

The Impact of Postrandomization Crossover of Therapy in Acute Coronary Syndromes Care

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Background—In the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) study, patients assigned enoxaparin or unfractionated heparin (UFH) were treated with alternative anticoagulant therapy after randomization at physician discretion, a practice made possible because the trial was open label. Using SYNERGY as an example, we demonstrate the difficulty of evaluating the effect of postrandomization events in clinical trials and discuss possible methodology.

Methods and Results—Patients with and without postrandomization crossovers were characterized and event rates analyzed. Statistical modeling was performed using inverse probability weighting and landmark analyses to evaluate the potential impact of postrandomization crossovers on event rates and treatment effect. Of 9978 SYNERGY patients, 9613 (96.3%) received at least 1 dose of randomized therapy and are included in these analyses. Of these, 740 (7.7%; 554 enoxaparin; 186 UFH) had postrandomization crossover. Crossover patients had higher unadjusted rates of 30-day death/myocardial infarction (MI) (18.9% versus 14.0%), thrombolysis in MI (TIMI) bleeding (16.9% versus 7.6%), Global Use of Strategies to Open Occluded Coronary Arteries bleeding (4.5% versus 2.3%), and transfusions (32.3% versus 15.2%). Adjustment for timing of crossover relative to the events attenuated the difference noted in death/MI but accentuated the association with TIMI bleeding. After adjustment using the inverse probability weighting technique, only a modest difference in the absolute treatment effect was observed between enoxaparin and UFH on death/MI (0.6% [unadjusted] versus 0.8% [adjusted]) and TIMI major bleeding (1.5% [unadjusted] versus 1.0% [adjusted]). The landmark analysis indicated a significant association between crossover from enoxaparin to UFH and TIMI bleeding but not in the other direction, and no crossover association was found in death/MI.

Conclusions—Postrandomization events in clinical trials are accompanied by substantial confounders that require careful consideration. In SYNERGY, postrandomization crossovers occurred in nearly 10% of patients, abetted by the open-label trial design. These patients had increased incidence of bleeding and death/MI, but after adjustment using several modeling techniques, only a modest impact of postrandomization crossovers on treatment effect was observed. The usual methods of analyzing end points cannot adequately address biases in changing treatment in these patients. The potential biases of membership in a postrandomization subgroup, as well as the methods used to account for the biases, should be considered when weighing the strength of results.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00043784.

(*Circ Cardiovasc Qual Outcomes*. 2011;4:211-219.)

Key Words: enoxaparin ■ heparin ■ acute coronary syndrome ■ clinical trial ■ crossover design

It is common in clinical trials to analyze treatment effects in subgroups within the trial that are defined by postrandomization treatment decisions. Such subgroups have been referred to as “improper” subgroups¹ because of the potentially

profound biases and confounders that lead to these decisions.² Therefore, attempts to analyze differences in treatment effects in these improper subgroups are also biased, and appropriate consideration and statistical analyses need to be applied.

Received January 23, 2009; accepted December 21, 2010.

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Guest Editor for this article was William S. Weintraub, MD.

The online-only Data Supplement is available at <http://circoutcomes.ahajournals.org/cgi/content/full/CIRCOUTCOMES.109.853598/DC1>.

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Circ Cardiovasc Qual Outcomes is available at <http://circoutcomes.ahajournals.org>

DOI: 10.1161/CIRCOUTCOMES.109.853598

Evaluating treatment effects when the intention-to-treat assignment does not necessarily reflect actual treatment received can be problematic as well.

Inhibition of the coagulation cascade has become a fundamental treatment approach for patients with non-ST-segment elevation (NSTEMI) acute coronary syndromes (ACS). Multiple drugs have been developed in an effort to blunt the adverse consequences of coronary thrombosis in this situation. Because of the multiple therapeutic options, individual physicians often develop standard approaches to patient management based in part on existing practice habits. Clinicians may select the agent or combination of agents with which they have the greatest comfort, even when a different drug has already been initiated by another physician. For example, given the ease of use and benefits of enoxaparin in patients with NSTEMI ACS who are managed with a conservative strategy,^{3–5} many patients are started on enoxaparin early in the course of treatment. Because of uncertainty about the use of enoxaparin in the catheterization laboratory, however, many clinicians switch patients to unfractionated heparin (UFH) at the time of the decision to proceed to coronary angiography or percutaneous coronary intervention (PCI).

In the current era of ACS management, therapy switching may be more common because of limited research resources and rapid identification of and initial anticoagulant therapy given to patients with ACS presenting in the emergency department. This switching of therapy poses a problem for clinical trials, which have adapted to the challenge by incorporating postrandomization crossover therapy into their protocols and allowing for the randomization of patients already started on anticoagulant agents.^{6,7} In fact, the practice of crossover was encouraged in the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events), TIMI 11B (Thrombolysis In Myocardial Infarction 11b), and A to Z (Aggrastat to Zocor) trials at the time of catheterization, although its impact on outcomes was not examined in detail.^{3,4,8}

The Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial used an open-label design.⁹ The primary results showed that enoxaparin was noninferior to UFH for the primary end point of death or myocardial infarction (MI) at 30-day follow-up, with a modest excess in bleeding. Within this study, there was an important group of patients who experienced the protocol violation of postrandomization crossover of assigned study therapy to the alternative drug (enoxaparin to UFH or UFH to enoxaparin). Crossover was facilitated, in part, by the open-label design of the study. The present post hoc analyses seek to explore and illustrate the challenges and limitations in randomized clinical trials of analyses of treatment differences when a significant number of treatment protocol violations occur and to compare estimates of the impact of postrandomization crossover on the observed rates of death or MI and bleeding events.

