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Analysis of the Bypass Angioplasty Revascularization Investigation Trial Using a Multi-State Model of Clinical Outcomes

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Abstract

Current cardiovascular randomized trials typically use composite outcomes. We hypothesized that the Bypass Angioplasty Revascularization Investigation (BARI) outcomes and conclusions would differ using a multi-state model relative to the intervention for the composite outcome of death and nonfatal Q-wave myocardial infarction (MI). We employed a multi-state model which uses transition paths to simultaneously assess multiple endpoints. Using the 10-year follow up BARI data, we post hoc analyzed outcomes according to three transition paths: 1) from intervention to MI; 2) from intervention to death; 3) from MI to death. Among 1829 patients randomized to the intervention of percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG), 700 (38%) experienced the composite event D/MI which included 230 (13%) nonfatal MI, and 470 (26%) death without antecedent nonfatal MI, while 79 of 230 (34%) experienced death following nonfatal MI. Outcomes of the three individual transition paths were analyzed by a multi-state model. Contrary to standard survival analyses, after adjustment for baseline clinical covariates, outcomes following PTCA or CABG were not significantly different for intervention to MI ($p=0.33$) or intervention to death ($p=0.23$), but MI to death favored CABG ($p=0.02$). Deconstruction of the BARI data using a multi-state model identifies a significant difference in individual transition stage outcomes and therefore trial conclusions in contrast to the standard methods of survival analysis. These observations suggest multi-state models should be considered in the design and analysis of randomized cardiovascular trials which use composite outcomes.

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Keywords

bypass; angioplasty; coronary; revascularization; multi-state model

Multiple endpoints, such as death, non-fatal stroke, and non-fatal myocardial infarction (MI), are ubiquitous in cardiovascular clinical trials. To detect a treatment effect, composite outcomes, e.g. death/stroke/MI, are commonly utilized. A given therapeutic intervention may selectively influence one of individual outcomes but not the other(s), potentially resulting in erroneous intervention conclusions. With more than one outcome of interest, separate analyses are ideally performed for each outcome, however these are typically underpowered, and separate analyses fail to take into account correlations between different outcomes. In contrast, composite outcomes may disguise the treatment effect for specific outcomes. Multi-state models analyze data with survival as the ultimate outcome when intermediate state(s) are identified. The treatment effect is investigated through patients' transitions among various states. Prior work in a variety of non-cardiological medical interventions has identified the value of this modeling¹⁻⁶. For example, Anderson et al.¹ applied a multi-state model to study liver cirrhosis and Putter et al.⁴ used a multi-state model to investigate the treatment for breast cancer. Multi-state models have been used in a wide variety of health condition trials for both accuracy and cost considerations³⁻⁶. We hypothesized that the Bypass Angioplasty Revascularization Investigation (BARI) outcomes and conclusions would differ using a multi-state model to deconstruct the individual transitions relative to the intervention for mortality and the composite outcome of death and nonfatal Q-wave myocardial infarction.

Methods

The BARI, a randomized clinical trial in 1829 patients with multi-vessel coronary artery disease tested CABG (n=914) versus PTCA (n=915) at 18 centers in the United States and Canada with 10-year follow up⁷. The primary outcome was mortality from all causes and the secondary outcome was a composite measure of mortality from all cause and the diagnosed nonfatal Q-wave MI. For illustration and comparison, we first conducted the Kaplan-Meier and Cox regression analyses for both the primary outcome and secondary outcome. Then we conducted the analysis of the BARI data using a multi-state model, which has been intensively investigated under the framework of stochastic (or random) processes⁸⁻⁹.

Multi-state models evaluate the movement of patients among various states. There are generally three kinds of states: 1) initial; 2) intermediate (or transitional); 3) final (or absorbing). The initial state is defined to be the starting status for each patient, for example, just after randomization and before intervention. An example of an intermediate or transitional state is development of Q-wave nonfatal MI. Should the patient progress to death, the development of Q-wave nonfatal MI is an intermediate state. An example of the final or absorbing state is when the patient cannot move to other states once reaching this state, e.g. death.

