

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Christopher McFarren, MD Fadi Matar, MD Christiano Caldeira, MD David J. Maron, MD	Catherine Jahrsdorfer, RN, BSN		
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Gary J. Luckasen, MD (from Dec. 2016)	Adam J. Jaskowiak	Loveland, CO	Medical Center of the Rockies (1)
	Joel Klitch		
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Srinivasa Potluri, MD	Precilia Vasquez	Plano, TX	Baylor Research Institute at Legacy Heart Center (1) **
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Gurpreet S. Wander, DM Rohit Tandon, MD			
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Ambuj Roy, DM Neeraj Parakh, DM Sunil Kumar Verma, DM Rajiv Narang, DM Sundeep Mishra, DM Nitish Naik, DM Gautam Sharma, DM	Chandini Suvarna, BDS	New Delhi	All India Institute Of Medical Sciences (67)

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United Kingdom (539)			
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Keith AA Fox, MBChB (past)			
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Kathryn Carruthers (past)			
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	Lisa Chaytor  Leanne Cox Julie Morrow Kay Rowe Stephanie Kelly, RN	Cottingham	The University of Hull/Castle Hill Hospital (19)
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	James Harrison, BSc(Hons), PG dip		
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	Amy J. Richards, BSc		(11)
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Iqbal Karimullah, MBBS	RGN		
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	Wenda Crawford, RN Joanne Kelly, RN Lorraine McGregor, RN		
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Ariel Diaz, MD			
Philippe Rheault, MD		Trois-Rivieres, QC	Centre Hospitalier de Regional Trois-Rivieres (71)



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Catherine Lemay, MD			
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Pierre Gervais, MD			
Alain Rheault, MD			
	Katia Drouin, RN		
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	Christine Masson		
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Brazil (399)

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PhD

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Expedito Eustáquio Ribeiro Silva, MD			
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Alexandre Schaan de Quadros, MD	Aline Peixoto Deiro		
Renato Abdala Karam Kalil, MD	Alice Manica Muller		
José Luiz da Costa Vieira, MD	Maria Antonieta Pereira de Moraes	Porto Alegre	Instituto de Cardiologia de Porto Alegre (41)
Gabriel Grossmann , MD	Bruna Maria Ascoli		
Pedro Píccaro de Oliveira, MD	Sílvia Zottis Poletti		
Leonardo Bridi, MD			
Simone Savaris, MD			
João V Vitola, MD, PhD			
Rodrigo J Cerci, MD, Msc	Sandra S. Zier, BSc		
Fabio R Farias, MD, Msc	Vilmar Veiga Jr, BSc	Curitiba	Quanta Diagnostico & Terapia (33)
Miguel M Fernandes, MD, PhD			
José Antonio Marin- Neto, MD, PhD			
André Schmidt, MD, PhD			
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João Reynaldo Abbud Chierice, MD	Guilherme G Rucatti, PsyD		
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Luis F. Smidt, MD	Mauren P Haeffner, BSc		
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Flavio Lyra, MD			
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Mokhtar, RN  
Nor Asiah Basri, RN  
Irni Yusnida, RN  
Humayrah Hashim

Kuala Lumpur

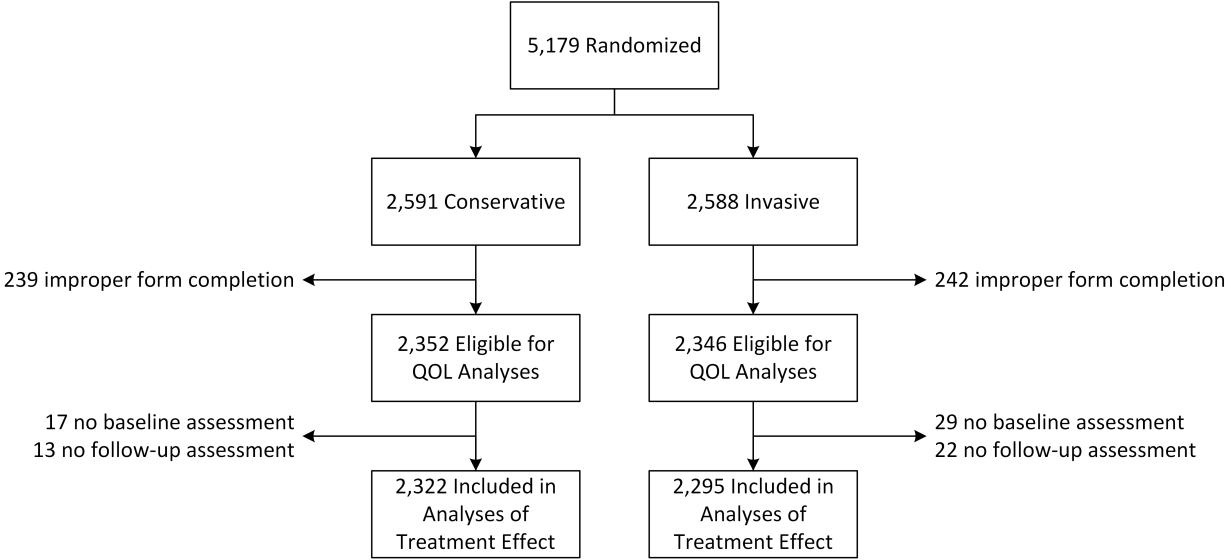
Institut Jantung  
Negara (2)

*\* Countries participated in Economics Quality of Life (EQoL) Questionnaires*

*\*\*This site received one participant in transfer that was randomized at another site*