WHAT IS KNOWN

- Postrandomization events in clinical trials are accompanied by substantial confounders that require careful consideration.
- Although imperfect, statistical approaches can be used to limit the biases and confounders, and rigorous modeling techniques are available to do analyses in an attempt to account for potential confounders.

WHAT THE STUDY ADDS

- We conducted post hoc analyses of SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors) data to illustrate the challenges and limitations in randomized clinical trials of analyses of treatment differences when outcomes in subgroups defined by postrandomization events (eg, treatment crossovers) occur; we also compared estimates of the impact of postrandomization crossover on the observed rates of death or myocardial infarction and bleeding events.
- After adjustment using several modeling techniques, only a modest impact of postrandomization crossovers on treatment effect was observed, and thus, we emphasize that the usual methods of analyzing end points cannot adequately address biases in changing treatment in these patients.
- The potential biases of membership in a postrandomization subgroup, as well as the methods used to account for the biases, should be considered when weighing the strength of results.

Methods

Patient Population

The design of the SYNERGY trial and its primary results have been reported previously.^{9,10} Patients with NSTEMI with planned invasive management and at high risk for poor outcomes were recruited. All patients gave informed written consent.

Study Drug Treatment

Patients could have already been directed to begin therapy, including anticoagulant agents, by the treating physician before enrollment. Enoxaparin or UFH was given in an open-label fashion immediately after enrollment according to the randomly assigned treatment. The treatment was to be continued until the patient required no further anticoagulation per the treating physician and at least through angiography and PCI, if performed. Intravenous UFH was given according to a weight-adjusted nomogram (bolus of 60 U/kg [maximum 4000 U] and initial infusion of 12 U/kg per hour [maximum 1000 U/h]).⁸ Enoxaparin was given subcutaneously at a dose of 1 mg/kg every 12 hours. Recommendations for enoxaparin dosing were provided in the study protocol. Recommendations for the dosing of UFH during the study and, in particular, during cardiac procedures also were provided (online-only Data Supplement Appendix A). For patients already on therapy before enrollment, guidelines were provided for transitioning to the randomized therapy (online-only Data Supplement Appendix B).

Information was collected on standard data collection forms. Reasons for early discontinuation of therapy and whether another anticoagulant therapy was administered were systematically collected. For the purpose of this article, the crossover information was reviewed by at least 1 investigator (KWM or NSK) to categorize the

Table 1. Reasons for Postrandomization Crossover by Assigned Treatment

	Enoxaparin (n=554)	UFH (n=186)
Inappropriate crossovers		
Physician preference	180 (32.5)	42 (22.6)
CABG	120 (21.7)	18 (9.7)
Patient transfer	36 (6.5)	6 (3.2)
Accidental	37 (6.7)	12 (6.5)
Total	373 (67.3)	78 (41.9)
Appropriate crossovers		
Bleeding	36 (6.5)	4 (2.2)
Change in diagnosis	1 (0.2)	0
Adverse event (nonbleeding)	10 (1.8)	1 (0.5)
Renal failure	4 (0.7)	0
Exclusion criteria	3 (0.5)	1 (0.5)
Total	54 (9.7)	6 (3.2)
Miscellaneous		
Withdrew consent	9 (1.6)	6 (3.2)
Thrombolysis	8 (1.4)	0
Patient died	2 (0.4)	2 (1.1)
Other	56 (10.1)	16 (8.6)
No reason reported	78 (14.1)	51 (27.4)

Data are presented as no. (%). CABG indicates coronary artery bypass graft.

protocol violations as either appropriate or inappropriate (see Table 1 for categories).

Some of the previous SYNERGY reports that included information on crossovers defined this subgroup based on the location on the form where the treatment information was given (eg, hospital arrival, during randomized therapy, preprocedure). For this study, the actual times of treatment start and stop were used to label treatment received, regardless of the page on which the information was written. The improper subgroup of crossover included patients who received UFH after randomization to enoxaparin or enoxaparin after randomization to UFH. Patients were evaluated in an “as randomized” manner; excluded were those patients who did not receive at least 1 dose of assigned therapy (9613/9978; 96.4%). Thus, the patients excluded received either no drug or crossed at the time of randomization, providing the opportunity to explore the evaluation of the crossovers postbaseline.

Postrandomization crossovers were identified during the routine surveillance of trial operations. Sites were instructed to follow the protocol, and some sites were stopped from further enrollment if reassurance was not provided that routine practice of postrandomization crossover would cease. The statistical analysis plan did not specifically identify this group of patients defined by postrandomization crossovers as a preplanned subgroup analysis.

Statistical Methods

Values are presented as counts and percentages or medians with interquartile ranges. Baseline characteristics and demographics of patients who had postrandomization crossover were compared with those who did not.

Although one cannot fully account for the multiple biases associated with analyses of subgroups defined by postrandomization events, statistical techniques exist to help approximate the unbiased relationship. One method that has been suggested for evaluating this nonrandomized postbaseline factor is the use of a Cox proportional hazards model with crossover as the time-dependent covariate.

