained cost-effective in over 80% of simulations for WTP thresholds above \$43,000. At a WTP threshold of \$100,000/QALY, CA was cost-effective in over 98% of simulations.