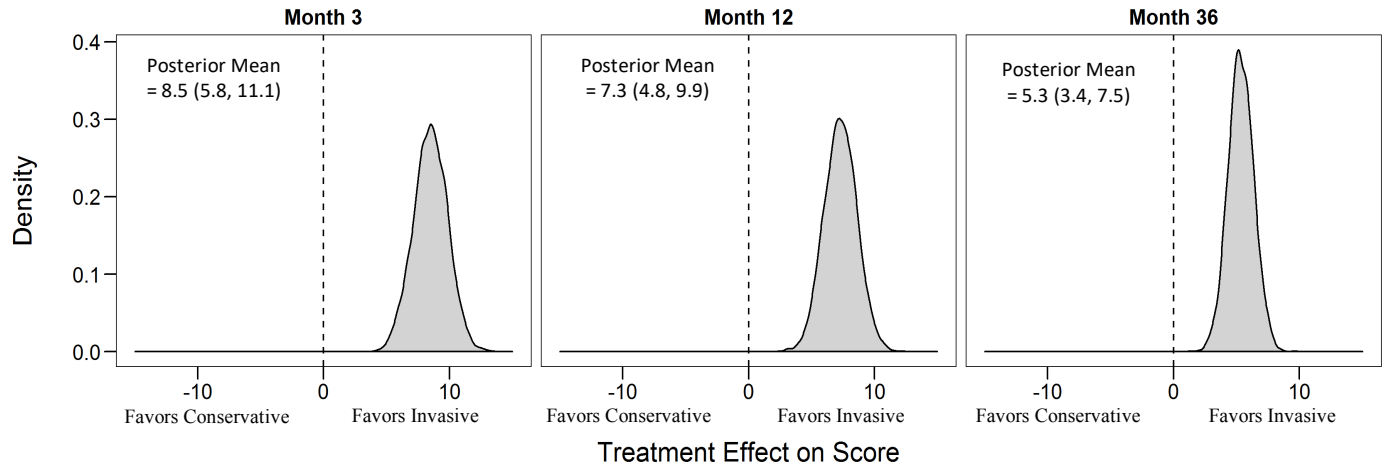


**3 Supplemental Figure 1: Consort Diagram of Patient Flow**

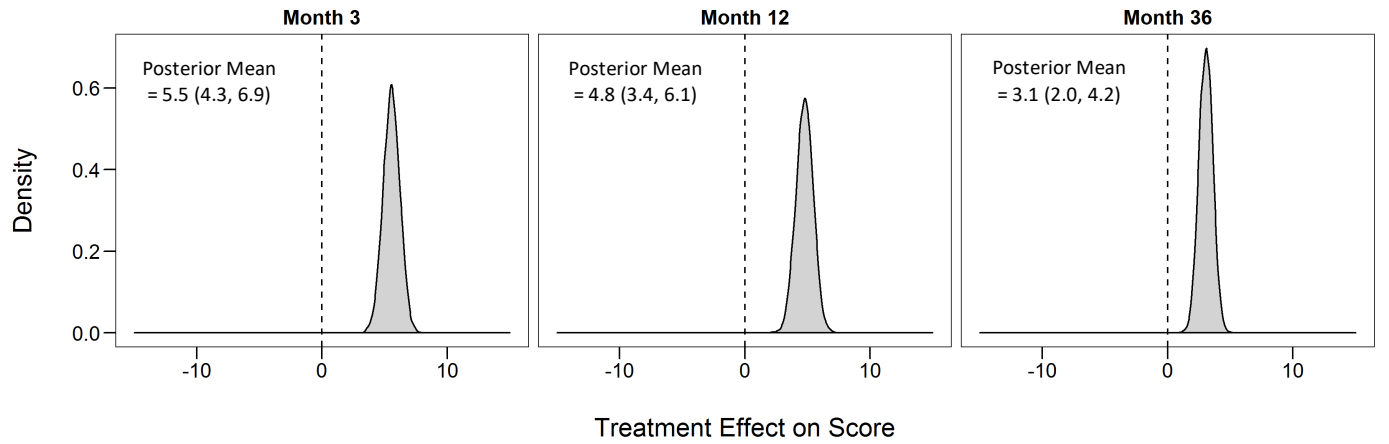


**4 Supplemental Figure 2: Distributions of the Expected Differences in Seattle Angina Questionnaire Summary Scores from an Initially Invasive Strategy**

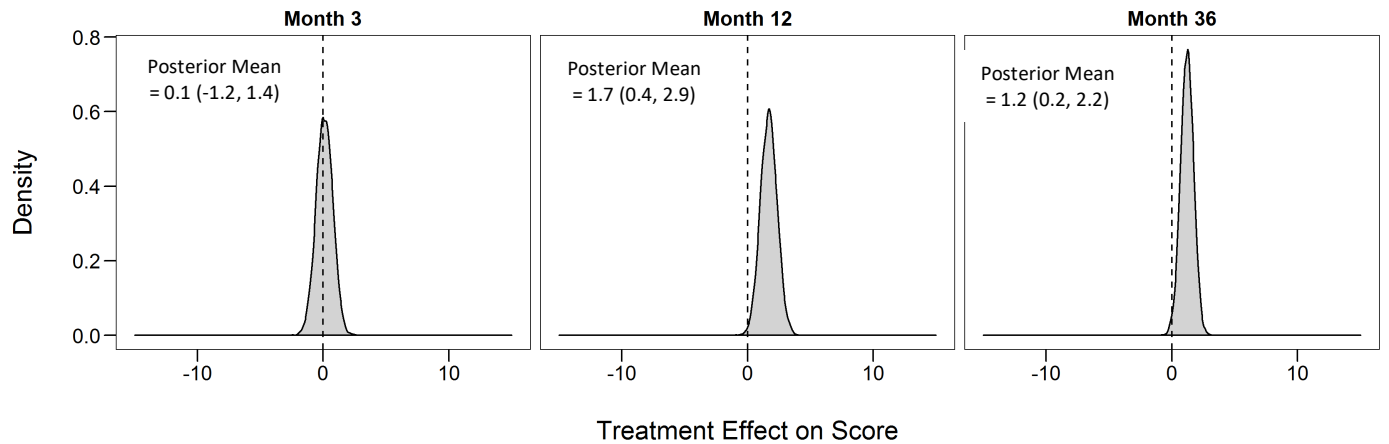
Supplemental Figure 2A: Patients with Daily/Weekly Angina at Baseline



