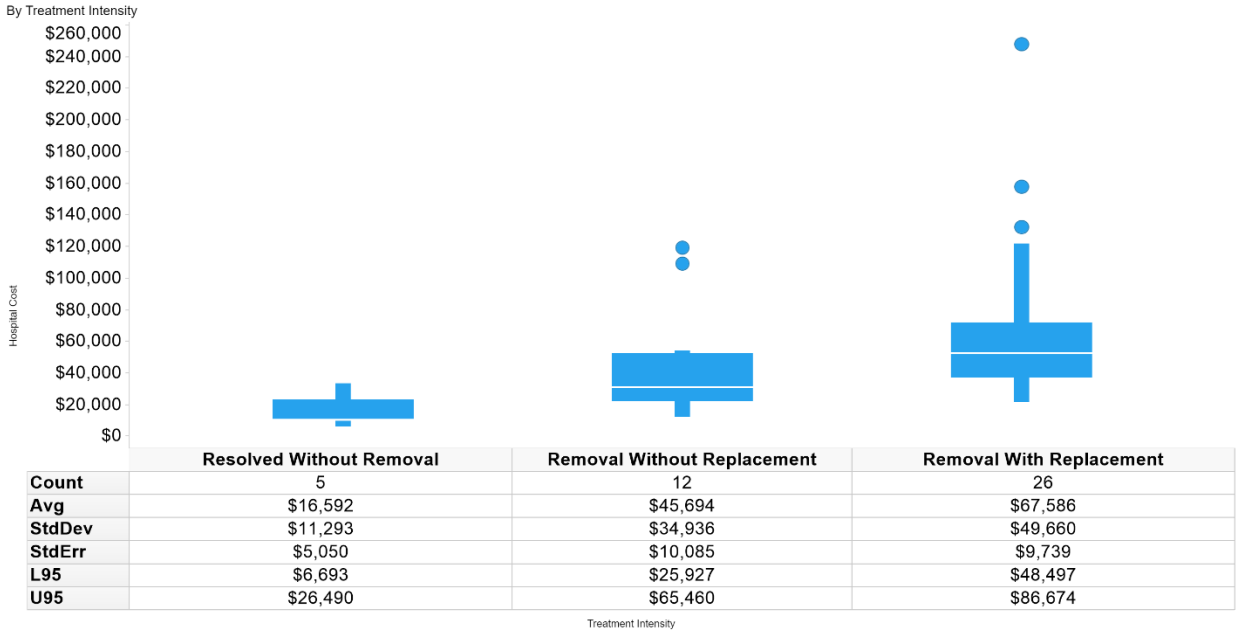
SUPPLEMENTAL MATERIAL

Supplemental Figure

Figure S1. Infection Treatment Cost by Treatment Intensity. The model accounts for different treatment intensities in the decision tree, so the hospital cost data from WRAP-IT were analyzed with these intensities in mind, using the same method as the WRAP-IT impact of infection manuscript.[1]



	Resolved Without Removal	Removal Without Replacement	Removal With Replacement
Count	5	12	26
Avg	$16,592	$45,694	$67,586
StdDev	$11,293	$34,936	$49,660
StdErr	$5,050	$10,085	$9,739
L95	$6,693	$25,927	$48,497
U95	$26,490	$65,460	$86,674

[1] Wilkoff BL, Boriani G, Mittal S, Poole JE, Kennergren C, Corey R, Love J, Augostini R, Faerestrand S, Wiggins SS, et al. Impact of Cardiac Implantable Electronic Device Infection: A Clinical and Economic Analysis of the WRAP-IT Trial. Circ Arrhythm Electrophysiol. 2020. DOI:10.1161/CIRCEP.119.008280

Supplemental Tables

Table S1. Mortality at 12 Months by Infection Status and Treatment Intensity - The model accounts for different treatment intensities in the decision tree, so the mortality data from WRAP-IT were analyzed with these intensities in mind, using the same method as the WRAP-IT impact of infection manuscript.[1]

Infection Status and Treatment Intensity	Number of Deaths (K-M Mortality Rate, Standard Error) at 1 Year	Number at Risk at Day 365
Infection and Complete Extraction	7 (14.6%, 5.1%)	37
Infection and No Extraction*	3 (23.8%, 12.1%**)	9
No Infection	348 (5.2%, 0.3%)	3

* Patients treated with partial extraction were assumed to have same mortality risk as those with no extraction, as part of the infected system was still present after treatment.

** Standard error resulted in 95% confidence interval extending to negative numbers, so standard error was adjusted to be 10% of the mean value in analysis.