There are different types of multi-state model formulations³. The simplest one is a two-state model with only one transition from the intervention state to the death state, illustrated in Figure 1A. The standard survival model belongs to this category. Another example is the competing risk model with an initial state and several absorbing states, such as death from different causes, illustrated in Figure 1B. The illness-death model is a multi-state model with one initial state, one intermediate state, and one absorbing state, illustrated in Figure 1C. There are also multi-state models with more than one intermediate state, such as repeated events and the bone marrow transplantation model².

The BARI data belongs to the illness-death model with the initial state being the intervention initiation, the intermediate state being diagnosed Q-wave nonfatal MI, and the final state being death. Figure 2 presents the illness-death graph for BARI data with corresponding sample sizes and event percentages for three transition paths – from intervention to death, from intervention to MI and from MI to death. Both the Kaplan-Meier and Cox regression analyses are conducted for each transition path. We choose p-values less or equal to 0.05 to indicate statistical significance. We further stratified results according to procedural MI defined within 30 days after CABG (procedural CABG-MI) and within 7 days after PTCA (procedural PTCA-MI) for the transition path from MI to death. The multi-state model analysis is carried out using the *mstate* R-package⁵.

Results

Table 1 presents the baseline characteristics of the 1829 patients from BARI data and shows that patients from CABG and PTCA groups were comparable regarding to their baseline (pre- intervention state) aspects. The Kaplan-Meier curves with 10-year follow up for mortality and the composite outcome D/MI are illustrated in Figure 3 and demonstrate no significant treatment effects.

Cox regression analyses for mortality and the composite outcome D/MI adjusted by treatment, age, sex, high school education, race, prior history of MI, heart failure, hypertension, history of diabetes, renal dysfunction, and left ventricular ejection fraction are detailed in Table 2. They show that the treatment effects for PTCA versus CABG are not significant for either mortality or composite outcome D/MI. For both outcomes, being older, having heart failure, hypertension, diabetes, renal dysfunction, and smaller LV ejection fraction are significantly related to shorter survival, but being female is significantly related to longer survival for the outcome being mortality and is not significant for the composite outcome. Because Q-wave nonfatal MI is time-related, we then conducted the Cox regression analysis for mortality as the outcome adjusted by the time-dependent covariate nonfatal Q-wave MI with other covariates. Table 3 demonstrates that the time-dependent nonfatal Q-wave MI is significantly related to shorter survival, but there are no significant treatment effects for PTCA versus CABG. The other significant predictors include age, female, heart failure, hypertension, diabetes, renal dysfunction and LV ejection fraction.

To consider the dynamic relationship between the development of nonfatal Q-wave MI and mortality from all causes, we used a multi-state model to deconstruct the composite outcome D/MI to its individual components. We first analyzed each transition path through Cox

regression analysis. Table 4 lists the results from Cox regression analyses for two transition paths from intervention to MI and from intervention to death. It can be seen that the treatment effects for PTCA versus CABG in both transition paths are not significant. For the transition path from intervention to death, it can be seen that being younger, having history of MI or hypertension are significantly related to shorter survival after the intervention without developing MI. For the transition path from intervention to MI, it is shown that being older, being male, having heart failure, hypertension, diabetes, renal function and smaller LV ejection fraction are significantly related to develop MI after the intervention before experiencing death.

Table 5 contains the Cox regression results for the transition path from MI to death with and without including the time length variable from the intervention to MI. It shows that with and without including the time length variable, the treatment effects for PTCA versus CABG are both significant favoring CABG. Age, diabetes, and LV ejection fraction are significant predictors for death. The effect of the added time length variable is not significant and this illustrates that the assumption of Markov property may be reasonable. The Markov property is usually assumed in the multi-state model and the test of the effect of the time length variable is used to test the assumption of the Markov property³.

For each transition path, we also conducted nonparametric Kaplan-Meier analysis for the two treatment groups (Figure 4) which demonstrates no difference in outcomes for transition path from intervention to MI or for that from intervention to death, but a significant intervention effect favoring CABG for the transition path from MI to death. The Kaplan-Meier and Cox regression analyses demonstrate that the treatment effects are not significant for the transition paths from intervention to death and from intervention to MI, but are significant favoring CABG for the transition path from MI to death.