Another method of potential usefulness is landmark analysis. Using this approach, the time from randomization until event was divided into time intervals from 0 to 12, 12 to 24, 24 to 36, 36 to 48,

48 to 60, and 60 to 72 hours. Within each of these intervals, patients were included in the interval if they had not crossed to the opposite randomized treatment before the beginning of that interval and had not had an event before the end of the interval. All patients who had postrandomization crossover within an interval were compared with those who had not yet crossed or never crossed. All analyses were made after adjusting for important factors related to outcomes: both baseline and crossover-related factors occurring before or during the interval. These postbaseline factors included PCI, coronary artery bypass graft, and recurrent ischemia. If the hazards within each interval were fairly similar, then these intervals were combined using a generalized linear model to obtain an estimate of the association of crossover with outcome across all of the intervals. The baseline variables selected for these models are based on previously published models.¹¹

Finally, inverse probability weighting (IPW) analysis¹² was used. The IPW analysis is a method developed to estimate what the observed treatment effect would be in SYNERGY if no patients had incurred a postrandomization crossover. The probability of not having a postrandomization crossover is estimated as a function of the covariates using a Cox regression model. Outcomes of the patients who did not cross over to the other treatment are then inverse weighted by the probability of not having a postrandomization crossover, and the estimate of the event rate is calculated as the weighted average of these outcomes.

The IPW method also was applied to estimate expected outcome event rates that would have been observed if the randomized treatment assignment was continued as specified in the protocol or the investigator stopped the initial treatment early for appropriate reasons. Here, outcomes of patients who had not had inappropriate crossovers were inverse weighted by the probability of not having inappropriate crossover, and the estimate of the event rate was calculated as the weighted average of these outcomes. All analyses were performed using SAS version 8.2 (SAS Institute; Cary, NC) and R version 2.0.1 (Vienna, Austria) software.

Results

Overall, 9978 patients were randomized in the SYNERGY trial (4993 enoxaparin; 4985 UFH). Figure 1 shows the pattern of anticoagulant therapy before randomization, through the randomization process, and postrandomization. Overall, 4141 (82.9%) patients who were assigned enoxaparin received only enoxaparin, and 4732 (94.9%) patients assigned to UFH received only UFH. Of the 9978 total patients, 365 (3.7%) received no assigned study drug (298 enoxaparin; 67 UFH). A total of 183 (1.2%) patients changed the type of randomized drug used more than once.

Overall, there were 740 (7.7%) patients who had a postrandomization crossover event: 554 enoxaparin-assigned patients crossed over to UFH, and 186 UFH-assigned patients crossed over to enoxaparin. Forty percent of these crossovers occurred after receiving 72 hours of the initial treatment. Reasons for switching according to treatment assignment are shown in Table 1. The most common reason was physician preference.

The baseline clinical characteristics and demographics of patients who had postrandomization crossover compared with those who did not are shown in Table 2. Figure 2 compares the unadjusted in-hospital bleeding (Global Use of Strategies to Open Occluded Coronary Arteries [GUSTO] severe, TIMI major, and transfusion) and ischemic (30-day and 6-month death or MI and 1-year mortality) outcomes by study drug assignment of those patients who had postrandomization crossover with those who did not. Based on these “naïve” analyses of unadjusted results, it appears that crossover is

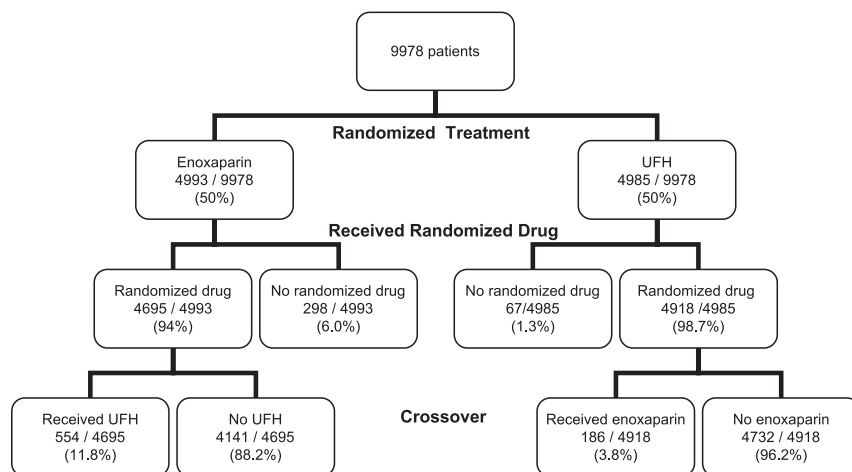


Figure 1. Anticoagulant therapy through the randomization process and postrandomization.

associated with greater treatment differences in efficacy and transfusion outcomes and with worse outcomes regardless of treatment. These data do not account for the timing of events relative to the crossing.