Supplemental Figure 2B: Patients with Angina Several Times per Month at Baseline

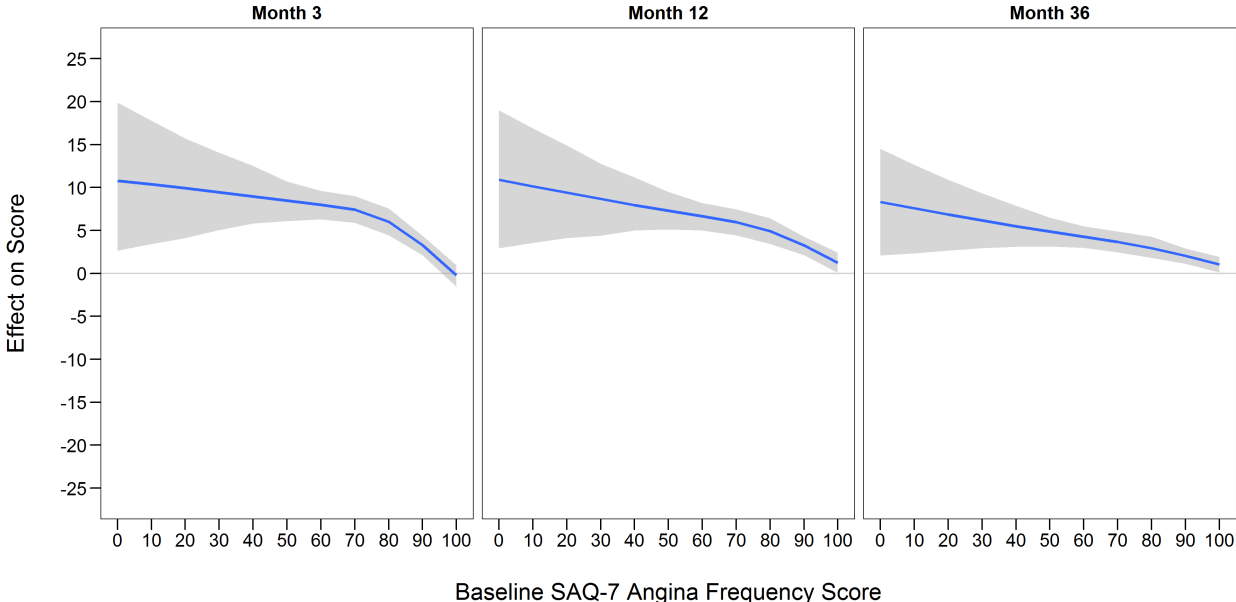


Supplemental Figure 2C: Patients with No Angina at Baseline

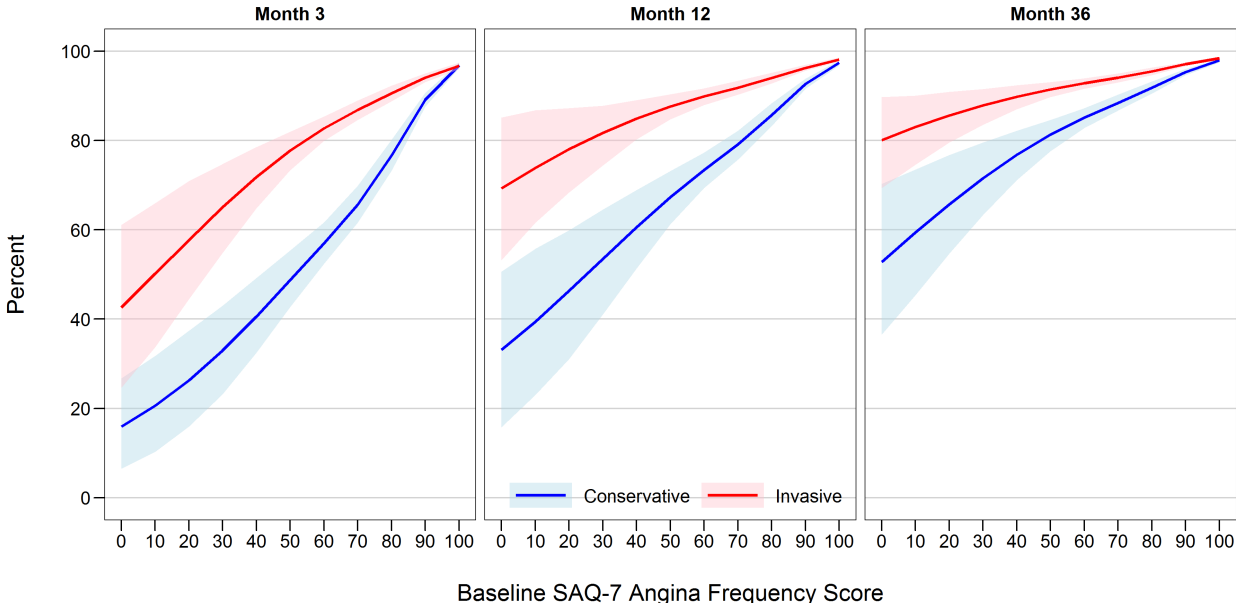


**5 Supplemental Figure 3: Effect of Treatment on SAQ Summary Score, as a Function of Patients' Baseline Angina**

**(a) Effect of Invasive vs. Conservative Treatment on SAQ Summary Score**

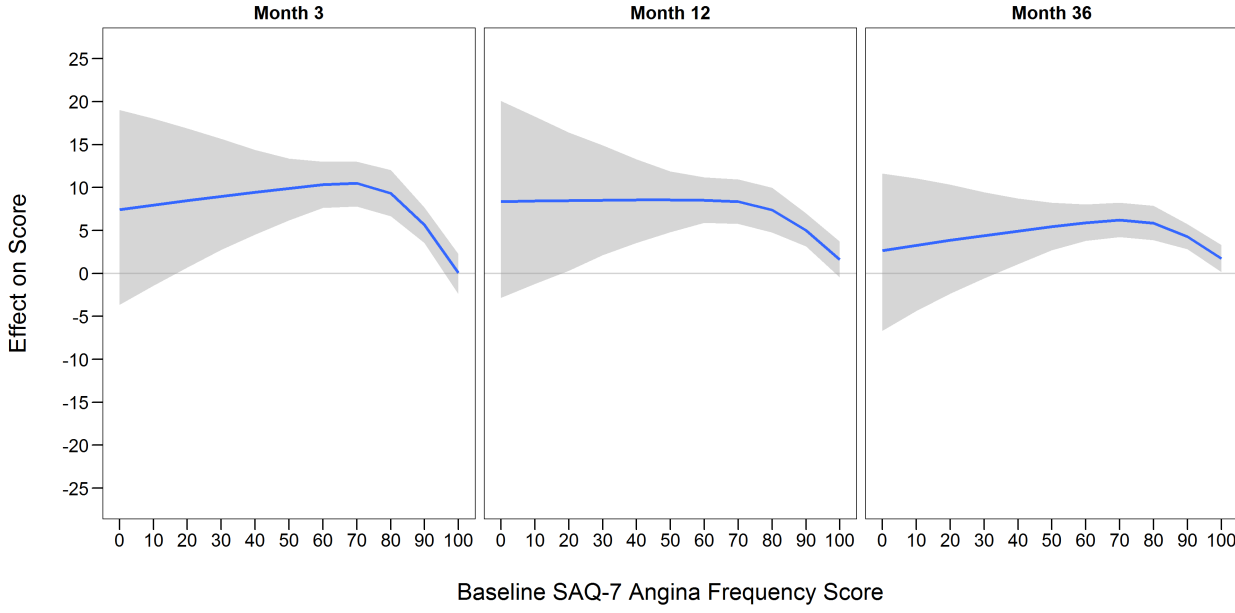


**(b) Probability of SAQ Summary Score  $\geq 75$ , by Treatment**

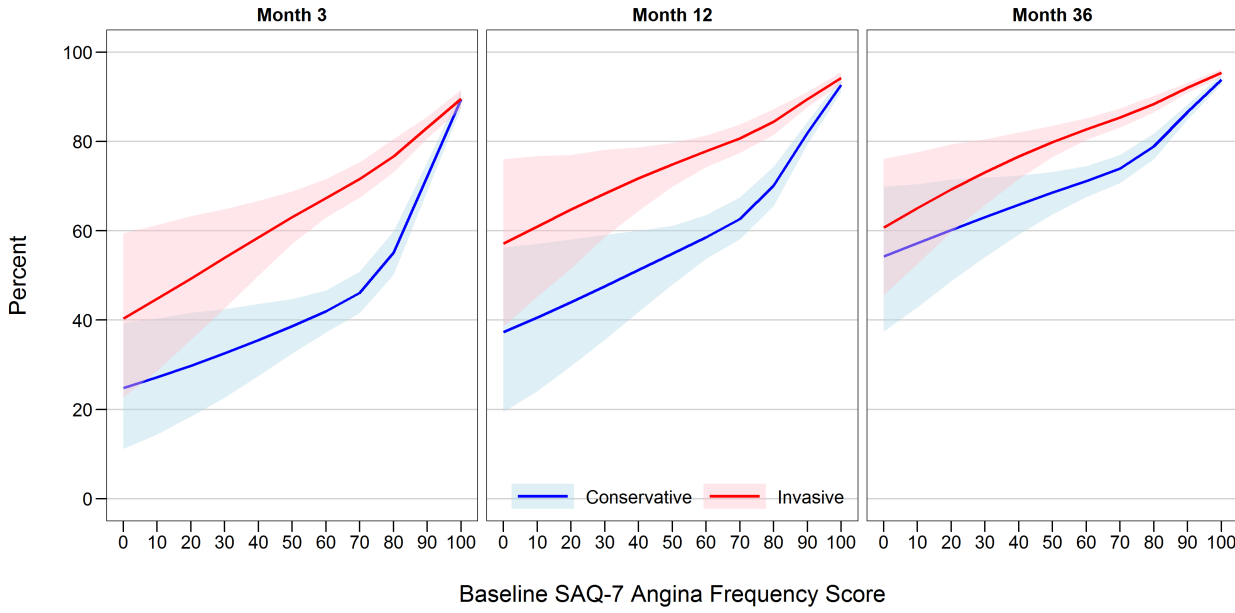


**6 Supplemental Figure 4: Effect of Treatment on SAQ Quality of Life Score, as a Function of Patients' Baseline Angina**

**(a) Effect of Invasive vs. Conservative Treatment on SAQ Quality of Life Score**



**(b) Probability of SAQ Quality of Life Score  $\geq 75$ , by Treatment**



## 7 Supplemental Table 1. Baseline Characteristics of Included and Excluded Patients

	Included n = 4617	Excluded n = 81	P-Value
Randomized Treatment			0.018
Invasive	2295 (49.7%)	51 (63.0%)	
Conservative	2322 (50.3%)	30 (37.0%)	
Age at Randomization			0.988
Mean ± SD	64.4 ± 9.5	64.4 ± 10.5	
Sex			0.833
Male	3545 (76.8%)	63 (77.8%)	
Female	1072 (23.2%)	18 (22.2%)	
Race			0.007
American Indian or Alaska Native	12 (0.3%)	0 (0.0%)	
Asian	979 (21.4%)	27 (34.6%)	
Native Hawaiian or Other Pacific Islander	11 (0.2%)	1 (1.3%)	
Black or African American	200 (4.4%)	4 (5.1%)	
White	3358 (73.5%)	45 (57.7%)	
Multiple Races	10 (0.2%)	1 (1.3%)	
Missing	47	3	
Ethnicity			0.261
Hispanic or Latino	740 (16.0%)	11 (13.6%)	
Not Hispanic or Latino	3526 (76.4%)	60 (74.1%)	
Unknown	351 (7.6%)	10 (12.3%)	
Hypertension			0.013
No	1086 (23.5%)	13 (16.0%)	
Yes	3516 (76.2%)	66 (81.5%)	
Unknown	15 (0.3%)	2 (2.5%)	
Diabetes	1836 (39.8%)	38 (46.9%)	0.192
Prior MI			0.165
No	3653 (79.1%)	71 (87.7%)	
Yes	951 (20.6%)	10 (12.3%)	
Unknown	13 (0.3%)	0 (0.0%)	
Baseline Smoking Status			0.430
Never Smoked	1861 (40.3%)	36 (44.4%)	
Former Smoker	2147 (46.5%)	32 (39.5%)	
Current Smoker	607 (13.2%)	13 (16.0%)	
Missing	2		
CCS Angina Class			0.917
None	1005 (21.8%)	18 (22.2%)	
I	1302 (28.2%)	20 (24.7%)	
II	2094 (45.4%)	39 (48.1%)	
III	214 (4.6%)	4 (4.9%)	
IV	1 (0.0%)	0 (0.0%)	
Not known	1 (0.0%)	0 (0.0%)	