To evaluate the clinical validity of our results, we compared demographics for the transition path from MI to death and found that subjects in the PCTA group were more hypertensive (67% vs 49%, p -value=0.02) compared to those in the CABG group. We further evaluated separate multi-state models for patients with and without diabetes history. We found no significant treatment effects for transition paths from intervention to MI and from intervention to death for patients with and without diabetes, however, CABG outperformed PTCA for patients with diabetes for the transition from MI to death (p -value<0.001), while there is no significant treatment difference for patient without diabetes (p -value=0.76).

We further analyzed results for the transition path from MI to death stratified by procedural and non-procedural MI. Among the total 230 MIs, 45/121 (37%) were procedural CABG-MI while 18/109 (17%) were procedural PTCA-MI. We compared procedural CABG-MI, procedural PTCA-MI, non-procedural CABG-MI, and non-procedural PTCA-MI adjusted by other covariates and presented the results in Table 6. It can be seen that the procedural CABG-MI has better survival than the non-procedural CABG-MI and the procedural PTCA-MI. Age, diabetes, and LV ejection fraction are significant predictors for death.

Discussion

Deconstruction of the 10 year follow-up BARI data using a multi-state model identifies a significant difference in individual transition stage outcomes and therefore conclusions in contrast to the standard methods of survival analysis. Standard survival analyses with Cox regression and Kaplan-Meier estimation for mortality or the composite outcome of death and Q-wave nonfatal MI of the 10-year follow up BARI data show no differences in outcomes for CABG or PTCA. Inclusion of nonfatal Q-wave MI, as a time-dependent covariate in the Cox regression analysis and other adjusted covariates also failed to demonstrate treatment differences. However, the analysis using a multi-state model demonstrates significant treatment differences favoring CABG for patients in a transition path of nonfatal Q-wave MI to death.

These results suggest that standard survival analyses without consideration of the intermediate state – developing MI – may disguise the differing effect of PTCA versus CABG on survival after developing an MI. Using the multi-state model, we can break the process into three transitions and find that for patients with MI, having CABG has longer survival than PTCA; whereas for patients without MI, the effect of CABG versus PTCA survival is not significantly different. This post hoc multi-state model analysis of the existing BARI 10-year follow up data exemplifies the potential value of newer trial approaches for accuracy and cost considerations.

The clinical validity of the current findings is supported by a prior report based on the combined BARI clinical trial and registry of eligible patient cohort¹⁰, as well as the recent CARDIA¹¹ and FREEDOM¹² randomized clinical trials. The BARI investigators found that among patients with diabetes who experienced an acute MI during the study, a previous CABG significantly reduced the risk of death compared with no prior CABG¹⁰. Our results from the multi-state model (Tables 4, 5) are concordant with these prior results with regard to diabetes. Notably, the multi-state model was able to achieve similar results more directly comparable to the prior BARI analyses¹⁰, and at less expense than the clinical trials^{11,12}. This totality of evidence suggests that CABG-revascularization alters the impact of nonfatal Q-wave MI, likely due to less LV systolic dysfunction/heart failure/arrhythmia which are transitions to mortality. However, because these transition variables are seldom captured in clinical trials, we can only suggest this possibility.

Over the last two decades, a number of studies have compared PTCA versus CABG for mortality and composite outcomes. Several of these studies found no outcome differences^{7, 12-14}, while others found PTCA¹⁵ or CABG¹⁶⁻¹⁷ to be superior. Notably, a recent meta-analysis demonstrated superiority of CABG in patients with diabetes¹⁸. Our current results suggest that the composite outcomes used in these trials may lead to differing results due to the CABG and PTCA interventions selectively influencing on one of individual outcome but not the other(s). In addition to providing varying results according to the composite outcomes used, this multi-state model example suggests that the use of composite outcomes may result in erroneous trial conclusions.

Multi-state models are now commonly used in areas other than cardiovascular clinical trials, including liver cirrhosis¹, bone marrow transplant^{2, 19}, breast cancer⁴, heart transplant⁶, lymphocytic leukemia²⁰, psoriatic arthritis²¹, and colon cancer²². While of demonstrated utility, there are two important limitations to conducting the multi-state model analysis. First, the Markov or semi-Markov property is often assumed in practice. Although there are several extended Markov models^{5–6}, standard methods for detecting the violations of this assumption are rare. Second, most of the available software for multi-state model analysis is imbedded in statistical packages and not straightforward to use. Each requires a different data structure and making comparisons among different models is difficult, although a systematic review of existing software is available⁶.

