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Statistical Analysis Methods for Providing Inferences between Primary Response Measures and Exposure to Study Medication

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ABSTRACT

Differential exposure to study medications in long-term studies of drugs complicates analyses of and inferences from the data collected, particularly with respect to the usual intention-to-treat population. Analysis methods which incorporate exposure are developed, presented and illustrated by applying them to primary response data from a long term, placebo controlled, clinical trial of gemfibrozil (the Primary Helsinki Heart Study). The analysis methods address the extent to which endpoints are correlated with the actual use of the compound rather than the extent to which endpoints are correlated with the random assignment to double-blind study medications.

Key Words: Exposure Analysis, Long-term CHD Studies, Intent-to-Treat

I. INTRODUCTION

In many clinical trials, patients are treated with a fixed daily dose of study medication for a fixed length of time. The length of time on treatment is at least as long as expected to be necessary in order to observe a beneficial response to treatment, if the treatment provides benefit. For some drugs, the benefits are expected to accrue only from long-term treatment.

The primary objectives of clinical trials of a drug for the treatment or prevention of disease, should be "Is the drug safe and efficacious"[1]? And "How is the safety and efficacy of the drug related to its use?"

Analyses of efficacy response data on the intent-to-treat (ITT) population (generally referred to as intent-to-treat analysis) from clinical trials are performed routinely. In performing these analyses, patients are usually classified as responders or non-responders, regardless of the length of time on treatment, and then treatment regimens are compared in terms of either response proportions or time to response patterns. Such analyses address the question of randomization group differences [1], and therefore, are aimed at assessing the degree to which efficacy response is correlated with random assignment to treatment groups. Parenthetically then, ITT analyses may be interpreted as analyses which include all patients who are randomized but which do not factor in or adjust for differential exposure to study medications. In long term studies with high drop out rates, reflecting a wide range of time on study medication, analyses that relate efficacy response to exposure to study medication may be more revealing as to the effects of the drug under the conditions of use, than the usual ITT

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analyses. One approach [2, 3] to exposure analyses is to introduce a dose metameter or exposure index, which is monotonic in the length of time a patient is in the study and taking study medication, and then correlate response with this exposure metameter. Penultimately, a regression analysis of response on the exposure index is performed for each treatment group separately. The treatment groups may then be subsequently compared in terms of the parameters of the regression models; e.g. in terms of slopes or intercepts. This approach may be particularly illustrative in displaying relationships between response and exposure within treatment groups.

The regression analysis of response on exposure index within the placebo group addresses the extent to which response is correlated with exposure to study and no drug treatment. The regression analysis of response on the exposure index within a drug treated group addresses the extent to which response is correlated with exposure to study plus treatment with the drug. Therefore, comparing these two groups in terms of regression response/exposure parameters provides an inference as to the effect of drug adjusted for differential exposure to study medication.

This approach is somewhat similar to that of Efron and Feldman [4] who interpret exposure as the proportion of scheduled study medication actually taken. Their objective is to estimate a portion of the dose response curve within the treatment group so that response, were all patients fully compliant, may be estimated. It should be pointed out that their methods explicitly deal with continuous, non-time dependent, rather than dichotomous time dependent response measures. Another approach [5] is to directly compare treatment groups in terms of response patterns adjusted for exposure. Cox's proportional hazard's model [6] may be used for this comparison using exposure as a time dependent covariate. In this paper, we extend those methods by applying them to the primary response measures from the Primary Helsinki Heart Study, double blind and open label data.

II. DEVELOPMENT OF EXPOSURE ANALYSIS METHODS

The Primary Helsinki Heart Study (HHS) was a landmark study in dyslipidemic, middle-aged, Finnish males, who were otherwise healthy and without a history of myocardial infarction. Four thousand, eighty-one (4,081) patients who satisfied eligibility criteria were randomized to either gemfibrozil (2,046) or placebo (2,035) and followed in double-blind manner for five years. Results from this study [2, 3] established that increases in high-density-lipoproteins (HDL) and decreases in low-density-lipoproteins (LDL) - particularly increases in HDL, attributed to gemfibrozil over the 5 year double blind study period, were significantly correlated with a reduction of risk of coronary heart disease (CHD).

Following completion of the 5 year double-blind study period, all patients living at that time, including those who dropped out during the double-blind period, were given the option of taking gemfibrozil or no drug, and participate in open label follow-up for an additional period of time. This led to 4 open label study groups: PN, PG, GN, GG. The symbols PN, PG, GN, and GG represent the subgroups of patients at the beginning of open label (i) who were on placebo during double blind and chose to take no drug during open label, (ii) who were on placebo during double blind and chose to take gemfibrozil during open label, (iii) who were on gemfibrozil during double blind and chose to take no drug during open label, and (iv) who

were on gemfibrozil during double blind and chose to take gemfibrozil during open label, respectively.