	Included n = 4617	Excluded n = 81	P-Value
New Onset Angina Within 3 Months	722 (16.5%)	6 (8.2%)	0.056
Missing	252	8	
Heart Failure	1786 (38.7%)	34 (42.0%)	0.546
Current NYHA Heart Failure Class			0.011
I	917 (51.3%)	10 (29.4%)	
II	869 (48.7%)	24 (70.6%)	
Prior Cerebrovascular Disease	365 (7.9%)	7 (8.6%)	0.813
Missing	13		
Prior Stroke			0.128
No	4472 (96.9%)	76 (93.8%)	
Yes	144 (3.1%)	5 (6.2%)	
Unknown	1 (0.0%)	0 (0.0%)	
Peripheral Vascular Disease			0.505
No	4407 (95.5%)	76 (93.8%)	
Yes	199 (4.3%)	5 (6.2%)	
Unknown	11 (0.2%)	0 (0.0%)	
History of Depression			0.154
No	4258 (92.2%)	77 (95.1%)	
Yes	339 (7.3%)	3 (3.7%)	
Unknown	20 (0.4%)	1 (1.2%)	
Baseline BMI (kg/m <sup>2</sup> )			0.415
Mean ± SD	28.9 ± 5.2	28.4 ± 5.2	
Missing	37	6	
Stress Test: Degree of Ischemia			0.275
None	247 (5.4%)	3 (3.8%)	
Mild	331 (7.2%)	10 (12.5%)	
Moderate	1637 (35.5%)	23 (28.8%)	
Severe	2348 (51.0%)	43 (53.8%)	
Uninterpretable	44 (1.0%)	1 (1.3%)	
Missing	10	1	
Stress Test Modality			0.072
Nuclear (PET/SPECT)	2490 (53.9%)	41 (50.6%)	
Echocardiographic Stress	1052 (22.8%)	12 (14.8%)	
Cardiac Magnetic Resonance	218 (4.7%)	5 (6.2%)	
ETT without Imaging	857 (18.6%)	23 (28.4%)	
Anterior Ischemia	1228 (32.8%)	23 (41.1%)	0.193
Missing	877	25	
SAQ Summary Score			0.092
Mean ± SD	74.2 ± 18.9	68.8 ± 21.4	
Median (IQR)	77.0 (62.0, 89.0)	68.0 (58.0, 83.0)	
Missing	2	46	

	<b>Included n = 4617</b>	<b>Excluded n = 81</b>	<b>P-Value</b>
SAQ Physical Limitation Score			0.667
Mean ± SD	79.3 ± 23.6	77.4 ± 23.6	
Median (IQR)	83.0 (67.0, 100.0)	79.0 (58.0, 100.0)	
Missing	339	53	
SAQ Angina Frequency Score			0.301
Mean ± SD	81.4 ± 19.6	78.0 ± 22.2	
Median (IQR)	90.0 (70.0, 100.0)	80.0 (60.0, 100.0)	
Missing	5	46	
SAQ Quality of Life Score			0.055
Mean ± SD	62.0 ± 26.4	53.5 ± 29.2	
Median (IQR)	63.0 (38.0, 88.0)	50.0 (25.0, 75.0)	
Missing	11	46	

**8 Supplemental Table 2. Brief Symptom Questionnaire Completion Rates and Reasons for Missingness**

Month	Number of Patients Who...			Completed	Skipped	Withdrawn	Lost to Follow-up
	Died	Were Censored Due to Completion of Trial	Were Eligible for Assessment				
<b>Conservative Treatment Group (N=2,352)</b>							
0	0	0	2352	2335 (99.3%)	17 ( 0.7%)	0 ( 0.0%)	0 ( 0.0%)
1.5	4	0	2348	2146 (91.4%)	188 ( 8.0%)	3 ( 0.1%)	11 ( 0.5%)
3	7	0	2345	2156 (91.9%)	164 ( 7.0%)	4 ( 0.2%)	21 ( 0.9%)
6	15	0	2337	2188 (93.6%)	111 ( 4.7%)	8 ( 0.3%)	30 ( 1.3%)
12	27	2	2323	2157 (92.9%)	114 ( 4.9%)	11 ( 0.5%)	41 ( 1.8%)
18	51	18	2283	2105 (92.2%)	126 ( 5.5%)	13 ( 0.6%)	39 ( 1.7%)
24	63	300	1989	1799 (90.4%)	135 ( 6.8%)	16 ( 0.8%)	39 ( 2.0%)
30	80	638	1634	1478 (90.5%)	99 ( 6.1%)	17 ( 1.0%)	40 ( 2.4%)
36	87	863	1402	1253 (89.4%)	86 ( 6.1%)	17 ( 1.2%)	46 ( 3.3%)
42	106	1140	1106	967 (87.4%)	78 ( 7.1%)	18 ( 1.6%)	43 ( 3.9%)
48	111	1376	865	740 (85.5%)	62 ( 7.2%)	18 ( 2.1%)	45 ( 5.2%)
54	118	1629	605	509 (84.1%)	42 ( 6.9%)	19 ( 3.1%)	35 ( 5.8%)
60	121	1815	416	343 (82.5%)	24 ( 5.8%)	19 ( 4.6%)	30 ( 7.2%)
66	128	1988	236	183 (77.5%)	9 ( 3.8%)	20 ( 8.5%)	24 (10.2%)
72	129	2113	110	69 (62.7%)	0 ( 0.0%)	20 (18.2%)	21 (19.1%)
78	129	2177	46	5 (10.9%)	0 ( 0.0%)	20 (43.5%)	21 (45.7%)
<b>Invasive Treatment Group (N=2,346)</b>							
0	0	0	2346	2317 (98.8%)	29 ( 1.2%)	0 ( 0.0%)	0 ( 0.0%)
1.5	6	0	2340	2051 (87.6%)	270 (11.5%)	4 ( 0.2%)	15 ( 0.6%)
3	13	0	2333	2064 (88.5%)	231 ( 9.9%)	10 ( 0.4%)	28 ( 1.2%)
6	18	0	2328	2175 (93.4%)	107 ( 4.6%)	13 ( 0.6%)	33 ( 1.4%)
12	39	0	2307	2132 (92.4%)	118 ( 5.1%)	13 ( 0.6%)	44 ( 1.9%)
18	53	13	2280	2090 (91.7%)	125 ( 5.5%)	13 ( 0.6%)	52 ( 2.3%)
24	66	295	1985	1806 (91.0%)	111 ( 5.6%)	14 ( 0.7%)	54 ( 2.7%)
30	78	640	1628	1457 (89.5%)	101 ( 6.2%)	16 ( 1.0%)	54 ( 3.3%)
36	91	871	1384	1213 (87.6%)	100 ( 7.2%)	17 ( 1.2%)	54 ( 3.9%)
42	107	1142	1097	957 (87.2%)	70 ( 6.4%)	18 ( 1.6%)	52 ( 4.7%)
48	119	1381	846	731 (86.4%)	52 ( 6.1%)	18 ( 2.1%)	45 ( 5.3%)
54	123	1625	598	503 (84.1%)	37 ( 6.2%)	18 ( 3.0%)	40 ( 6.7%)
60	130	1827	389	321 (82.5%)	15 ( 3.9%)	18 ( 4.6%)	35 ( 9.0%)
66	136	1988	222	165 (74.3%)	10 ( 4.5%)	19 ( 8.6%)	28 (12.6%)
72	136	2097	113	65 (57.5%)	2 ( 1.8%)	19 (16.8%)	27 (23.9%)
78	136	2157	53	8 (15.1%)	0 ( 0.0%)	19 (35.8%)	26 (49.1%)