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Figure 1.

A: A graphical representation of two-state model.

B: A graphical representation of competing risk model.

C: A graphical representation of the illness-death model.

Figure 2.

A graphical representation of the multi-state model for the BARI data, showing each transition with corresponding sample size and percentage.

Figure 3.

The Kaplan-Meier curves for death and the composite outcome D/MI. The curves for CABG are drawn using solid lines and those for PTCA are drawn using dashed lines. The thick and black lines are for death and the thin and red lines are for the composite outcome D/MI.

Figure 4.

The Kaplan-Meier curves for each transition in the multi-state model. The curves for CABG are drawn using solid lines and those for PTCA are drawn using dashed lines. A difference between the two treatments is noted for transition of MI to death in the multi-state model.

Table 1

Baseline Characteristics of 1829 BARI patients assigned to coronary artery bypass grafting or percutaneous transluminal coronary angioplasty.

	Coronary artery bypass grafting (n=914)	Percutaneous transluminal coronary angioplasty (n=915)
Age (yr) mean (sd)	60.6±9.6	61.3±9.2
Women	26%	27%
White	89.4%	91.4%
Black	7.4%	4.9%
Other race	3.2%	3.7%
High-school education or less	71%	71%
Myocardial Infarction History	55%	54%
Heart Failure	9%	9%
Hypertension	49%	49%
Renal Dysfunction	2%	3%
Diabetes History	20%	19%
Left Ventricular Ejection Fraction	60.3 (12.5)	60.2 (12.3)

Table 2

Parameter estimates for Cox regression analyses for death and composite outcome death/Myocardial Infarction.

Variable	Coef	SE	P-value
Death			
Percutaneous transluminal coronary angioplasty	0.132	0.096	0.17
Age	0.049	0.006	<0.001
Black	0.147	0.278	0.60
White	-0.194	0.242	0.42
High-school education	-0.118	0.114	0.30
Female	-0.239	0.113	0.03
Myocardial Infarction History	0.029	0.102	0.78
Heart Failure	0.661	0.133	<0.001
Hypertension	0.287	0.101	0.004
Diabetes History	0.859	0.108	<0.001
Renal Dysfunction	0.642	0.258	0.01
Left Ventricular Ejection Fraction	-0.017	0.004	<0.001
Composite Outcome death/ Myocardial Infarction			
Percutaneous transluminal coronary angioplasty	0.002	0.083	0.98
Age	0.026	0.005	<0.001
Black	0.166	0.268	0.54
White	0.027	0.232	0.91
High-school education	-0.086	0.098	0.38
Female	-0.190	0.100	0.06
Myocardial Infarction History	0.141	0.090	0.12
Heart Failure	0.565	0.124	<0.001
Hypertension	0.357	0.089	<0.001
Diabetes History	0.636	0.097	<0.001
Renal Dysfunction	0.531	0.243	0.03
Left Ventricular Ejection Fraction	-0.011	0.004	0.003

Table 3

Parameter estimates for Cox regression analysis for mortality as the outcome with time-dependent myocardial infarction.

Variable	Coef	SE	P-value
Percutaneous transluminal coronary angioplasty	0.140	0.096	0.14
Time-dependent myocardial infarction	0.435	0.142	0.002
Age	0.050	0.006	<0.001
Black	0.179	0.279	0.52
White	-0.190	0.242	0.43
High-school education	-0.129	0.114	0.26
Female	-0.240	0.113	0.03
Myocardial Infarction History	0.009	0.102	0.93
Heart Failure	0.630	0.134	<0.001
Hypertension	0.271	0.101	0.008
Diabetes History	0.866	0.108	<0.001
Renal Dysfunction	0.658	0.259	0.01
Left Ventricular Ejection Fraction	-0.017	0.004	<0.001

Table 4

Parameter estimates for Cox regression analyses for the transition paths from intervention to death and from intervention to Myocardial Infarction.