One error often seen in evaluating end points of a postrandomization subgroup is the assignment of treatment to the subgroup itself (Table 3). As previously stated, the patients who experienced crossover had a greater treatment effect (17.5% versus 23.0%) than those who did not (13.8% versus 14.3%) for death or MI. However, a number of the events in the crossover patients occurred while the patients were still receiving the original randomized therapy (43 enoxaparin; 28 UFH). These events occurred during the period of no crossing. If these patients are moved to the no-crossover group, then the rate of outcomes is less for those who crossed (10.5% enoxaparin; 9.0% UFH) than for those who did not (14.7% enoxaparin; 14.8% UFH). The treatment difference diminished compared with the naïve results. For TIMI bleeding, most of the events in patients who received enoxaparin and crossed to UFH occurred after crossover (77 after versus 17 before). For the patients who crossed from UFH to enoxaparin, the timing was similar after and before crossover (15 after versus 13 before). Thus, accounting for timing had a much greater effect on the patients randomized to UFH. The rate of TIMI bleeding dropped from 17.2% to 14.5% in the enoxaparin patients and from 15.5% to 8.9% in the UFH patients.

The timing of the crossover relative to the outcomes is appropriately modeled within a Cox proportional hazards time-dependent model. If type of drug used across time is the time-dependent variable, then there is no difference in the treatment effect for death or MI ($P=0.240$) or for TIMI bleeding ($P=0.681$). Instead of drug use over time, if randomized therapy is included as a baseline factor and crossover is included as a time-dependent covariate, then we find that the randomized therapy is again not statistically significant ($P=0.438$ and $P=0.112$, respectively). However, crossover is significantly associated with TIMI bleeding ($P<0.001$) but not with death or MI ($P=0.195$). In the patients randomized to enoxaparin, the increased risk of TIMI bleeding was only marginally significant between those who

did and did not cross ($P=0.075$). In patients randomized to UFH, the increased risk was very significant ($P<0.001$).

Some of the factors associated with crossover may be patient characteristics. Others are likely to be events and treatments that occur during the hospitalization. The landmark analysis adjusted for a number of these covariates and estimated the association of crossing with outcomes at varying time intervals. The results of this analysis are seen in Figure 3A and 3B, which shows the odds ratios (ORs) and 95% CIs for association of crossover with 30-day death or MI and bleeding.

The trend was for crossing to be associated with worse outcomes, especially after ≈ 24 hours. After accounting for the factors leading up to each landmark period and the crossover during the periods, randomized treatment remained nonsignificant in association with 30-day death or MI ($P=0.8816$). Crossover itself was not statistically significant ($P=0.2656$). For TIMI bleeding, both randomized treatment and crossover were statistically significant when evaluated across all of the landmark periods ($P=0.0088$ and $P<0.001$, respectively).

IPW indicated that the outcomes of the study would have changed little had no patient crossed. Baseline covariates and precrossover factors are included into models to determine estimates of what the outcome rates would have been if patients had not crossed. For 30-day death or MI, the original rates were 13.9% and 14.5% (enoxaparin versus UFH). After applying IPW, the rates were 13.3% and 14.2%, respectively. For TIMI bleeding, the rates changed from 9.1% versus 7.6% to 8.2% versus 7.2%, respectively. Some crossing of treatment appeared to be for legitimate reasons. Estimates of what the outcome rates would have been if patients had crossed only when appropriate were 13.9% versus 14.4% for death or MI and 9.0% versus 7.3% for TIMI bleeding.

As a sensitivity analysis, the time-dependent Cox proportional hazards model and censored analyses (as performed for the primary manuscript with treatment defined by randomized assignment and timing of therapy by case report form checkboxes) were replicated after excluding patients who did not receive their assigned therapy. The results for the Cox models and the censored safety analysis were similar to those in the primary manuscript. The exception was the censored

Table 2. Baseline Demographics and In-Hospital Procedures and Medications

	No Postrandomization Crossover (n=8873)	Postrandomization Crossover (n=740)	Postrandomization Crossover Study Drug	
			Enoxaparin (n=554)	UFH (n=186)
Age, y	68.0 (61.0, 75.0)	67.0 (60.5, 75.0)	67.0 (60.0, 75.0)	68.0 (61.0, 74.0)
Female sex	33.9	30.9	31.8	28.5
Region				
Australia/New Zealand	4.2	4.1	4.3	3.2
Europe	18.7	18.4	14.1	31.2
North America	71.9	76.1	80.3	63.4
Race				
White	85.9	85.0	85.4	83.9
Black	6.3	6.5	6.3	7.0
Asian	1.0	2.3	2.5	1.6
Hispanic	4.9	3.8	3.8	3.8
Native American	0.5	0.4	0.2	1.1
Pacific Islander	0.3	0.4	0.4	0.5
Other	1.2	1.6	1.4	2.2
Weight, kg	80.0 (70.0, 91.0)	80.0 (70.0, 92.0)	80.0 (70.0, 92.0)	80.0 (70.0, 93.0)
Heart rate, beats/min	71.0 (62.0, 81.0)	73.0 (64.0, 83.0)	72.0 (64.0, 80.0)	76.0 (65.0, 87.0)
Blood pressure, mm Hg				
Systolic	130.0 (117.0, 147.0)	130.0 (116.0, 146.0)	130.0 (115.0, 146.0)	130.0 (120.0, 146.0)
Diastolic	72.0 (62.0, 81.0)	73.0 (64.0, 81.0)	72.0 (63.0, 81.0)	75.0 (67.0, 81.0)
Killip class				
I	88.0	80.4	81.7	76.7
II	9.5	16.3	15.0	20.5
III	2.0	2.5	2.6	2.3
IV	0.5	0.5	0.7	0.6
History of hypertension	68.3	65.9	63.5	73.1
History of diabetes mellitus	29.3	30.7	29.1	35.5
Prior angina	45.7	47.2	43.9	57.1
Prior infarction	28.2	28.8	28.2	30.8
Prior CABG	16.8	15.1	13.9	18.8
Prior PCI	20.4	18.0	17.5	19.4
Prior congestive heart failure	9.0	11.9	10.8	15.1
Prior stroke	4.9	5.4	5.4	5.4
History of peripheral vascular disease	9.8	11.9	12.4	11.8
Smoking status				
Never	41.0	38.2	38.4	37.6
Previous	35.0	35.8	34.8	38.7
Current	24.0	25.9	26.7	23.7
Hypercholesterolemia	59.3	55.1	54.8	56.0
Family history of CAD	45.7	44.4	44.5	43.8
Time from symptom onset to enrollment, h	14.6 (8.5, 20.6)	14.4 (8.3, 21.3)	14.3 (8.4, 21.1)	14.7 (7.8, 22.0)
Time from hospital admission to enrollment, h	8.0 (3.4, 15.4)	8.4 (3.5, 15.2)	8.7 (3.6, 15.6)	6.8 (3.2, 14.3)
UFH, prerandomization	30.7	30.0	31.0	26.9
Enoxaparin, prerandomization	44.6	44.1	43.5	45.7

