TECHNICAL APPENDIX for the VICTOR Platform

Anirban Basu[1,2], David Veenstra[1], Josh Carlson[1], Wei-Jhih Wang[1], Kelley Branch[3], Jeff Probstfield[3]

[1]The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, School of Pharmacy, University of Washington, Seattle

[2]The Departments of Health Services and Economics, University of Washington, Seattle

[3]Division of Cardiology, Department of Medicine, University of Washington, Seattle

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INTRODUCTION

Value of Information for Cardiovascular Trials and Other Comparative Research (VICTOR) is a web-based platform that can help researchers planning a comparative cardiovascular disease study using clinical trial or other research designs to estimate the potential value of their study. Such estimates may be useful in justifying the significance of a proposed study, assisting in research prioritization, or even selecting study designs. The valuation technique follows standard Bayesian value of information (VOI) methods. VICTOR computes VOI estimates based on inputs that are gathered in a research proposal that the investigators submit to a funder. VICTOR combines this proposal-specific clinical information with disease progression models, predictive models, US population sizes, and mortality rates. A variety of cardiovascular endpoints can be selected. The value of the study is expressed in terms of life years gained at a population and the per-patient level.

WHAT IS VALUE OF INFORMATION (VOI)?

Value of Information (VOI) is an approach that applies methods from economic theory and decision analysis to estimate the clinical and economic returns to society from a clinical study. VOI analyses can form quantitative estimates of the potential impact of a research study by quantifying three factors: 1) How much will a research study decrease uncertainty in the estimates of the population-level effects that are being studied; 2) How clinical practice will be influenced by the findings (often immediate adoption of research findings in clinical practice is assumed to generate upper bounds on the value of research); and 3) how much of these changes in clinical practice will lead to improved health outcomes for the target population.

Ultimately, VOI can also inform the return on investment (ROI) of research by comparing the impact of the research to the costs of conducting the study.

WHAT DOES THIS DOCUMENT DESCRIBE?

This document describes the underlying cardiovascular simulation model that VICTOR employs to calculate VOI estimates. It identifies the parameters that VICTOR asks investigators to provide as part of these calculations and the parameters that are already embedded in the simulation model. For the embedded parameters, the document presents all the sources and estimates used and also provides a validation of these estimates by comparing them to external data.

THE VICTOR MODEL

Minimal modeling approach

The underlying cardiovascular model(s) in the VICTOR platform uses what is termed a 'minimal modeling' approach. The purpose of minimal modeling is to conduct VOI calculations without developing a complex disease simulation model that follows patients from treatment initiation through end of life, accounting for all potential health states during the lifetime. A minimal model follows patients over a limited time-period and is able to apply expected payoffs at the end of that time-period when a prior clinical trial directly provides data on a comprehensive measure of the benefit of the interventions examined, or prior clinical and epidemiological evidence could be linked with ease to estimate a comprehensive measure of the benefit of the interventions examined. The advantage of minimal model lies in obtaining effects of treatments on comprehensive lifetime outcomes faster than running a full model, and thereby being able to compute VOI metrics faster.