Data from the open label period, 3 years past the end of the double-blind period, on the primary endpoints: cardiac endpoints (CE), all cause mortality (ACM), and cancer diagnosis (CA), were available for summarization and analysis. All cause mortality was categorized as cardiac related (CR) or non- cardiac related (NCR). Non-cardiac related death was further broken down according to cancer (CAD) versus non-cardiac, non- cancer (NCRCA). These data are summarized according to the four open label groups in Tables 1 through 7. In addition to the open label results, Tables 1 - 7 also present the results from the double-blind period for these major events.

As has been mentioned, the usual ITT analyses are aimed at assessing the degree to which response is correlated with random assignment to treatment groups, and do not take into account differential exposure to study medication. A patient who was on study medication for only 1 day and one who was on study medication for several years would both contribute the same information in this analysis. In fact, since response information on the major events was obtained on all patients in the HHS, including those who withdrew, the usual ITT analysis would treat all patients as having full exposure to the intervention to which they were originally randomized over the entire length of follow-up, and also ignore the fact that many patients switched off or onto gemfibrozil at the beginning of the open-label period.

More than 30% of the patients who entered the study and were randomized to study medication voluntarily withdrew from the study prior to the scheduled completion of the double-blind phase. In addition, many of these patients were exposed to study medication for only a short period of time. Furthermore, 64 percent of the patients originally randomized to placebo elected to switch to gemfibrozil, and 40 percent of the patients originally randomized to gemfibrozil, elected to switch off gemfibrozil (take no drug) at the beginning of the open label period.

To account for differential exposure to study medication and the choice made at the beginning of open label as to take or not take gemfibrozil during open label, methods discussed in section I were used to regress response: times to the seven major events, on these factors as well as other explanatory variables. This permits an assessment to be made as to whether there is evidence of an association between the times to events distributions and explanatory or regression variables.

The regression variables were: (1) the baseline measurements which were previously used [2, 3] as fixed covariates in the analysis of major events in double-blind portion of the study: past and present smoking habits, age, systolic blood pressure, HDL and LDL; (2) the original double-blind random treatment group assignment (T) as a fixed covariate; (3) switching status at the beginning of the open label period (S) as a time dependent covariate; (4) the interaction between random group assignment and switching status (T*S); and (5) exposure (E) to study conditions. Specifically,

T = +1 if the patient was randomized to gemfibrozil,
= -1 if the patient was randomized to Placebo;
S = 0 as long as the patient was in double-blind,
= +1 if the patient did not switch at the beginning of open label,
= -1 if the patient switched at the beginning of open label;
T*S = the interaction between S and T, and
E = time dependent covariate representing the total time the patient participated in the study under study conditions.

Running this model on the data using the BMDP P2L [7] subroutine provides estimates of the log relative risk of the effect of each model covariate parameter and the associated standard error and P-Value. The estimates of log relative risk for the effect of each regression parameter are adjusted for the effects of the other regression parameters appearing in the model. Of particular interest is the comparative inference between the original randomized groups, adjusted for the other covariates appearing in the model.

The estimate of relative risk may be obtained by exponentiating the estimate of log relative risk. The estimate of relative risk from exposure may be obtained by multiplying the estimate of log relative risk by mean exposure time prior to exponentiating. Confidence intervals may be obtained by exponentiating the limits of 95% confidence intervals constructed on log relative risk.

III. RESULTS

Tables 8, 9, 10, 11, 12, 13, and 14, respectively summarize the results of Cox's time to event regression analysis for the seven major events: cardiac endpoints (CE), all cause mortality (ACM), cardiac related deaths (CR), non-cardiac related deaths (NCR), non- cardiac-non-cancer (NCRCA) deaths, cancer deaths (CAD), and cancer diagnoses (CA). In these tables, estimates of log relative risk (Log RR) and of relative risk (RR), the standard error of log relative risk (STD.ERR), P-Values assessing the statistical significance of the estimate of relative risk, and 95% confidence intervals (CI'S) on relative risk are presented.

Table 15 presents a summary of the comparative inferential effects of the original randomized groups. In constructing Table 15, the information from Tables 8 - 14 on the randomized group parameter was summarized for easier reference.