(Continued)

Table 2. Continued

	No Postrandomization Crossover (n=8873)	Postrandomization Crossover (n=740)	Postrandomization Crossover Study Drug	
			Enoxaparin (n=554)	UFH (n=186)
In-hospital procedures				
Catheterization	92.0	95.9	96.8	93.5
Time to angiography, h	21.6 (6.6, 42.6)	24.0 (14.3, 49.6)	24.8 (16.9, 52.7)	21.2 (4.8, 41.9)
PCI	47.4	45.9	49.8	34.4
Time to PCI, h	22.2 (6.3, 46.9)	47.5 (21.4, 100.2)	50.2 (25.0, 118.1)	26.8 (11.7, 53.1)
CABG	16.9	38.4	37.0	42.5
Time to CABG, h	89.2 (44.7, 164.2)	109.5 (49.3, 182.3)	97.3 (47.0, 169.7)	134.3 (67.7, 280.3)
Any blood transfusion	15.2	32.3	30.3	38.2
Medication on admission				
β -blocker	66.8	68.9	70.0	65.6
ACE inhibitor	33.7	35.1	32.9	41.9
Statin	42.2	41.5	39.9	46.2
Clopidogrel	28.5	29.1	28.0	29.4
Aspirin	91.7	92.3	92.6	91.4
Medication on discharge				
β -blocker	78.4	79.3	78.3	82.3
ACE inhibitor	58.4	59.6	57.2	66.7
Statin	71.1	70.7	71.5	68.3
Clopidogrel	54.7	46.5	49.3	38.2
Aspirin	89.8	87.0	88.4	82.8

Data are presented as median (quarter 1, quarter 3) or as percent. ACE indicates angiotensin-converting enzyme; CABG, coronary artery bypass graft; CAD, coronary artery disease.

analysis of death or MI. In this case, the randomized treatment difference was no longer significant (hazard ratio, 0.96; 95% CI, 0.86 to 1.07).

Discussion

This analysis from a contemporary pragmatic international trial shows that when an open-label trial design was used, $\approx 10\%$ of patients were treated with the non-study drug-assigned therapy, and this decision typically was not driven by clear clinical need. In SYNERGY, crossover of anticoagulant therapy could occur at 2 different time points during clinical care and protocol follow-up. The first was at the time of randomization when patients who had already been started on anticoagulant therapy were randomly assigned to an alternative agent. This switching was allowed by the protocol. The second was after randomization when a clinical decision was made to treat the patient with an alternative anticoagulant. Therapy begun before randomization was an independent predictor of worse outcomes, and consistent treatment with only 1 anticoagulant before and after randomization was associated with fewer outcomes in patients treated with enoxaparin compared with UFH.⁶ The current analyses extend the statistical issues to include both postrandomization crossover and the timing of the postrandomization crossover.

Unadjusted analyses show that when anticoagulant regimens were switched after randomization in SYNERGY, ischemic events and bleeding were more common. Many potential reasons for this finding can be considered, and the

analyses themselves have the inherent limitations both of unadjusted and postrandomization comparisons. Several factors need to be considered in this example of postrandomization crossovers in SYNERGY. The timing of the postrandomization crossover relative to the initial drug (the randomized drug in this example), the events that led to the crossover, and the timing of the crossing relative to the outcome all provide their own unique biases.

The generalizability of the results of the crossing analyses would be questionable. The clinical correlate is that when treatment is started on a patient in the emergency department, the decision to subsequently cross is unknown. Thus, use of these results in the emergency department would be difficult and should be viewed cautiously.

The hazards of analyses performed on subgroups defined by postrandomization events have been recognized and described.² A classic approach would have been to perform a time-dependent covariate analysis or a censored analysis, but these approaches have important limitations. The hazard ratio is assumed constant across all time, which may not be an appropriate assumption. One can adjust for multiple factors that occur during the hospitalization, but inclusion of these factors into the model make interpretation of results more difficult. The landmark technique provides valuable information about the changes in risk for crossing over time. However, decisions about the size of the landmark periods can be somewhat arbitrary and could influence results.