**9 Supplemental Table 3: Odds Ratios (95% Highest Posterior Density Intervals) for Better Health Status with the Invasive vs. Conservative Strategy, by Time of Follow Up**

<b>Month</b>	<b>SAQ-7 Summary Score</b>	<b>SAQ-7 Angina Frequency Score</b>	<b>SAQ-7 Quality of Life Score</b>	<b>SAQ-7 Physical Limitation Score</b>	<b>Rose Dyspnea Score</b>	<b>EQ-5D Visual Analog Scale</b>
1.5	1.51 (1.29, 1.75)	1.76 (1.47, 2.05)	1.35 (1.14, 1.56)	1.17 (0.98, 1.38)	1.55 (1.31, 1.81)	1.34 (1.14, 1.56)
3	2.09 (1.76, 2.45)	2.99 (2.43, 3.57)	1.93 (1.59, 2.26)	1.42 (1.15, 1.71)	1.68 (1.38, 2.01)	1.56 (1.30, 1.83)
6	2.33 (1.93, 2.77)	3.17 (2.52, 3.90)	2.09 (1.72, 2.49)	1.75 (1.37, 2.15)	1.66 (1.34, 2.04)	1.92 (1.59, 2.30)
12	2.29 (1.89, 2.71)	2.95 (2.30, 3.65)	1.98 (1.60, 2.35)	1.94 (1.50, 2.39)	1.68 (1.31, 2.05)	1.75 (1.43, 2.07)
24	1.80 (1.52, 2.12)	2.01 (1.61, 2.44)	1.74 (1.45, 2.04)	1.62 (1.28, 1.97)	1.44 (1.17, 1.73)	1.44 (1.20, 1.69)
36	1.87 (1.59, 2.18)	2.11 (1.73, 2.55)	1.81 (1.52, 2.10)	1.68 (1.35, 2.05)	1.44 (1.17, 1.69)	1.52 (1.27, 1.78)
48	1.96 (1.57, 2.36)	2.23 (1.66, 2.81)	1.89 (1.52, 2.30)	1.75 (1.30, 2.23)	1.44 (1.12, 1.78)	1.60 (1.28, 1.93)

**10 Supplemental Table 4: Treatment Effect on Predicted Time-Averaged Scores through 48 Months for a Typical Patient Posterior Means and 95% Highest Posterior Density Intervals**

**All Patients**

	<b>CON</b>	<b>INV</b>	<b>Difference</b>
SAQ-7 Summary Score	86.0 (85.4, 86.6)	89.3 (88.8, 89.8)	3.3 (2.7, 4.0)
SAQ-7 Angina Frequency Score	94.0 (93.5, 94.6)	96.8 (96.5, 97.1)	2.8 (2.3, 3.3)
SAQ-7 Quality of Life Score	79.0 (78.0, 80.0)	84.0 (83.1, 84.9)	5.0 (3.9, 6.1)

**Daily/Weekly Angina**

	<b>CON</b>	<b>INV</b>	<b>Difference</b>
SAQ-7 Summary Score	78.9 (77.3, 80.6)	85.2 (83.8, 86.5)	6.3 (4.4, 8.0)
SAQ-7 Angina Frequency Score	87.4 (85.9, 89.0)	93.7 (92.7, 94.6)	6.2 (4.5, 8.1)
SAQ-7 Quality of Life Score	69.6 (67.4, 71.9)	77.0 (74.9, 79.0)	7.4 (4.8, 10.1)

**Monthly Angina**

	<b>CON</b>	<b>INV</b>	<b>Difference</b>
SAQ-7 Summary Score	85.2 (84.4, 86.0)	88.9 (88.2, 89.6)	3.7 (2.7, 4.6)
SAQ-7 Angina Frequency Score	94.2 (93.6, 94.8)	97.0 (96.6, 97.3)	2.8 (2.1, 3.4)
SAQ-7 Quality of Life Score	77.2 (75.7, 78.6)	83.3 (82.0, 84.6)	6.2 (4.5, 7.8)

**No Angina**

	<b>CON</b>	<b>INV</b>	<b>Difference</b>
SAQ-7 Summary Score	91.5 (90.7, 92.2)	92.6 (91.8, 93.3)	1.1 (0.2, 1.9)
SAQ-7 Angina Frequency Score	98.9 (98.7, 99.1)	99.3 (99.1, 99.4)	0.4 (0.2, 0.6)
SAQ-7 Quality of Life Score	86.8 (85.3, 88.4)	88.8 (87.3, 90.2)	2.0 (0.4, 3.6)

**11 Supplemental Table 5. Odds Ratios for Higher SAQ-7 Summary Score with the Invasive vs. Conservative Strategy based on Joint Model with Survival**

<b>Month</b>	<b>Primary Analysis Model Ignoring Deaths</b>	<b>Joint Model with Survival</b>
1.5	1.51 (1.29, 1.75)	1.51 (1.29, 1.74)
3	2.09 (1.76, 2.45)	2.09 (1.76, 2.45)
6	2.33 (1.93, 2.77)	2.33 (1.93, 2.76)
12	2.29 (1.89, 2.71)	2.28 (1.85, 2.69)
24	1.80 (1.52, 2.12)	1.79 (1.49, 2.09)
36	1.87 (1.59, 2.18)	1.87 (1.58, 2.18)
48	1.96 (1.57, 2.36)	1.95 (1.57, 2.35)

## 12 Supplemental Table 6 – Interpreting the SAQ-7 and Clinically-important Intra-individual Changes in Scores

When interpreting health status outcomes, it is critically important to understand the clinical importance of differences in PROs. Mean differences of a continuous variable between groups in a clinical trial, such as ISCHEMIA, represent population averages, and do not shed much light on the impact of treatment on an individual patient’s change in health status, which depends strongly on where they start. Some patients have much larger, while others have much smaller, changes in health status. The primary analysis in ISCHEMIA tests whether or not, on average, there were larger changes with the invasive, as compared with the conservative, strategy. From the Bayesian analyses, there is almost zero probability that there was no average benefit from an invasive strategy in the overall population, although the benefit was much larger in those with more frequent angina and non-existent at 3 months in those without angina. Nevertheless, trying to infer clinical significance from the mean changes across the population is not an appropriate way to understand the benefits to future patients presenting for care and wanting to engage in shared decision-making about their treatment. Specifically, dichotomizing the mean differences in the population as being – or not being – clinically significant runs counter to the goals of supporting more personalized, patient-centered care.

Accordingly, once it was determined that there was a significant average benefit from an invasive strategy, we sought to define how many patients realized a clinically significant benefit. This is a matter of interpretation, as what is clinically important is a judgment that lies in the eyes of the beholder. We do not feel confident defining what is ‘clinically important,’ as we believe that this information should be shared with patients and that patients should be empowered to define whether or not that magnitude of difference is important to them. The primary effort in the main paper was to show the proportion of patients, as a function of their baseline angina, who were either angina free (SAQ Angina Frequency score = 100; Figure 3) or had good to excellent health status (SAQ Summary Score  $\geq 75$ ; Figure S3) or good to excellent disease-specific quality of life (SAQ Quality of Life score  $\geq 75$ ; Figure S4).