The minimal model in VICTOR

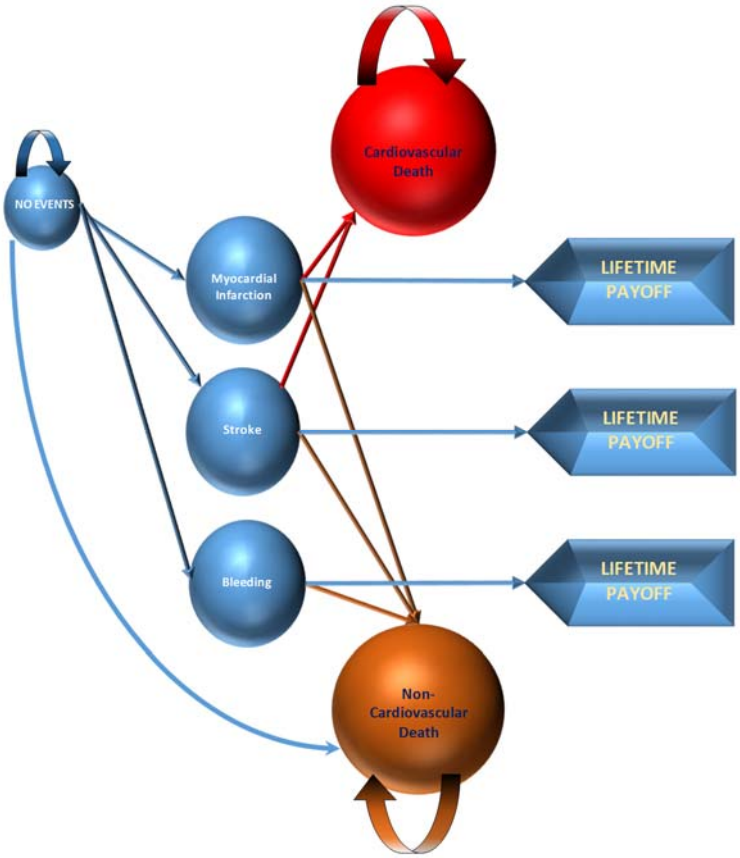


Figure 1: THE VICTOR MINIMAL MODEL

The minimal model in VICTOR is a simple Markov model continues to follow a cohort of patients until they experience one of the primary or secondary endpoints or the end of the treatment effectiveness duration, specified by the user. At that point a life-time payoff (e.g. life-expectancy) is calculated based on age, population characteristics (e.g. what fraction are males) and the type of event using validated life–tables. The minimal model of VICTOR is illustrated here.

VICTOR parameters for life-expectancy calculations and validation.

For the VICTOR Platform, this implies that whenever the model is asked to stop accruing the benefits of an intervention, lifetime payoffs at that point should be readily available in order to calculate the expected outcomes over the lifetime of patients. Since the VICTOR currently models life-expectancy, one must obtain estimates of life-expectancy at any age and with and without any event such as MI or stroke.

Our life expectancy estimate come from the following sources:

1. General Life expectancy by gender – CDC 2009 Life tables[i]
2. Standard Mortality Ratios (SMRs) for Myocardial Infarction[ii]
3. Standard Mortality Ratios (SMRs) for Stroke[iii]

Age-specific and time-from-event-specific SMRs (Table 1 and 2) were applied to standard gender-specific life-table estimates to obtain age and gender-specific probabilities of death and age, gender and event-specific life expectancies. Life-expectancy estimates were smoothed over age using a non-parametric locally-weighted regression. Uncertainty in life-expectancies were obtained from the reported uncertainty of the SMRs. These results are presented in Figures 2 and 3.

Although results in Figures 2 and 3 are based on a 0% discount rate, analyses were repeated under different positive discount rates to obtain estimates for discounted life expectancies.

Life expectancy estimates were obtained from ages 30 – 89 years. External validation of these estimates were conducted in comparison to MI-specific life-expectancy estimated by Bucholz et al.[iv] using Medicare data for patients of age 65 years or older (Figure 4).

RESULTS

Table 1: Standard Mortality Ratios for myocardial infarctions (MI).[ii]