Table S2. Long-Term Life Expectancy and Heart Failure Hospitalizations by CIED Type - The model assigns a lumped value for quality adjusted life years (QALYs) and cost at the 12-month time point after the decision tree portion of the model is complete. To do this, we created estimates of life expectancy and heart failure (HF) hospitalizations expected for patients with each device type by creating weighted averages of the individual patient types detailed in Mealing *et al.*[2] in the supplement tables S10-S13 (Weights for each patient type were found for the same dataset in Woods *et al.*[3] Table 1).

Mealing *et al.* Tables S10-S13	**QRS Duration**	**LBBB**	**NYHA Class**	**Median Survival (yrs)**	Mean Survival Per NYHA	Average per LBBB Weighted by NYHA	Therapy Final Average Weighted by LBBB	**Average HF Hosp. (lifetime)**	Average Hosp. Per NYHA	Average per LBBB Weighted by NYHA	Therapy Final Average Weighted by LBBB
No CIED	<120ms	No	I	8.96				1.58			
No CIED	120-150ms	No	I	6.37				1.44			
No CIED	≥150ms	No	I	6.06	7.13			1.19	1.40		
No CIED	<120ms	No	II	10.61				1.78			
No CIED	120-150ms	No	II	7				1.54			
No CIED	≥150ms	No	II	6.66	8.09			1.28	1.53		
No CIED	<120ms	No	III	5.78				2.14			
No CIED	120-150ms	No	III	4.08				1.91			
No CIED	≥150ms	No	III	3.58	4.48			1.49	1.85		
No CIED	<120ms	No	IV	2.32				1.94			
No CIED	120-150ms	No	IV	2.02				2.03			
No CIED	≥150ms	No	IV	1.82	2.05	6.23		1.59	1.85	1.67	
No CIED	120-150ms	Yes	I	7.23				1.58			
No CIED	≥150ms	Yes	I	6.56	6.90			1.27	1.43		
No CIED	120-150ms	Yes	II	7.82				1.66			
No CIED	≥150ms	Yes	II	7.9	7.86			1.45	1.56		

[2] Mealing S, Woods B, Hawkins N, Cowie MR, Plummer CJ, Abraham WT, Beshai JF, Klein H and Sculpher M. Cost-effectiveness of implantable cardiac devices in patients with systolic heart failure. Heart. 2016;102:1742-1749. DOI: 10.1136/heartjnl-2015-308883.

[3] Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, Klein H, Sculpher M, Plummer CJ, Cowie MR. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. Heart. 2015;101:1800-1806. DOI: 10.1136/heartjnl-2015-307634.

No CIED	120-150ms	Yes	III	4.19				1.94			
No CIED	≥150ms	Yes	III	4.2	4.20			1.68	1.81		
No CIED	120-150ms	Yes	IV	2.16				2.1			
No CIED	≥150ms	Yes	IV	2.03	2.10	5.99	6.14	1.73	1.92	1.67	1.67
ICD	<120ms	No	I	11.08				1.47			
ICD	120-150ms	No	I	9.25				1.52			
ICD	≥150ms	No	I	8.06	9.46			1.19	1.39		
ICD	<120ms	No	II	12.83				1.63			
ICD	120-150ms	No	II	9.9				1.59			
ICD	≥150ms	No	II	8.86	10.53			1.27	1.50		
ICD	<120ms	No	III	7.32				2.05			
ICD	120-150ms	No	III	6				2.1			
ICD	≥150ms	No	III	4.89	6.07	9.28		1.55	1.9	1.59	
ICD	120-150ms	Yes	I	9.48				1.55			
ICD	≥150ms	Yes	I	8.12	8.80			1.2	1.38		
ICD	120-150ms	Yes	II	10.05				1.6			
ICD	≥150ms	Yes	II	9.6	9.83			1.33	1.47		
ICD	120-150ms	Yes	III	5.61				1.98			
ICD	≥150ms	Yes	III	5.11	5.36	8.57	9.01	1.58	1.78	1.53	1.57
CRT-P	120-150ms	No	III	4.29				1.35			
CRT-P	≥150ms	No	III	4.31	4.30			1.19	1.27		
CRT-P	120-150ms	No	IV	2.21				1.33			
CRT-P	≥150ms	No	IV	2.27	2.24	4.10		1.18	1.26	1.27	
CRT-P	120-150ms	Yes	III	5.05				1.54			
CRT-P	≥150ms	Yes	III	5.82	5.44			1.5	1.52		
CRT-P	120-150ms	Yes	IV	2.67				1.54			
CRT-P	≥150ms	Yes	IV	2.9	2.79	5.18	4.51	1.45	1.50	1.52	1.36
CRT-D	120-150ms	No	I	8.37				1.24			
CRT-D	≥150ms	No	I	8.71	8.54			1.1	1.17		
CRT-D	120-150ms	No	II	9.15				1.31			
CRT-D	≥150ms	No	II	9.48	9.32			1.16	1.24		