An alternative approach is to examine what is a clinically important difference in SAQ scales. To gain a better appreciation of this, we propose first looking at the instrument itself to provide a clinical context for interpreting the clinical importance of intra-individual changes in scores. Because the SAQ items have Likert responses, each category of response will have a different impact on that domain’s score. This is because the scales are normalized to a range of 0 to 100, which higher scores indicating better health status, to facilitate interpretability. From the ‘shift’ in score for each scale, a clinical insight into what different scores mean can be gained. This strategy has been described by Wyrwich et al. (Am Heart J 2004;147:615–22.). Using the SAQ Angina Frequency scale as an example, we provide the exact items that define the score below:

1. Over the past 4 weeks, on average, how many times have you had **chest pain, chest tightness or angina**?

I have had **chest pain, chest tightness or angina**...

		3 or more			
4 or more	1-3 times	times per week	1-2 times	Less than	None over the
times per day	per day	but not every day	per week	once a week	past 4 weeks
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

---

2. Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (nitroglycerin tablets or spray) for your **chest pain, chest tightness or angina**?

I have taken nitroglycerin...

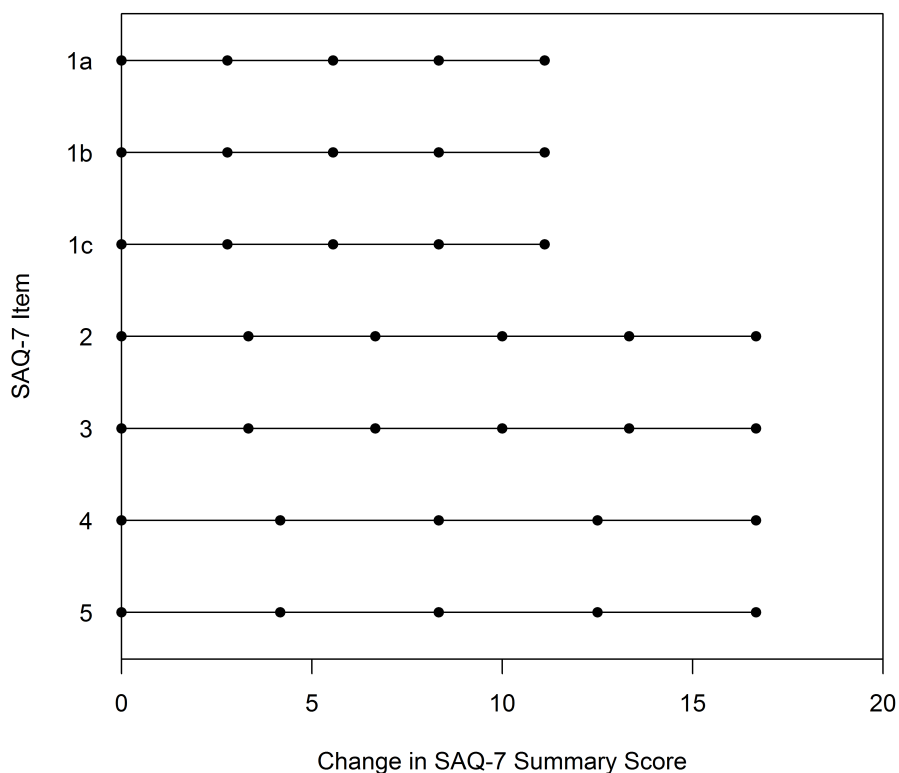
		3 or more				
4 or more	1-3 times	times per week	1-2 times	Less than	None over the	
times per day	per day	but not every day	per week	once a week	past 4 weeks	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Each 'shift' in response on either of these 2 items changes the SAQ Angina Frequency score by 10 points. For example, if a patient had angina 1-2 times per week at baseline and took no nitroglycerin, then they would have a score of 80. If they went from 1-2 angina episodes per week to less than 1 episode a week, that would be a change of 10 points, resulting in an Angina Frequency score of 90. While many would view such a change (from 1-2 times/week to less than once a week) as clinically important, others may feel that a 20-point change is minimally important. We often use these thresholds of clinically important change in responder analyses to show the proportion of patients who have experienced clinical changes of different magnitudes.

Importantly, we do not feel it is correct to apply this to mean differences in a population. For example, if there were a 10-point difference, on average, in the population, almost certainly many patients would have changes >10 while many would have changes <10. That is why we are very hesitant to artificially categorize the mean differences in the population as clinically important or not.

While we consider a 10-point change for an individual in the SAQ Angina Frequency scale to be clinically important, different thresholds are needed for the SAQ Summary Score. We believe that a 5-point or greater difference in SAQ Summary Score for an individual is clinically important. To support this assertion, we graphed the impact on the score for each 'shift' in response on one of the 7 items (the first 3 are the SAQ Physical Limitation items, the next 2 are the SAQ Angina Frequency Scale and the last 2 are the SAQ Quality of Life items). While different shifts in different items alter the Summary Score differently, it is clear that there is no change in any single response that would change the SAQ Summary Score by >5 points. When we declare that a 5-point change is clinically important, we are demanding that at least 2 items improve by one category, or that at least one item improve by 2 categories. To define the face validity of these shifts, the SAQ-7 questionnaire is provided in Section 11 of this Supplement.

### Change in SAQ-7 Summary Score Per Unit Increase in Item Response



To provide insights into the likelihood of small, but important (defined as  $\geq 10$  points on the SAQ Angina Frequency scale and  $\geq 5$  points on the SAQ Summary Score) clinical changes or a moderate to large clinical change (defined as  $\geq 20$  points on the SAQ Angina Frequency scale and  $\geq 10$  points on the SAQ Summary Score), we show in the tables below the model-estimated probability in each arm of a typical patient experiencing these magnitudes of changes at 3, 12 and 36, as a function of their baseline angina frequency. When interpreting these differences, it is important to realize that there is less difference in those with severe angina and those with minimal angina at the time of randomization. This is because the use of guideline-based medical therapy improved health status outcomes in the most symptomatic patients beyond these minimal thresholds (e.g. both a patient with a 20-point improvement and one with an 80-point improvement who had a baseline Angina Frequency score of 20 would exceed a 10- or 20-point improvement threshold, although the latter patient clearly got more benefit and would be angina-free) is not captured by this type of responder analysis. For those with minimal angina at randomization, there was limited opportunity to further improve. Accordingly, we feel that describing the proportion who were angina-free at follow-up (Figure 3 of the paper) is more helpful in applying the results of ISCHEMIA to future patients.

Probability of Improvement  $\geq 5$  Points (95% Credible Interval) in SAQ-7 Summary Score, as function of Baseline Angina Frequency over time