Age at MI	Year since MI	SMR for First MI			SMR for Repeat MI		
		Mean	(95%	CI)	Mean	(95%	CI)
FOR MALES							
30-54	1	3.877	3.357	4.479	7.590	5.145	11.266
30-54	2	2.898	2.610	3.218	5.673	4.000	8.094
30-54	3	2.490	2.199	2.821	4.874	3.370	7.095
30-54	4	2.611	2.277	2.994	5.111	3.490	7.531
30-54	5	2.989	2.571	3.476	5.851	3.940	8.743
30-54	6	2.666	2.181	3.260	5.219	3.343	8.200
30-54	7	2.076	1.451	2.969	4.064	2.224	7.468
30-54	7+	2.000	1.500	3.000	3.915	2.299	7.546
55-64	1	3.370	3.098	3.667	6.504	5.096	8.240
55-64	2	2.260	2.117	2.412	4.362	3.482	5.420
55-64	3	1.944	1.798	2.101	3.752	2.958	4.721
55-64	4	1.903	1.740	2.081	3.673	2.862	4.676
55-64	5	2.148	1.945	2.372	4.146	3.200	5.330
55-64	6	2.141	1.886	2.430	4.132	3.102	5.461
55-64	7	2.194	1.800	2.674	4.234	2.961	6.009
55-64	7+	2.000	1.500	3.000	3.860	2.468	6.742
65-74	1	3.445	3.273	3.626	6.132	5.334	6.985
65-74	2	2.137	2.049	2.229	3.804	3.339	4.293
65-74	3	1.954	1.859	2.053	3.478	3.029	3.954
65-74	4	1.924	1.817	2.037	3.425	2.961	3.923
65-74	5	2.002	1.874	2.140	3.564	3.054	4.122
65-74	6	1.988	1.824	2.165	3.539	2.972	4.170
65-74	7	1.772	1.533	2.048	3.154	2.498	3.945
65-74	7+	1.750	1.500	2.000	3.115	2.444	3.852
75-84	1	3.026	2.920	3.136	5.068	4.615	5.521
75-84	2	1.973	1.914	2.033	3.304	3.026	3.579
75-84	3	1.895	1.828	1.965	3.174	2.890	3.459
75-84	4	1.824	1.745	1.907	3.055	2.758	3.357
75-84	5	1.908	1.807	2.014	3.196	2.857	3.545
75-84	6	1.686	1.562	1.820	2.824	2.469	3.204
75-84	7	1.477	1.288	1.694	2.474	2.036	2.982
75-84	7+	1.500	1.000	2.000	2.512	1.581	3.521
85+	1	2.482	2.378	2.590	3.525	3.190	3.924
85+	2	1.727	1.661	1.795	2.453	2.228	2.720
85+	3	1.570	1.489	1.655	2.230	1.998	2.507
85+	4	1.691	1.581	1.809	2.402	2.121	2.741
85+	5	1.595	1.449	1.756	2.266	1.944	2.661
85+	6	1.821	1.593	2.081	2.587	2.137	3.153
85+	7	1.588	1.210	2.084	2.256	1.623	3.157
85+	7+	1.500	1.000	2.000	2.131	1.342	3.030

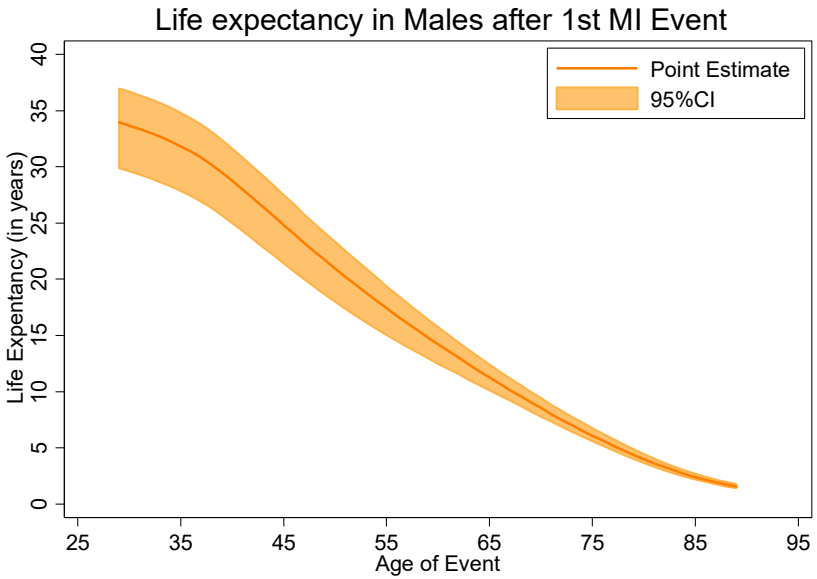
Table 1 (contd.): Standard Mortality Ratios for myocardial infarctions (MI).[ii]