Although the IPW technique is novel, we believe that it provides the most robust method by which to assess the

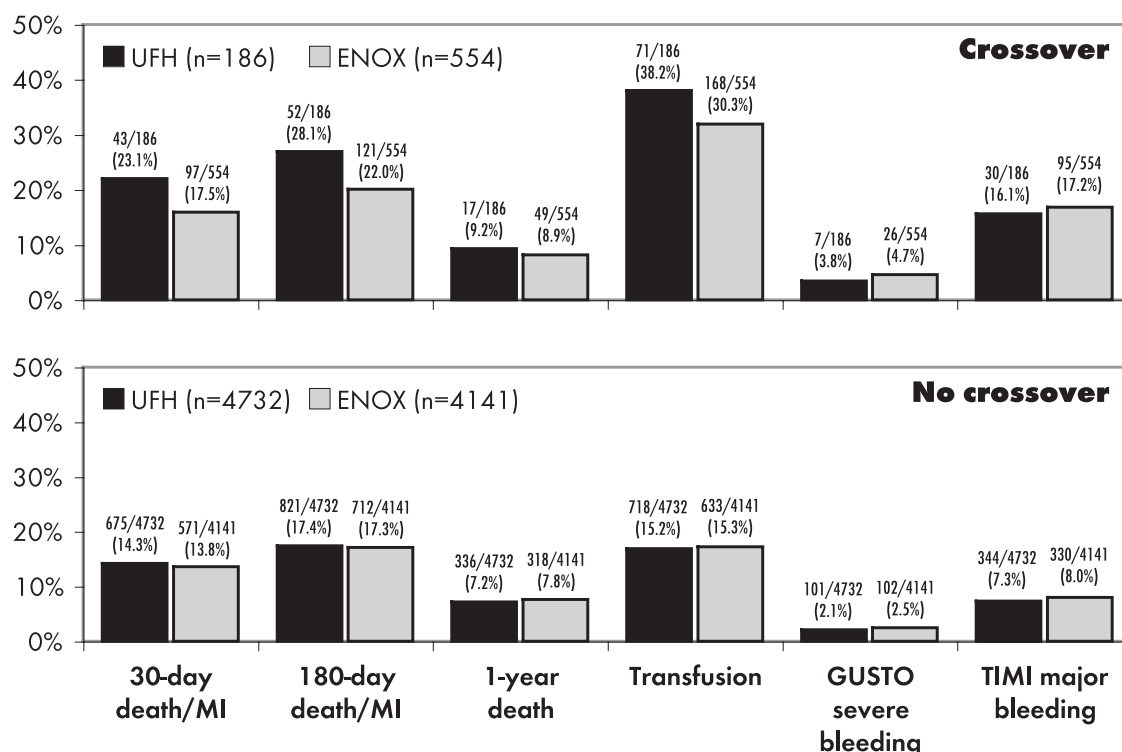


Figure 2. Unadjusted in-hospital bleeding (GUSTO severe, TIMI major, and transfusion) and ischemic (30-day and 6-month death or MI and 1-year mortality) outcomes by study drug assignment. ENOX indicates enoxaparin.

impact of appropriate postrandomization crossovers on the observed treatment effects of assigned study therapy, and it showed only a modest impact (absolute difference enoxaparin versus UFH, without [0.6%] and with [0.8%] modeling). The absolute difference in TIMI major bleeding between enoxaparin and UFH was modest as well (1.5% versus 1.0%).

A possible explanation for the lack of an observed substantial impact of postrandomization crossover is that physicians may have performed crossovers based on an assessment that the patients were failing the assigned therapy and that the alternative therapy would be preferable. This assessment was

made possible by the open-label trial design. Alternatively, the modeling itself may have imprecisely adjusted for the true impact of postrandomization crossover and observed treatment effect. The only way to truly know the impact would be to perform a randomized trial of postrandomization crossover with clinically accepted algorithms for transition of anticoagulant agents.

Clinical and Research Implications

Improper analyses in clinical trial databases need to be interpreted with caution. Modeling techniques such as the

Table 3. Event Rates for Crossing

Group*	Death or MI to 30 Days		TIMI Bleeding	
	Enoxaparin	UFH	Enoxaparin	UFH
Overall rates	668/4695 (14.2)	718/4918 (14.6)	425/4695 (9.1)	374/4918 (7.6)
No cross	571/4141 (13.8)	675/4732 (14.3)	330/4141 (8.0)	344/4732 (7.3)
Any cross	96/548 (17.5)	42/183 (23.0)	94/547 (17.2)	28/181 (15.5)
Patients who cross				
Only includes events after cross	53/548 (9.7)	14/183 (7.7)	77/547 (14.1)	15/181 (8.3)
Only includes events before cross	43/548 (7.9)	28/183 (15.3)	17/547 (3.1)	13/181 (7.2)
No cross before the end point†	614/4184 (14.7)	703/4760 (14.8)	347/4158 (8.4)	357/4746 (7.5)
Cross‡	53/505 (10.5)	14/155 (9.0)	77/530 (14.5)	15/168 (8.9)

Data are presented as no./n (%). These analyses account for the timing of event relative to crossing. Events occurring before the crossing become "no cross" because they occurred while the patient was still in the initial therapy. "Cross" excludes these patients with events before crossing.