Baseline SAQ-7 Angina			Invasive	Conservative	Difference
Month	Frequency Score				
3	Daily Angina	0	100.0 (100.0, 100.0)	99.9 (99.9, 100.0)	0.0 (0.0, 0.1)
		10	99.9 (99.9, 100.0)	99.8 (99.6, 99.9)	0.2 (0.0, 0.3)
		20	99.8 (99.7, 99.9)	99.3 (98.8, 99.6)	0.5 (0.2, 1.0)
	Weekly Angina	30	99.5 (99.3, 99.7)	98.2 (97.3, 99.0)	1.3 (0.5, 2.2)
		40	98.8 (98.4, 99.2)	95.8 (94.3, 97.1)	3.1 (1.7, 4.6)
		50	97.4 (96.7, 98.0)	90.9 (88.8, 93.1)	6.4 (4.3, 8.7)
	Monthly Angina	60	94.2 (93.1, 95.2)	81.8 (78.9, 84.6)	12.4 (9.4, 15.4)
		70	86.8 (84.5, 89.0)	65.6 (61.5, 69.8)	21.2 (16.6, 25.8)
		80	60.6 (55.7, 65.4)	34.4 (30.2, 39.0)	26.1 (19.5, 32.5)
	No Angina	90	29.0 (25.6, 32.4)	17.5 (15.1, 19.7)	11.5 (7.3, 15.5)
100		0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
12	Daily Angina	0	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.0 (0.0, 0.0)
		10	100.0 (100.0, 100.0)	99.9 (99.9, 100.0)	0.1 (0.0, 0.1)
		20	99.9 (99.9, 100.0)	99.7 (99.5, 99.9)	0.2 (0.1, 0.4)
	Weekly Angina	30	99.8 (99.7, 99.9)	99.2 (98.8, 99.6)	0.6 (0.2, 1.0)
		40	99.5 (99.3, 99.7)	98.1 (97.4, 98.8)	1.4 (0.7, 2.2)
		50	98.7 (98.3, 99.0)	95.6 (94.4, 96.7)	3.1 (2.0, 4.3)
	Monthly Angina	60	96.8 (96.1, 97.4)	90.3 (88.5, 92.1)	6.4 (4.6, 8.3)
		70	91.8 (90.3, 93.3)	79.1 (75.7, 82.1)	12.7 (9.3, 16.3)
		80	71.3 (67.1, 75.7)	48.9 (43.7, 53.9)	22.4 (15.8, 29.0)
	No Angina	90	40.0 (36.1, 44.3)	24.7 (21.7, 27.9)	15.3 (10.2, 20.4)
100		0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
36	Daily Angina	0	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.0 (0.0, 0.0)
		10	100.0 (100.0, 100.0)	100.0 (99.9, 100.0)	0.0 (0.0, 0.0)
		20	100.0 (99.9, 100.0)	99.9 (99.8, 99.9)	0.1 (0.0, 0.2)
	Weekly Angina	30	99.9 (99.8, 99.9)	99.6 (99.5, 99.8)	0.2 (0.1, 0.4)
		40	99.7 (99.6, 99.8)	99.1 (98.8, 99.4)	0.6 (0.3, 0.8)
		50	99.1 (98.9, 99.3)	97.9 (97.4, 98.4)	1.2 (0.7, 1.8)
	Monthly Angina	60	97.8 (97.4, 98.1)	95.1 (94.3, 95.9)	2.7 (1.8, 3.6)
		70	94.0 (93.0, 95.0)	88.4 (86.6, 90.2)	5.6 (3.6, 7.7)
		80	76.9 (73.4, 80.0)	64.2 (60.0, 68.4)	12.7 (7.6, 18.2)
	No Angina	90	46.0 (42.3, 49.7)	34.6 (31.4, 38.1)	11.5 (6.4, 16.2)
100		0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	

Probability of Improvement  $\geq 10$  Points (95% Credible Interval) in SAQ-7 Summary Score, as function of Baseline Angina Frequency over time

Baseline SAQ-7 Angina			Invasive	Conservative	Difference
Month	Frequency Score				
3	Daily Angina	0	100.0 (99.9, 100.0)	99.9 (99.7, 100.0)	0.1 (0.0, 0.2)
		10	99.9 (99.8, 100.0)	99.6 (99.2, 99.8)	0.3 (0.1, 0.7)
		20	99.7 (99.5, 99.8)	98.7 (97.9, 99.4)	1.0 (0.3, 1.8)
	Weekly Angina	30	99.1 (98.7, 99.5)	96.7 (95.1, 98.1)	2.5 (1.0, 4.1)
		40	97.9 (97.1, 98.6)	92.6 (90.1, 94.9)	5.3 (3.0, 8.1)
		50	95.4 (94.2, 96.5)	84.9 (81.5, 88.2)	10.5 (7.0, 13.9)
	Monthly Angina	60	89.7 (87.8, 91.4)	70.6 (66.8, 74.7)	19.0 (14.6, 23.2)
		70	74.5 (70.9, 78.1)	45.8 (41.3, 50.4)	28.7 (23.1, 34.6)
		80	40.4 (35.6, 45.4)	18.8 (15.8, 21.8)	21.6 (15.9, 27.2)
	No Angina	90	13.4 (11.6, 15.4)	7.4 (6.3, 8.5)	6.0 (3.8, 8.2)
	100	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
12	Daily Angina	0	100.0 (100.0, 100.0)	100.0 (99.9, 100.0)	0.0 (0.0, 0.1)
		10	100.0 (99.9, 100.0)	99.8 (99.7, 99.9)	0.1 (0.0, 0.3)
		20	99.9 (99.8, 99.9)	99.5 (99.1, 99.7)	0.4 (0.1, 0.8)
	Weekly Angina	30	99.6 (99.4, 99.8)	98.6 (97.8, 99.2)	1.1 (0.4, 1.8)
		40	99.0 (98.7, 99.4)	96.6 (95.3, 97.7)	2.5 (1.3, 3.8)
		50	97.7 (97.0, 98.2)	92.4 (90.5, 94.3)	5.2 (3.4, 7.4)
	Monthly Angina	60	94.1 (92.9, 95.2)	83.4 (80.5, 86.1)	10.8 (7.7, 13.7)
		70	83.3 (80.4, 85.9)	62.7 (58.1, 67.2)	20.6 (15.2, 25.8)
		80	52.3 (47.0, 57.4)	29.7 (25.5, 34.1)	22.6 (15.8, 29.2)
	No Angina	90	20.2 (17.5, 23.0)	11.1 (9.6, 12.9)	9.1 (5.9, 12.3)
	100	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
36	Daily Angina	0	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.0 (0.0, 0.0)
		10	100.0 (100.0, 100.0)	99.9 (99.9, 100.0)	0.1 (0.0, 0.1)
		20	99.9 (99.9, 100.0)	99.8 (99.6, 99.9)	0.2 (0.0, 0.3)
	Weekly Angina	30	99.8 (99.7, 99.9)	99.3 (99.1, 99.6)	0.4 (0.2, 0.7)
		40	99.4 (99.2, 99.6)	98.4 (97.9, 98.9)	1.0 (0.5, 1.5)
		50	98.4 (98.1, 98.8)	96.3 (95.4, 97.1)	2.2 (1.3, 3.1)
	Monthly Angina	60	95.9 (95.2, 96.5)	91.2 (89.8, 92.6)	4.7 (3.2, 6.2)
		70	87.4 (85.5, 89.4)	77.2 (74.0, 80.1)	10.3 (6.9, 14.0)
		80	59.6 (55.1, 64.1)	44.2 (39.7, 48.7)	15.3 (9.4, 22.0)
	No Angina	90	24.4 (21.7, 27.3)	16.7 (14.7, 18.8)	7.8 (4.3, 11.1)
	100	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	



Probability of Improvement  $\geq$  10 Points (95% Credible Interval) in SAQ-7 Angina Frequency Score, as function of Baseline Angina Frequency over time