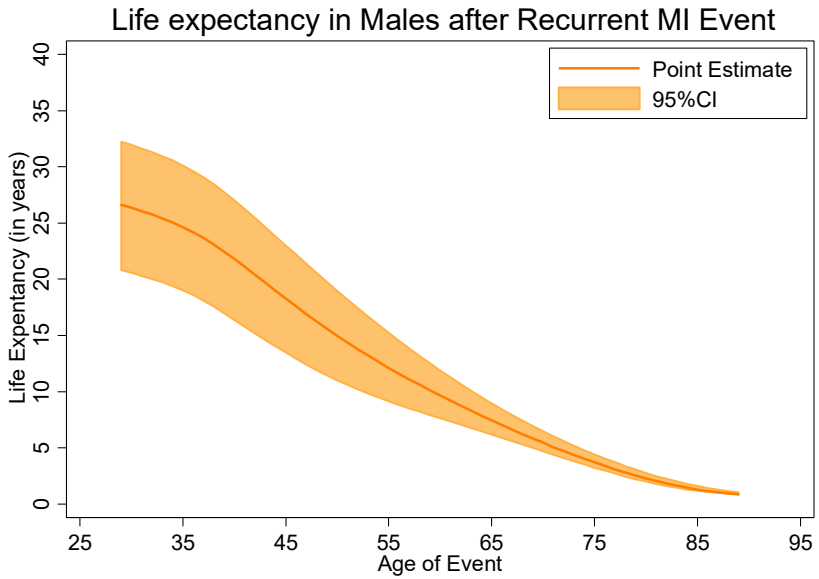
Age at MI	Year since MI	SMR for First MI			SMR for Repeat MI		
		Mean	(95%	CI)	Mean	(95%	CI)
FOR FEMALES							
30-54	1	8.456	6.573	10.885	19.027	12.752	28.519
30-54	2	6.468	5.388	7.765	14.553	10.453	20.344
30-54	3	5.347	4.276	6.685	12.031	8.295	17.515
30-54	4	5.554	4.330	7.123	12.497	8.400	18.662
30-54	5	6.045	4.556	8.022	13.601	8.839	21.018
30-54	6	5.507	3.777	8.030	12.391	7.327	21.039
30-54	7	5.225	2.811	9.711	11.756	5.453	25.443
30-54	7+	5.000	3.000	10.000	11.250	5.820	26.200
55-64	1	6.674	5.823	7.649	12.881	10.191	16.217
55-64	2	3.857	3.443	4.321	7.444	6.025	9.161
55-64	3	3.680	3.234	4.188	7.102	5.660	8.879
55-64	4	3.436	2.951	4.000	6.631	5.164	8.480
55-64	5	3.453	2.883	4.135	6.664	5.045	8.766
55-64	6	3.732	2.990	4.660	7.203	5.233	9.879
55-64	7	3.345	2.310	4.845	6.456	4.043	10.271
55-64	7+	2.000	1.500	3.000	3.860	2.625	6.360
65-74	1	5.330	4.963	5.725	9.487	8.337	10.706
65-74	2	3.410	3.218	3.613	6.070	5.406	6.756
65-74	3	3.072	2.868	3.290	5.468	4.818	6.152
65-74	4	3.084	2.851	3.335	5.490	4.790	6.236
65-74	5	3.140	2.864	3.441	5.589	4.812	6.435
65-74	6	3.331	2.972	3.734	5.929	4.993	6.983
65-74	7	2.685	2.189	3.294	4.779	3.678	6.160
65-74	7+	2.000	1.000	3.000	3.560	1.680	5.610
75-84	1	3.904	3.752	4.062	6.168	5.704	6.621
75-84	2	2.410	2.329	2.494	3.808	3.540	4.065
75-84	3	2.388	2.294	2.485	3.773	3.487	4.051
75-84	4	2.395	2.284	2.511	3.784	3.472	4.093
75-84	5	2.333	2.198	2.475	3.686	3.341	4.034
75-84	6	2.434	2.253	2.629	3.846	3.425	4.285
75-84	7	2.174	1.898	2.490	3.435	2.885	4.059
75-84	7+	2.000	1.000	3.000	3.160	1.520	4.890
85+	1	2.505	2.419	2.594	3.357	3.121	3.606
85+	2	1.630	1.579	1.684	2.184	2.037	2.341
85+	3	1.612	1.547	1.679	2.160	1.996	2.334
85+	4	1.729	1.642	1.820	2.317	2.118	2.530
85+	5	1.788	1.669	1.915	2.396	2.153	2.662
85+	6	1.703	1.537	1.887	2.282	1.983	2.623
85+	7	1.305	1.051	1.621	1.749	1.356	2.253
85+	7+	1.500	1.000	2.000	2.010	1.290	2.780