CRT-D	120-150ms	No	III	5.52				1.72			
CRT-D	≥150ms	No	III	5.36	5.44			1.46	1.59		
CRT-D	120-150ms	No	IV	2.86				1.95			
CRT-D	≥150ms	No	IV	2.81	2.84	7.84		1.68	1.82	1.36	
CRT-D	120-150ms	Yes	I	10.18				1.42			
CRT-D	≥150ms	Yes	I	10.18	10.18			1.23	1.33		
CRT-D	120-150ms	Yes	II	10.99				1.49			
CRT-D	≥150ms	Yes	II	11.85	11.42			1.35	1.42		
CRT-D	120-150ms	Yes	III	6.32				1.9			
CRT-D	≥150ms	Yes	III	7.02	6.67			1.77	1.84		
CRT-D	120-150ms	Yes	IV	3.37				2.21			
CRT-D	≥150ms	Yes	IV	3.56	3.47	9.59	9.05	2.02	2.12	1.57	1.50
IPG[4]	N/A	N/A	N/A	N/A			8.5				1.5

[4] Brunner M, Olschewski M, Geibel A, Bode C, Zehender M. Long-term Survival After Pacemaker Implantation. Prognostic Importance of Gender and Baseline Patient Characteristics. Eur Heart J. 2004;25:88-95. DOI: 10.1016/j.ehj.2003.10.022

Table S3. Costs Per Healthcare Utilization by CIED Type – this is supporting data that is used in the calculations to create the lumped long-term cost assignments, which are detailed in Table ST4.

CIED Type	HF Hospitalization Cost[5]	Annual Device Follow-up Cost*	Device Replacement Cost**	Device Longevity (Years)[6]	Annualized Cost of Replacements***	Device Mix[7]
ICD	$14,631	$120	$22,889	12.4	$1,845.87	26.1%
CRT-P	$14,631	$240	$17,841	10.9	$1,637	4.5%
CRT-D	$14,631	$240	$27,831	8.8	$3,163	49.1%
IPG	$14,631	$60	$10,184	10.9	$934	20.3%

* Frequency of long-term follow-up estimated at 1x/yr for IPG, 2x/yr for ICD, 4x/yr for CRT-P/D based on coverage and guideline recommendations. Cost of long-term follow-up estimated at $60/occurrence based on Medicare payment.

** Replacement hospital costs derived from average costs in Premier hospital cost database.

*** Cost of replacement divided by device longevity.

[5] Kilgore M, Patel HK, Kielhorn A, Maya JF, Sharma P. Economic burden of hospitalizations of Medicare beneficiaries with heart failure. Risk Manag Healthc Policy. 2017;10:63-70. DOI: 10.2147/RMHP.S130341.

[6] Munawar DA, Mahajan R, Linz D, Wong GR, Khokhar KB, Thiyagarajah A, Kadhim K, Emami M, Mishima R, Elliott AD, Middeldorp ME, Roberts-Thompson KC, Young GD, Sanders P, Lau DH. Predicted Longevity of Contemporary Cardiac Implantable Electronic Devices: A Call for Industry-Wide "Standardized" Reporting. Heart Rhythm. 2018;15:1756-1763. DOI: 10.1016/j.hrthm.2018.07.029

[7] Tarakji KG, Mittal S, Kennergren C, Corey R, Poole JE, Schloss E, Gallastegui J, Pickett RA, Evonich R, Philippon F, McComb JM, Roark SF, Sorrentino D, Sholevar D, Cronin E, Berman B, Riggio D, Biffi M, Khan H, Silver MT, Collier J, Eldadah Z, Wright DJ, Lande JD, Lexcen DR, Cheng A, Wilkoff BL; WRAP-IT Investigators. Antibacterial Envelope to Prevent Cardiac Implantable Device Infection. N Engl J Med. 2019;380:1895-1905. DOI: 10.1056/NEJMoa1901111.

Table S4. Long-Term Lumped Cost and Utility Assignments by CIED Type

CIED Type	Discounted Life Expectancy (Years)	Hospitalization Costs	Follow-Up Costs	Replacement Costs	Total Lifetime Costs	Discounted Lifetime Costs
No CIED*	6.14	$24,433	$0	$0	$24,433	$22,015
ICD	9.01	$22,930	$1,081	$16,653	$40,647	$35159
CRT-P	4.51	$19,926	$1,081	$7,375	$28,383	$26,183
CRT-D	9.05	$22,015	$2,173	$28,633	$52,820	$45,662
IPG	8.50	$21,947	$510	$7,941	$30,398	$26,485

* Represents lifetime status of patient who had infection treated with removal and no replacement.