A negative estimate indicates descriptively that patients originally randomized to the gemfibrozil group are at less risk of experiencing a major event than patients originally randomized to the placebo group. It should be kept in mind that the estimates of these risks are adjusted for the switching experience, the interaction between double-blind randomized group assignment and the switching experience, and differential exposure to study conditions.

Among the 7 major events, only the estimate of relative risk of cardiac endpoints is statistically significant; corresponding to a risk reduction of 13% for patients originally randomized to the gemfibrozil group as compared to patients originally randomized to the placebo group. The P-Values and confidence intervals for the relative risk of the other 6 major events are consistent with chance findings.

IV. SUMMARY AND DISCUSSION

Time to event data on the major events: cardiac endpoints (CE), all cause mortality (ACM), and cancer diagnosis (CA), from the double-blind portion and the 3-year open label extension of the Primary Helsinki Heart Study were analyzed. The classifications of all cause mortality: cardiac related (CR), non-cardiac related (NCR), non-cardiac non-cancer related (NCRCA), and cancer (CAD) related were also analyzed.

Statistical analyses utilized Cox's model to regress time to major events on explanatory variables taken at the time of randomization and occurring during study. The explanatory variables were: (1) baseline measurements: past and present smoking habits, age, systolic blood pressure, HDL and LDL; (2) the original double-blind random treatment group assignment; (3) switching status at the beginning of the open label period as a time dependent covariate; (4) the interaction between random group assignment and switching status; and (5) exposure to study conditions as a time dependent covariate. For a given patient, exposure to study conditions may be thought of as the total time a patient was participating in the study, in double blind and in open label, and returning for regular follow-up visits uninterruptedly.

Since due to withdrawal, patients were exposed to medication and study conditions for different lengths of time, and many patients originally randomized to placebo elected to switch to gemfibrozil and vice versa at the beginning of the open label period, it was felt that analyses adjusting for these effects were more appropriate than the usual intent-to-treat analyses. The statistical significance of the model parameters from these analyses are summarized below:

EFFECT	CE	ACM	CR	NCR	NCRCA	CAD	CA
DB TREAT(T)	S	NS	NS	NS	NS	NS	NS
SWITCHING(S)	NS	NS	NS	NS	NS	NS	NS
INTERACTION (T*S)	S	S	S	S	S	NS	S
EXPOSURE	S	S	S	S	S	S	S

S means P <= 0.05; NS means P > 0.05.

Although small, exposure effect is significant for all 7 major events. From Tables 8 - 14, it is noted that the estimate of log relative risk for the exposure parameter is negative for all major events. An interpretation of this estimate is that risk of experiencing such events decreases as a function of exposure. This interpretation is illustrated below by the general decrease in the percentages of patients experiencing major events across quartiles of exposure.

GROUP	EXP.[1]	CE	ACM	CR	NCR	NCRCA	CAD	CA
P	Q1	14.4	14.4	6.6	7.8	4.3	3.5	5.8
	Q2	6.1	2.2	1.0	1.2	0.8	0.4	2.0
	Q3	3.9	0.4	0.2	0.2	0.2	0.0	2.0
	Q4	1.9	0.0	0.0	0.0	0.0	0.0	0.6
G	Q1	12.4	14.0	4.9	9.2	5.5	3.8	5.2
	Q2	4.0	3.8	1.0	2.8	1.6	1.4	2.6
	Q3	2.9	1.2	1.0	0.2	0.0	0.2	0.8
	Q4	1.9	0.2	0.0	0.2	0.0	0.2	1.1

[1] EXP. = exposure time in study; Q1 = 1st quartile = 0-2157 days, Q2 = 2nd quartile = 2157-2778 days, Q3 = 3rd quartile = 2778-3219 days, Q4 = 4th quartile = > 3219 days.

Further, although the effect of switching isn't statistically significant for any major event, the interaction between the original randomized groups and switching status is statistically significant for a majority of the events. An interpretation of this result is that the difference between the group originally randomized to gemfibrozil and the group originally randomized to placebo is not the same for patients who switched versus those who did not switch.

Further, for the original randomization to treatment group parameter, among the 7 major events, only the estimate of the log-relative risk (-0.14) of cardiac endpoints is statistically significant. Corresponding to an estimated risk reduction of 13%, and a 95% confidence interval (CI) of 77% - 99%, for patients originally randomized to the gemfibrozil group as compared to patients originally a randomized to the placebo group. The P-Values and confidence intervals for the relative risk of the other 6 major events are consistent with an interpretation of chance findings (Table 15).