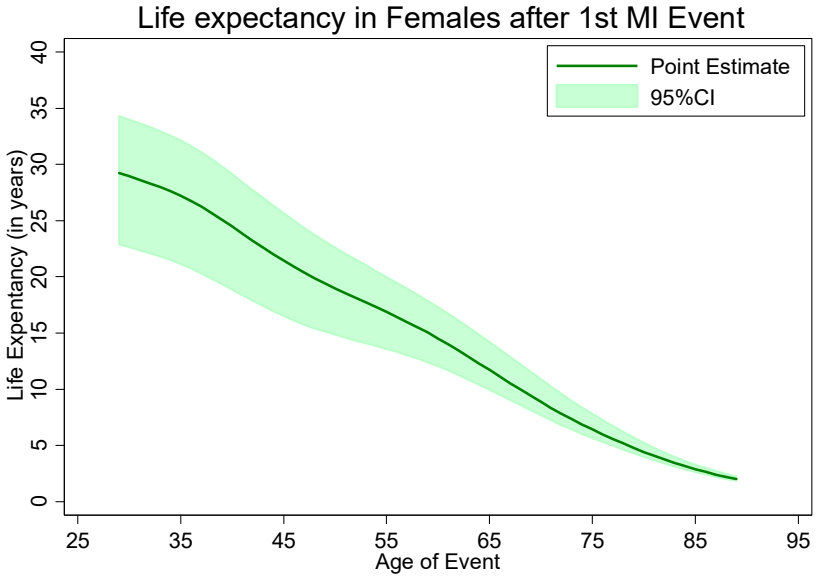
Table 2: Standard Mortality Ratios for Stroke among patients 25 years or older.[iii]

Year(s) since stroke	Mean SMR	(95%	CI)
0-1	4.73	4.34	5.15
1-5	2.31	2.15	2.47
5-10	2.37	2.17	2.58
10-15	2.28	1.92	2.7

Figure 2: AGE AND GENDER-SPECIFIC LIFE EXPECTANCIES AFTER MI







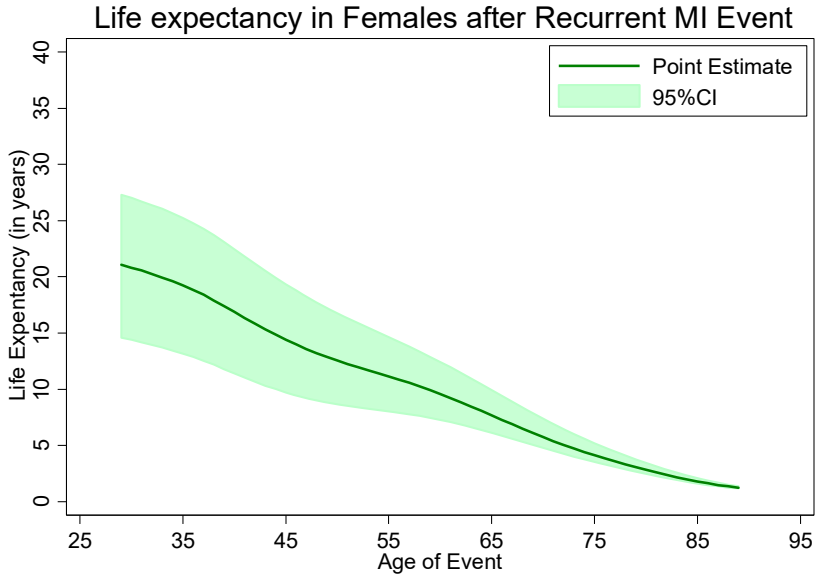
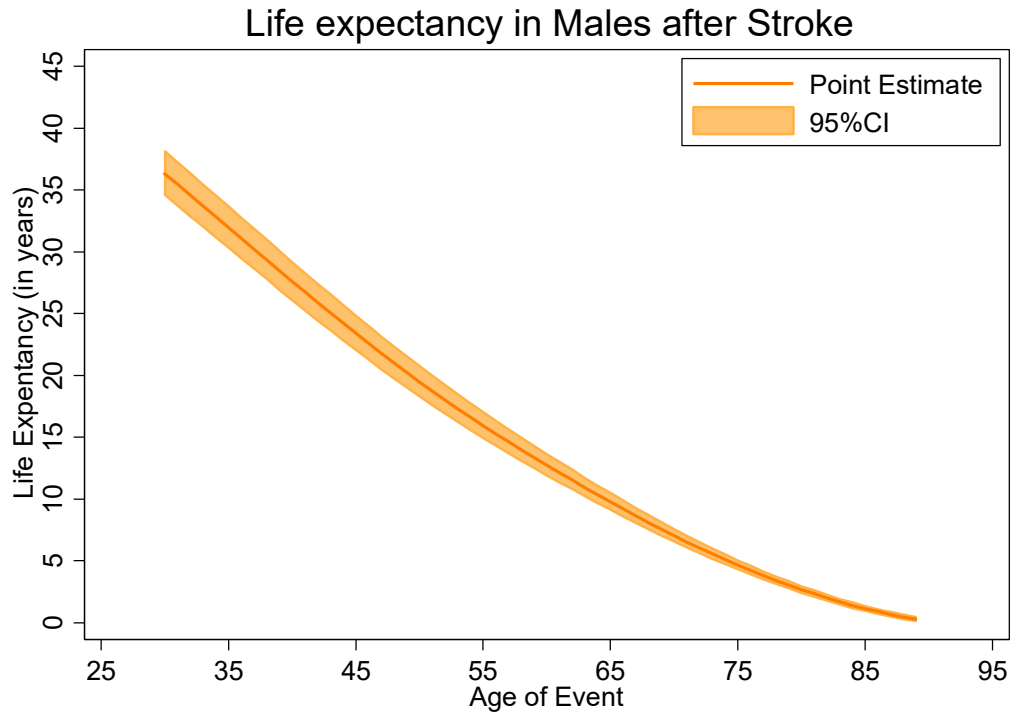