*Six patients had no date and time of crossover. Three patients had missing data for date and time of MI, and 3 patients had missing data for the date and time of TIMI bleeding.

†No cross or cross is after end point has already been reached.

‡End points occurring after the cross or no end points after the cross.

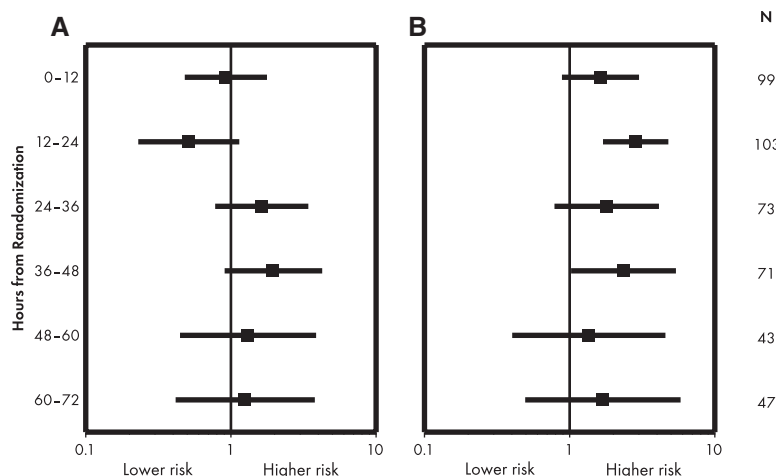


Figure 3. ORs and 95% CIs for association of crossover with 30-day death or MI (A) and bleeding (B) at 12-hour landmark periods from 0 to 72 hours. Each OR is the odds of the event for patients who crossed versus those who did not during that time period. Patients were excluded from subsequent periods once they crossed. Note that 297 patients crossed after 72 hours.

ones described here can be used in an attempt to limit the biases and confounders. These techniques are complex and often poorly understood. Clinicians and clinical investigators should recognize the limitations of these subgroup analyses and expect that appropriate modeling is attempted and that results are interpreted with the necessary caution. A more definitive evaluation of postrandomization crossovers would require a prospective randomization to crossover versus no crossover.

Clinical investigators should create procedures during study conduct that enable rapid assessment of study protocol compliance by site investigators. Lack of adherence to the protocol may compromise the integrity of the research effort. Intervention with education or suspension of recruitment for continued noncompliance at offending sites may need to be considered. Statistical approaches such as those of these analyses can be used but are imperfect.

Limitations

The purpose of the article is to discuss the limitations of some of the analytic methods used in cardiovascular analyses of postbaseline subgroups, using crossover therapy as an example. As shown, differences in the inexact methods of examining these data can affect conclusions about crossovers relative to outcomes. The examination of crossovers was by post hoc exploratory analysis. More importantly, crossovers were postrandomization events themselves. The decision to change treatments can be the result of any number of potential confounders, including patient characteristics, in-hospital events, concomitant medications, physician preference, or the hospital practice pattern. A number of these confounders are unmeasured, and thus, no amount of modeling can fully account for the inherent bias in the group selection. The reasons for postrandomization crossover are potentially imprecise due to limitations of data collection, which will influence results from the IPW methodology. Finally, we have used only 1 type of postrandomization factor when comparing methodologies. It is possible that other examples would have resulted in a different set of comparative results.

Conclusions

Evaluation of subgroups from clinical trials defined by postrandomization events has serious potential biases and

limitations. Rigorous modeling techniques are available to do analyses in an attempt to account for the potential confounders. The SYNERGY trial provides an illustration of such analyses: the outcomes and effects of randomized treatment on cardiac and bleeding outcomes. Postrandomization crossovers in SYNERGY occurred in $\approx 10\%$ of patients. In unadjusted analyses, patients with postrandomization crossovers had more ischemic and bleeding events. Using rigorous modeling techniques, the impact of postrandomization crossovers on outcomes by randomized treatment assignment was modest. The impact of potential confounders and biases associated with analyses of subgroups in clinical trials defined by postrandomization events should be considered carefully when evaluating results from such analyses.

Acknowledgments

We thank Amanda McMillan for her editorial assistance. We also thank Dr Butch Tsiatis for his expert statistical input and guidance.

Sources of Funding

The SYNERGY trial was funded by Sanofi-Aventis.

Disclosures

Dr Mahaffey has received research grants and consulting honoraria from Sanofi-Aventis. Dr Califf has received consultant and speaker's bureau honoraria from Sanofi-Aventis. Dr Antman has received research grants from Sanofi-Aventis. Dr Kleiman has received research grants from Sanofi-Aventis $> \$100K$. Dr Goodman has received speaker and consulting honoraria and research grant support from Sanofi-Aventis. Dr White has received research grants ($> \$10K$) and consulting honoraria ($< \$10K$) from Sanofi-Aventis. Dr Rao has received consultant honoraria from Sanofi-Aventis. Dr Hochman is a steering committee member for the SYNERGY trial. Dr Cohen has received research and grant support and speaker's bureau honoraria from Sanofi-Aventis. Dr Col has received consulting honoraria from Sanofi-Aventis. Dr Roe is an investigator and consultant for Sanofi-Aventis. Dr Ferguson has received research support, consulting fees, and speaker's bureau honoraria from Sanofi-Aventis within the past 5 years. Ms Pieper and Dr Lokhnygina have no conflicts to disclose.