Table S5. One-Way Sensitivity Analysis Details

Scenario	Base Case Value	Scenario Value	Description
Probability of Extraction - Low	0.843	0.756	
Probability of Extraction - High	0.843	0.930	
Infection Disutility – Low	-0.09	-0.149	
Infection Disutility - High	-0.09	-0.031	
Discount Rate – Low	3%	2%	
Discount Rate - High	3%	4%	
Post-Infection Mortality - Low	0.146	0.044	Complete Extraction
	0.238	0.190	Partial Extraction
	0.238	0.190	No Extraction
Post-Infection Mortality - High	0.146	0.248	Complete Extraction
	0.238	0.286	Partial Extraction
	0.238	0.286	No Extraction
Infection Cost - Low	$16,592	$6,491	Infection Treatment No Extraction
	$67,586	$48,108	Infection treatment partial extraction with replacement
	$45,694	$25,524	Infection treatment full extraction no replacement
	$67,586	$48,108	Infection treatment full extraction with replacement
Infection Cost - High	$16,592	$26,693	Infection Treatment No Extraction
	$67,586	$87,064	Infection treatment partial extraction with replacement
	$45,694	$65,864	Infection treatment full extraction no replacement
	$67,586	$87,064	Infection treatment full extraction with replacement
Life Expectancy - Low	7.83	6.26	Discounted Post 12 months, Replacement - CRT-D
	4.16	3.33	Discounted Post 12 months, Replacement - CRT-P
	7.41	5.93	Discounted Post 12 months, Replacement - IPG

	7.80	6.24	Discounted Post 12 months, Replacement - ICD
	5.54	4.43	Discounted Post 12 months, No Replacement - CRT-D
	5.54	4.43	Discounted Post 12 months, No Replacement - CRT-P
	5.54	4.43	Discounted Post 12 months, No Replacement - IPG
	5.54	4.43	Discounted Post 12 months, No Replacement - ICD
Life Expectancy - High	7.83	9.39	Discounted Post 12 months, Replacement - CRT-D
	4.16	4.99	Discounted Post 12 months, Replacement - CRT-P
	7.41	8.89	Discounted Post 12 months, Replacement - IPG
	7.80	9.35	Discounted Post 12 months, Replacement - ICD
	5.54	6.64	Discounted Post 12 months, No Replacement - CRT-D
	5.54	6.64	Discounted Post 12 months, No Replacement - CRT-P
	5.54	6.64	Discounted Post 12 months, No Replacement - IPG
	5.54	6.64	Discounted Post 12 months, No Replacement - ICD
Lifetime Costs - Low	$45,662	$27,397	Discounted Lifetime Cost Replacement - CRT-D
	$26,183	$15,710	Discounted Lifetime Cost Replacement - CRT-P
	$26,485	$15,891	Discounted Lifetime Cost Replacement- IPG
	$35,159	$21,095	Discounted Lifetime Cost Replacement - ICD
	$22,015	$13,209	Discounted Lifetime Cost No Replacement - CRT-D
	$22,015	$13,209	Discounted Lifetime Cost No Replacement - CRT-P
	$22,015	$13,209	Discounted Lifetime Cost No Replacement- IPG
	$22,015	$13,209	Discounted Lifetime Cost No Replacement - ICD
Lifetime Costs - High	$45,662	$63,926	Discounted Lifetime Cost Replacement - CRT-D
	$26,183	$36,657	Discounted Lifetime Cost Replacement - CRT-P
	$26,485	$37,078	Discounted Lifetime Cost Replacement- IPG
	$35,159	$49,222	Discounted Lifetime Cost Replacement - ICD
	$22,015	$30,821	Discounted Lifetime Cost No Replacement - CRT-D
	$22,015	$30,821	Discounted Lifetime Cost No Replacement - CRT-P
	$22,015	$30,821	Discounted Lifetime Cost No Replacement- IPG
	$22,015	$30,821	Discounted Lifetime Cost No Replacement - ICD

Table S6. Extended One-Way Sensitivity Analysis

Parameter	Parameter Value	ICER (per QALY)
Extended Lifetime Cost (Low)	Lifetime costs halved*	$109,900
Extended Lifetime Cost (High)	Lifetime costs doubled*	$118,009
TYRX Cost (Low)	$895	$102,824
TYRX Cost (Base Case)	$953	$112,603
TYRX Cost (High)	$995	$119,655

* The calculation of lifetime cost was based on the most appropriate evidence available for this specific patient population. However, we recognize that there is more uncertainty about this input than perhaps any of the others. This extended sensitivity analysis was performed to further demonstrate that the model is not overly sensitive to this input, so that even when these inputs were varied by extreme values the directional result is not markedly different.