Figure 3: AGE-SPECIFIC LIFE EXPECTANCIES AFTER STROKE



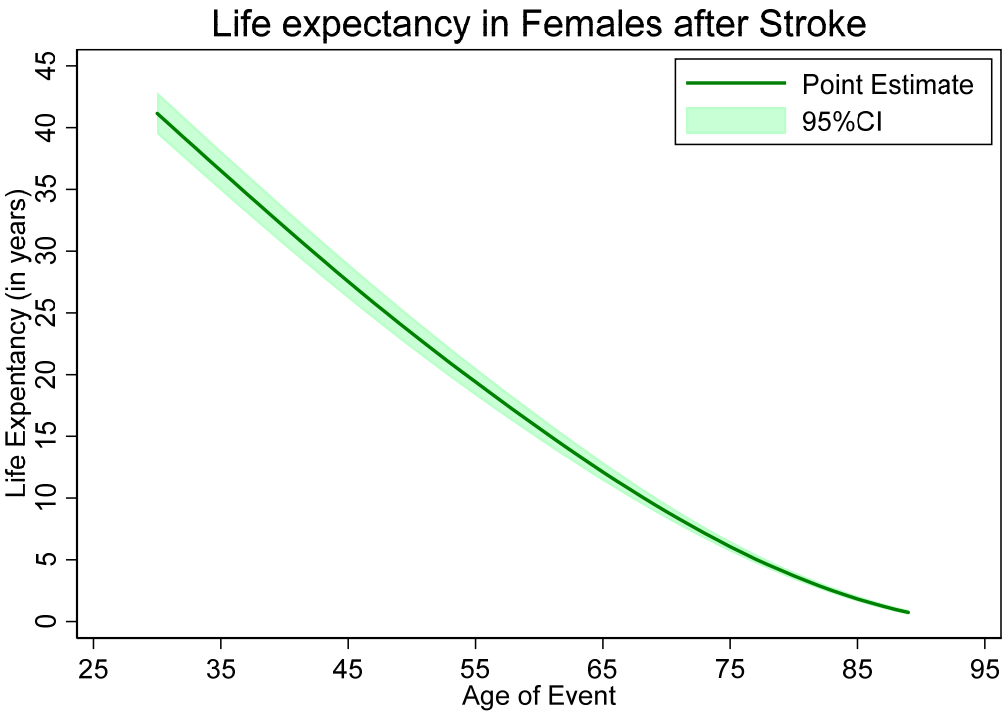
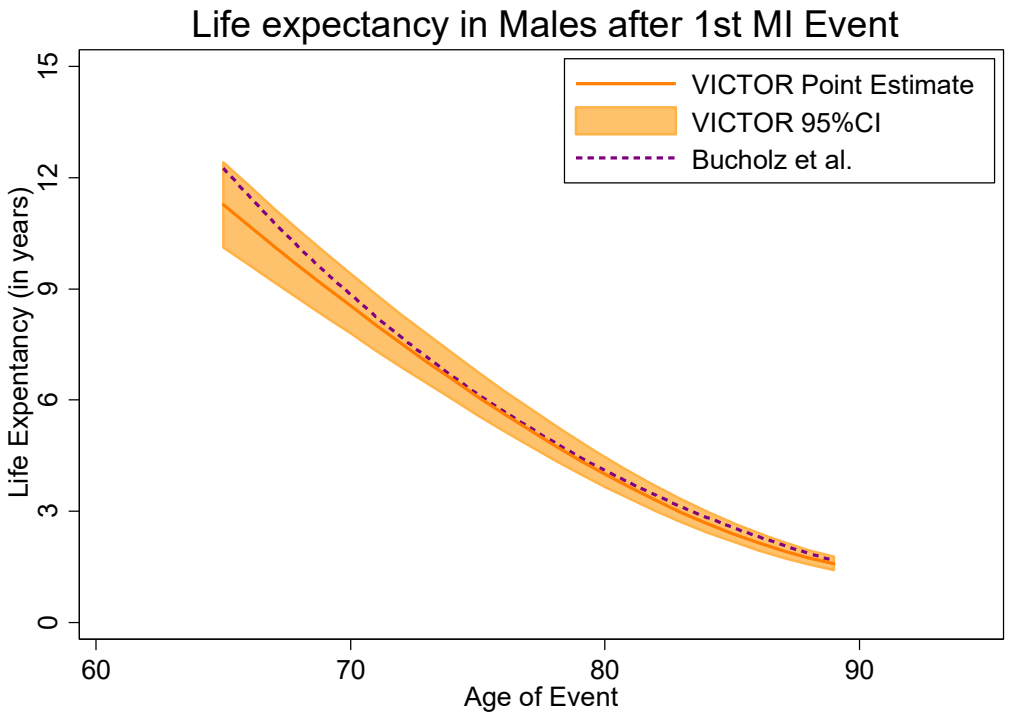
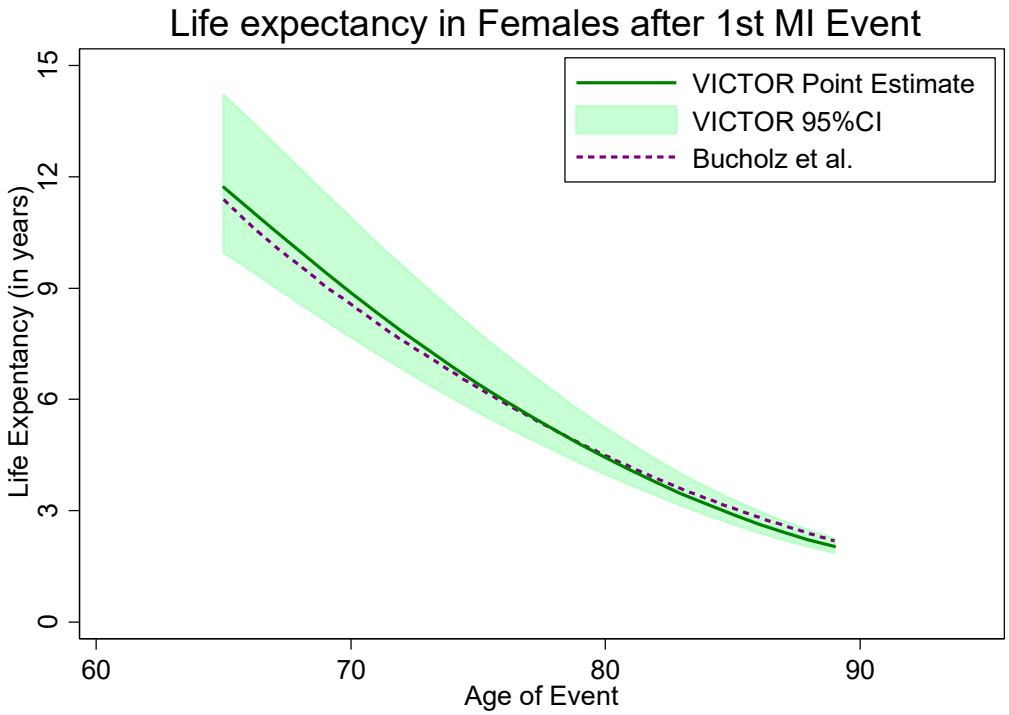


Figure 4: EXTERNAL VALIDATION AGAINST AGE, GENDER-SPECIFIC LIFE EXPECTANCIES AFTER MI ESTIMATED FROM MEDICARE BENEFICIARY DATA[iv]





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