It is interesting to note that the signs of the estimates of log relative risk for the original randomization to treatment groups parameter from the exposure/switching analyses performed are reasonable, in the sense that there is agreement between them and the observed data. A negative estimate would imply that patients originally randomized to the gemfibrozil group were at less risk of experiencing a major event than patients originally randomized to the placebo group; whereas a positive estimate would imply that patients originally randomized to the gemfibrozil group were at greater risk of experiencing a major event than patients originally randomized to the placebo group. As is illustrated below, there is agreement between the direction of the estimated risk reduction and that observed in the original randomized groups for all events analyzed.

	CE	ACM	CR	NCR	NCRCA	CAD	CA
OBSERVED	-	+	-	+	+	+	-
ESTIMATED	-	+	-	+	+	+	-

As Lovell [8] points out, what analysis one embraces, depends on the trial objective or question. Parenthetically, it should be added "and to the nature of the data." Since the objective of the Primary Helsinki Heart Study was to assess how coronary endpoint risk

reduction was correlated with the use of gemfibrozil, it is argued that the exposure analyses are more consistent with this objective. Exposure analyses as presented here utilize all patients who were randomized to study medication. Therefore, they are also consistent with the "analyze what you randomize" interpretation of ITT analyses.

In summary, analyses of the Primary Helsinki Heart Study [2, 3] established that increases in HDL and decreases in LDL, due to gemfibrozil over the 5 year double blind study period, were significantly correlated with a reduction of risk of cardiac endpoints, and provided no evidence that patients were at significantly greater risk of dying or developing cancer. Based upon the analyses presented here, of 8 year data (the 5 year double-blind data plus data from 3 additional years of open label follow-up) on these major events, which adjusted for patients switching onto and off gemfibrozil at the beginning of the open label period and differential exposure to study, there is no evidence to contradict the findings from the 5 year double blind experience.

Finally, it should be pointed out that the strict statistical validity of inferences from the methods presented assumed that the requirements under-girding the Cox proportional hazards model hold and that withdrawal or switching is independent of treatment group assignment.

TABLE 1. HHS Double Blind and Open Label Eight Year Follow-up Cardiac Endpoints (CE)

DOUBLE BLIND (DB) PHASE

STATISTIC	P	G
E/N	84/2035	56/2046
%	4.13	2.74

Ratio	G/P
%	66.3

OPEN LABEL (OL) PHASE

STATISTIC	PN	PG	GN	GG
E/N	19/686	28/1242	24/780	30/1181
%	2.77	2.25	3.08	2.54

Ratio	PG/PN	GG/GN
%	81.2	82.5

Difference	SWITCH	NO SWITCH
G - P (%)	+0.83	-0.23

DB = Double Blind period; OL = Open Label period; E/N = Number of events in the period divided by the number of patients at risk in the period.

TABLE 2. HHS Double Blind and Open Label Eight Year Follow-up All Cause Mortality (ACM)

DOUBLE BLIND(DB) PHASE

STATISTIC	P	G
E/N	43/2035	44/2046
%	2.11	2.15

Ratio	G/P
%	101.9

OPEN LABEL(OL) PHASE

STATISTIC	PN	PG	GN	GG
E/N	20/709	20/1283	27/795	30/1207
%	2.82	1.56	3.4	2.49

Ratio	PG/PN	GG/GN
%	55.3	73.2
Difference	SWITCH	NO SWITCH
G - P (%)	+1.84	-0.33

DB = Double Blind period; OL = Open Label period; E/N = Number of events in the period divided by the number of patients at risk in the period.

TABLE 3. HHS Double Blind and Open Label Eight Year Follow-up Cardiac Related Deaths (CR)

DOUBLE BLIND(DB) PHASE

STATISTIC	P	G
E/N	19/2035	14/2046
%	0.93	0.68

Ratio	G/P
%	73.6

OPEN LABEL(OL) PHASE

STATISTIC	PN	PG	GN	GG
E/N	7/709	12/1283	10/795	12/1207
%	0.99	0.94	1.26	0.99

Ratio	PG/PN	GG/GN
%	94.7	79.0
Difference	SWITCH	NO SWITCH
G - P (%)	+0.32	+0.003

DB = Double Blind period; OL = Open Label period; E/N = Number of events in the period divided by the number of patients at risk in the period.