	Coef	SE	P-value
Intervention to Death			
Percutaneous transluminal coronary angioplasty	-0.173	0.146	0.23
Age	-0.017	0.008	0.04
Black	-0.145	0.511	0.78
White	0.086	0.423	0.84
High-school education	-0.014	0.164	0.93
Female	-0.068	0.175	0.70
Myocardial Infarction History	0.492	0.163	0.003
Heart Failure	0.507	0.232	0.03
Hypertension	0.489	0.155	0.002
Diabetes History	0.278	0.180	0.12
Renal Dysfunction	-0.095	0.589	0.87
Left Ventricular Ejection Fraction	0.001	0.006	0.82
Intervention to Myocardial Infarction			
Percutaneous transluminal coronary angioplasty	0.100	0.102	0.33
Age	0.053	0.007	<0.001
Black	0.214	0.316	0.50
White	-0.079	0.279	0.78
High-school education	-0.124	0.123	0.31
Female	-0.274	0.122	0.02
Myocardial Infarction History	-0.011	0.110	0.92
Heart Failure	0.658	0.146	<0.001
Hypertension	0.293	0.108	0.01
Diabetes History	0.823	0.117	<0.001
Renal Dysfunction	0.726	0.269	0.01
Left Ventricular Ejection Fraction	-0.015	0.004	<0.001

Table 5

Parameter estimates for Cox regression analyses for the transition path from Myocardial Infarction to death with and without including the time length variable from Intervention to Myocardial Infarction.

	Coef	SE	P-value
Myocardial Infarction to Death			
Percutaneous transluminal coronary angioplasty	0.744	0.323	0.02
Age	0.032	0.015	0.03
Black	0.752	0.758	0.32
White	-0.156	0.590	0.79
High-school education	-0.267	0.321	0.41
Female	-0.075	0.320	0.81
Myocardial Infarction History	0.226	0.322	0.48
Heart Failure	0.342	0.354	0.33
Hypertension	0.050	0.307	0.87
Diabetes History	1.407	0.326	<0.001
Renal Dysfunction	0.143	1.060	0.89
Left Ventricular Ejection Fraction	-0.041	0.013	0.001
Myocardial Infarction to Death			
Percutaneous transluminal coronary angioplasty	0.668	0.326	0.04
Age	0.029	0.014	0.05
Race: Black	0.711	0.753	0.34
Race: White	-0.118	0.587	0.84
High-school education	-0.256	0.322	0.43
Female	-0.070	0.315	0.82
Myocardial Infarction History	0.207	0.323	0.52
Heart Failure	0.316	0.348	0.36
Hypertension	0.021	0.308	0.95
Diabetes History	1.375	0.321	<0.001
Renal Dysfunction	0.507	1.109	0.65
Left Ventricular Ejection Fraction	-0.042	0.013	0.001
Time from Intervention to Myocardial Infarction	0.537	0.393	0.17

Table 6

Parameter estimates for Cox regression analyses for the transition path from Myocardial Infarction to death with procedural percutaneous transluminal coronary angioplasty -Myocardial Infarction, procedural coronary artery bypass grafting - Myocardial Infarction, nonprocedural percutaneous transluminal coronary angioplasty - Myocardial Infarction, and nonprocedural coronary artery bypass grafting - Myocardial Infarction.

	Coef	SE	P-value
Myocardial Infarction to Death			
Non-procedural coronary artery bypass grafting - Myocardial Infarction	1.301	0.393	0.001
Non-procedural Percutaneous transluminal coronary angioplasty - Myocardial Infarction	0.107	0.895	0.91
Procedural Percutaneous transluminal coronary angioplasty - Myocardial Infarction	0.967	0.429	0.02
Age	0.034	0.015	0.02
Black	0.870	0.768	0.26
White	-0.040	0.590	0.95
High-school education	-0.414	0.326	0.20
Female	-0.119	0.319	0.71
Myocardial Infarction History	0.199	0.319	0.53
Heart Failure	0.230	0.354	0.52
Hypertension	0.106	0.318	0.74
Diabetes History	1.479	0.329	<0.001
Renal Dysfunction	0.965	1.262	0.44
Left Ventricular Ejection Fraction	-0.095	0.014	<0.001