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SUPPLEMENTAL MATERIAL

Appendix A. Study Drug Dosing

Enoxaparin

Enoxaparin will be supplied in 1-mL syringes in a concentration of 100 mg/mL. Enoxaparin will be shipped in bulk; each shipment will consist of a box containing 10 1-mL syringes.

Enoxaparin will be given subcutaneously at a dose of 1 mg/kg every 12 hours using the technique described in Appendix D (*not included herewith*).

The following are recommendations for dosing of enoxaparin during the study and, in particular, during cardiac procedures. Investigators are encouraged to contact the DCRI Clinical Helpline with questions.

1. Enoxaparin should be given immediately after enrollment if patients are assigned to enoxaparin.
2. Duration of therapy
 - Enoxaparin treatment should continue until the patient requires no further anticoagulation. Enoxaparin should be continued at least through angiography and any PCI.
 - Enoxaparin may be discontinued for the following indications: hospital discharge, after PCI (if no post-PCI enoxaparin therapy is indicated), bypass surgery, physician discretion, patient withdrawal.
3. During cardiac catheterization
 - Catheterization may be performed any time after enoxaparin dosing.

- Sheath should be pulled ≥ 6 –8 hours after last enoxaparin dose.

4. During PCI

- If the last enoxaparin dose was given < 8 hours before balloon inflation, then no additional enoxaparin is needed. If last enoxaparin dose was given ≥ 8 hours before balloon inflation, 0.3 mg/kg of enoxaparin should be given intravenously before proceeding with PCI.
- If no IV enoxaparin was used, the sheath should be pulled ≥ 6 –8 hours after last enoxaparin dose.
- If IV enoxaparin was used, the sheath may be pulled ≥ 4 –6 hours after the IV enoxaparin dose.

5. Before bypass surgery

- For elective procedures, discontinue enoxaparin ≥ 8 hours before surgery.
- For emergency procedures, stop enoxaparin and proceed with surgery regardless of timing of last enoxaparin dose.

Unfractionated Heparin

Unfractionated heparin will be given according to a weight-adjusted nomogram based on recent guidelines for management of patients with unstable angina or NSTEMI.

- Bolus of 60 U/kg and initial infusion of 12 U/kg/h. See Appendix E (*not included herewith*) for weight-adjusted dosing.

The following are recommendations for dosing of UFH during the study and, in particular, during cardiac procedures. Investigators are encouraged to contact the DCRI Clinical Helpline with questions.

1. Unfractionated heparin should be given immediately after enrollment if patients are assigned UFH.
2. Duration of therapy
 - UFH therapy should continue until the patient requires no further anticoagulation. Heparin should be continued at least through angiography and any PCI.
 - UFH may be discontinued for the following indications: hospital discharge, after PCI (if no post-PCI UFH therapy is indicated), bypass surgery, physician discretion, patient withdrawal.
3. Before cardiac catheterization
 - Catheterization should occur while patient remains on UFH.
 - Sheath should be pulled when the ACT is <150–180 seconds.
4. During PCI
 - UFH infusion should be stopped during PCI.
 - Additional intravenous UFH should be given to achieve an ACT of 250 seconds (or lower if GP IIb/IIIa inhibitors are used) or based on the individual site standards.
 - Sheath should be pulled when the ACT is <150–180 seconds.
5. Before bypass surgery
 - For elective procedures, stop UFH 6 hours before surgery.
 - For emergency procedures, stop UFH and proceed with surgery.

Appendix B. Procedure for Switching Agents

Patients already receiving enoxaparin or UFH are eligible for enrollment. When these patients are randomly assigned to study drug treatment, the assigned therapy may be the same treatment already being given or may be different. The following guidelines are to be followed.

1. Patient receiving enoxaparin, randomly assigned to enoxaparin:
 - Give first study dose of enoxaparin 12 hours after last dose of enoxaparin.
2. Patient receiving enoxaparin, randomly assigned to UFH:
 - Stop enoxaparin at enrollment.
 - If ≤ 8 hours after last enoxaparin dose, start UFH infusion at 12 U/kg/h (without bolus) 8 hours after the last enoxaparin dose.
 - If > 8 but ≤ 12 hours after last enoxaparin dose, start UFH infusion at 12 U/kg/h after a 30-U/kg bolus.
 - If > 12 hours after last enoxaparin dose, start UFH infusion at 12 U/kg/h after a 60-U/kg bolus.
3. Patient receiving UFH, randomly assigned to UFH:
 - Continue UFH.
 - Check aPTT if > 6 hours after the bolus dose and adjust to achieve an aPTT of 50–70 seconds.
4. Patient receiving UFH, randomly assigned to enoxaparin:
 - Stop UFH.
 - Give enoxaparin dose immediately, regardless of aPTT.

- In patients on UFH for >12 hours before randomization, give at least 2 doses of enoxaparin before PCI.

The Impact of Postrandomization Crossover of Therapy in Acute Coronary Syndromes Care

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Circ Cardiovasc Qual Outcomes. 2011;4:211-219; originally published online February 8, 2011;
doi: 10.1161/CIRCOUTCOMES.109.853598

Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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