Baseline SAQ-7 Angina			Invasive	Conservative	Difference
Month	Frequency Score				
3	Daily Angina	0	99.9 (99.9, 100.0)	99.7 (99.4, 99.9)	0.3 (0.0, 0.5)
		10	99.9 (99.9, 100.0)	99.6 (99.4, 99.9)	0.3 (0.1, 0.6)
		20	99.7 (99.5, 99.9)	98.4 (97.4, 99.2)	1.3 (0.4, 2.2)
	Weekly Angina	30	99.6 (99.4, 99.8)	98.0 (97.1, 98.8)	1.6 (0.8, 2.5)
		40	99.1 (98.8, 99.4)	95.8 (94.3, 97.1)	3.4 (2.0, 4.8)
		50	98.7 (98.4, 99.1)	94.1 (92.7, 95.5)	4.6 (3.2, 6.1)
	Monthly Angina	60	97.0 (96.4, 97.6)	87.0 (84.9, 89.2)	9.9 (7.7, 12.1)
		70	94.9 (93.9, 95.9)	80.4 (77.6, 83.2)	14.5 (11.4, 17.3)
		80	87.4 (85.0, 89.8)	64.3 (59.9, 68.5)	23.1 (18.3, 28.1)
	No Angina	90	81.1 (78.3, 84.0)	62.4 (58.7, 66.3)	18.6 (13.7, 23.3)
No Angina	100	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
12	Daily Angina	0	100.0 (100.0, 100.0)	99.9 (99.8, 100.0)	0.1 (0.0, 0.2)
		10	100.0 (99.9, 100.0)	99.9 (99.7, 100.0)	0.1 (0.0, 0.2)
		20	99.9 (99.8, 99.9)	99.3 (98.9, 99.7)	0.5 (0.1, 1.0)
	Weekly Angina	30	99.8 (99.7, 99.9)	99.2 (98.7, 99.5)	0.7 (0.3, 1.1)
		40	99.6 (99.4, 99.7)	98.2 (97.4, 98.8)	1.4 (0.7, 2.1)
		50	99.4 (99.2, 99.5)	97.4 (96.7, 98.1)	1.9 (1.2, 2.7)
	Monthly Angina	60	98.4 (98.0, 98.7)	93.9 (92.6, 95.1)	4.4 (3.2, 5.8)
		70	97.1 (96.4, 97.8)	90.3 (88.2, 92.1)	6.8 (4.9, 8.8)
		80	92.5 (90.7, 94.2)	79.3 (75.5, 82.9)	13.1 (9.1, 17.1)
	No Angina	90	89.2 (87.0, 91.3)	75.7 (72.0, 79.2)	13.5 (9.5, 17.6)
No Angina	100	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
36	Daily Angina	0	100.0 (100.0, 100.0)	100.0 (99.9, 100.0)	0.0 (0.0, 0.1)
		10	100.0 (100.0, 100.0)	99.9 (99.9, 100.0)	0.0 (0.0, 0.1)
		20	99.9 (99.9, 100.0)	99.7 (99.6, 99.9)	0.2 (0.1, 0.3)
	Weekly Angina	30	99.9 (99.9, 99.9)	99.7 (99.5, 99.8)	0.2 (0.1, 0.4)
		40	99.8 (99.7, 99.8)	99.3 (99.0, 99.5)	0.5 (0.3, 0.8)
		50	99.6 (99.5, 99.7)	98.9 (98.6, 99.2)	0.7 (0.4, 1.0)
	Monthly Angina	60	98.9 (98.7, 99.1)	97.4 (96.9, 97.9)	1.5 (1.0, 2.0)
		70	97.8 (97.4, 98.3)	95.6 (94.7, 96.4)	2.2 (1.4, 3.1)
		80	94.0 (92.8, 95.2)	89.3 (87.3, 91.1)	4.7 (2.5, 6.9)
	No Angina	90	91.3 (89.8, 92.7)	85.1 (82.8, 87.2)	6.2 (3.7, 8.6)
No Angina	100	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	

Probability of Improvement  $\geq$  20 Points (95% Credible Interval) in SAQ-7 Angina Frequency Score, as function of Baseline Angina Frequency over time

Baseline SAQ-7 Angina			Invasive	Conservative	Difference
Month	Frequency Score				
3	Daily Angina	0	99.9 (99.8, 100.0)	99.5 (99.1, 99.8)	0.4 (0.1, 0.8)
		10	99.6 (99.3, 99.8)	97.8 (96.3, 99.1)	1.8 (0.5, 3.3)
		20	99.5 (99.2, 99.8)	97.3 (95.7, 98.6)	2.2 (0.8, 3.7)
	Weekly Angina	30	98.8 (98.3, 99.3)	94.3 (91.7, 96.5)	4.5 (2.2, 7.1)
		40	98.3 (97.8, 98.9)	92.2 (89.5, 94.5)	6.2 (3.8, 8.8)
		50	96.0 (95.0, 96.9)	83.1 (79.6, 86.5)	12.9 (9.5, 16.7)
	Monthly Angina	60	93.3 (92.0, 94.6)	74.4 (70.9, 78.0)	18.9 (15.2, 22.7)
		70	82.0 (79.0, 84.9)	50.1 (45.7, 54.5)	32.0 (26.7, 37.3)
		80	68.8 (64.3, 73.7)	36.4 (32.1, 40.8)	32.4 (26.0, 38.7)
	No Angina	90	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	100	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
12	Daily Angina	0	100.0 (99.9, 100.0)	99.8 (99.6, 100.0)	0.2 (0.0, 0.4)
		10	99.8 (99.7, 99.9)	99.1 (98.4, 99.7)	0.7 (0.1, 1.5)
		20	99.8 (99.6, 99.9)	98.9 (98.2, 99.5)	0.9 (0.3, 1.7)
	Weekly Angina	30	99.5 (99.2, 99.7)	97.6 (96.2, 98.6)	1.9 (0.8, 3.3)
		40	99.2 (98.9, 99.5)	96.6 (95.2, 97.8)	2.6 (1.3, 4.0)
		50	97.9 (97.3, 98.5)	92.1 (90.0, 94.1)	5.9 (3.8, 8.1)
	Monthly Angina	60	96.3 (95.5, 97.1)	87.1 (84.5, 89.4)	9.2 (6.8, 11.9)
		70	89.0 (86.6, 91.3)	69.4 (64.8, 73.8)	19.7 (14.7, 24.6)
		80	79.6 (75.4, 83.4)	54.9 (48.9, 60.1)	24.7 (17.8, 31.2)
	No Angina	90	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	100	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
36	Daily Angina	0	100.0 (100.0, 100.0)	99.9 (99.9, 100.0)	0.1 (0.0, 0.1)
		10	99.9 (99.9, 100.0)	99.7 (99.4, 99.9)	0.3 (0.1, 0.5)
		20	99.9 (99.8, 100.0)	99.6 (99.3, 99.8)	0.3 (0.1, 0.6)
	Weekly Angina	30	99.7 (99.6, 99.8)	99.0 (98.6, 99.4)	0.7 (0.3, 1.2)
		40	99.6 (99.4, 99.7)	98.6 (98.1, 99.0)	1.0 (0.5, 1.5)
		50	98.7 (98.4, 99.0)	96.6 (95.7, 97.4)	2.1 (1.3, 3.0)
	Monthly Angina	60	97.5 (97.0, 97.9)	94.2 (93.1, 95.2)	3.3 (2.2, 4.4)
		70	91.6 (90.1, 93.1)	84.1 (81.6, 86.6)	7.5 (4.6, 10.4)
		80	83.2 (80.3, 86.1)	72.6 (68.5, 76.5)	10.6 (5.7, 15.2)
	No Angina	90	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
	100	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	

13 Supplement 7 – the 7-item Seattle Angina Questionnaire

**The Seattle Angina Questionnaire-7**

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness or angina over the past 4 weeks**.

Place an X in one box on each line.

Activity	Extremely limited	Quite a bit limited	Moderately Limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
a. Walking indoors on level ground	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Gardening, vacuuming or carrying groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Lifting or moving heavy objects (e.g. furniture, children)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Over the past 4 weeks, on average, how many times have you had **chest pain, chest tightness or angina**?

I have had **chest pain, chest tightness or angina**...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (nitroglycerin tablets or spray) for your **chest pain, chest tightness or angina**?

I have taken nitroglycerin...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. Over the past 4 weeks, how much has your **chest pain, chest tightness or angina** limited your enjoyment of life?

It has <b>extremely</b> limited my enjoyment of life	It has limited my enjoyment of life <b>quite a bit</b>	It has <b>moderately</b> limited my enjoyment of life	It has <b>slightly</b> limited my enjoyment of life	It has <b>not</b> limited my enjoyment of life at all
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. If you had to spend the rest of your life with your **chest pain, chest tightness or angina** the way it is right now, how would you feel about this?

<input type="checkbox"/> Not satisfied at all	<input type="checkbox"/> Mostly dissatisfied	<input type="checkbox"/> Somewhat satisfied	<input type="checkbox"/> Mostly satisfied	<input type="checkbox"/> Completely satisfied
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