TABLE 4. HHS Double Blind and Open Label Eight Year Follow-up Non-Cardiac Related Deaths (NCR)

DOUBLE BLIND (DB) PHASE

STATISTIC	P	G
E/N	24/2035	30/2046
%	1.18	1.47
Ratio	G/P	
%	124.3	

OPEN LABEL (OL) PHASE

STATISTIC	PN	PG	GN	GG
E/N	13/709	8/1283	17/795	18/1207
%	1.83	0.62	2.14	1.49
Ratio	PG/PN	GG/GN		
%	34	69.7		
Difference	SWITCH	NO SWITCH		
G - P (%)	+1.52	-0.34		

DB = Double Blind period; OL = Open Label period; E/N = Number of events in the period divided by the number of patients at risk in the period.

TABLE 5. HHS Double Blind and Open Label Eight Year Follow-up Non-Cardiac Non-Cancer Deaths (NCRCA)

DOUBLE BLIND (DB) PHASE

STATISTIC	P	G
E/N	13/2035	20/2046
%	0.64	0.98
Ratio	G/P	
%	152.7	

OPEN LABEL (OL) PHASE

STATISTIC	PN	PG	GN	GG
E/N	6/709	7/1283	5/795	11/1207
%	0.85	0.55	0.63	0.91
Ratio	PG/PN	GG/GN		
%	64.5	144.9		
Difference	SWITCH	NO SWITCH		
G - P (%)	+0.08	+0.06		

DB = Double Blind period; OL = Open Label period; E/N = Number of events in the period divided by the number of patients at risk in the period.

TABLE 6. HHS Double Blind and Open Label Eight Year Follow-up Cancer Deaths (CAD)

DOUBLE BLIND(DB) PHASE

STATISTIC	P	G
E/N	11/2035	10/2046
%	0.54	0.49

Ratio	G/P
%	90.5

OPEN LABEL(OL) PHASE

STATISTIC	PN	PG	GN	GG
E/N	7/709	1/1283	12/795	7/1207
%	0.99	0.08	1.51	0.58

Ratio	PG/PN	GG/GN
%	7.9	38.4
Difference	SWITCH	NO SWITCH
G - P (%)	+1.43	-0.41

DB = Double Blind period; OL = Open Label period; E/N = Number of events in the period divided by the number of patients at risk in the period.

TABLE 7. HHS Double Blind and Open Label Eight Year Follow-up Cancer Diagnoses (CA)

DOUBLE BLIND(DB) PHASE

STATISTIC	P	G
E/N	28/2035	25/2046
%	1.38	1.22

Ratio	G/P
%	88.4

OPEN LABEL(OL) PHASE

STATISTIC	PN	PG	GN	GG
E/N	10/693	13/1282	8/782	18/1207
%	1.44	1.01	1.02	1.49

Ratio	PG/PN	GG/GN
%	70.1	146.1
Difference	SWITCH	NO SWITCH
G - P (%)	+0.01	+0.05

DB = Double Blind period; OL = Open Label period; E/N = Number of events in the period divided by the number of patients at risk in the period.

TABLE 8. HHS Double Blind and Open Label Eight Year Follow-up: Relative Risk (RR) Estimates of Cardiac Events

PARAMETER	LOGRR@	RR	STD.ERR	P-VALUE	95%CI
RANDOMIZED GROUPS	-0.14	0.87	0.07	0.03	(0.77;0.99)
SWITCHING EFFECT	0.06	1.07	0.1	0.52	(0.88;1.29)
GROUP BY SWITCHING EFFECT INTERACTION	0.28	1.33	0.11	0.009	(1.07;1.64)
EXPOSURE	-0.001	0.99	0.0001	< 0.0001	(0.98;0.99)

@Log relative risk estimate of each parameter adjusted for baseline covariates, and the other parameters in the model.

TABLE 9. HHS Double Blind and Open Label Eight Year Follow-up: Relative Risk (RR) Estimates of All Cause Mortality

PARAMETER	LOGRR@	RR	STD.ERR	P-VALUE	95%CI
RANDOMIZED GROUPS	0.03	1.03	0.07	0.72	(0.89;1.19)
SWITCHING EFFECT	0.08	1.09	0.1	0.42	(0.89;1.33)
GROUP BY SWITCHING EFFECT INTERACTION	0.71	2.03	0.11	< 0.0001	(1.63;2.52)
EXPOSURE	-0.002	0.99	0.0001	< 0.0001	(0.998;0.99)

@Log relative risk estimate of each parameter adjusted for baseline covariates, and the other parameters in the model.

TABLE 10. HHS Double Blind and Open Label Eight Year Follow-up: Relative Risk (RR) Estimates of Cardiac Deaths

PARAMETER	LOGRR@	RR	STD.ERR	P-VALUE	95%CI
RANDOMIZED GROUPS	-0.11	0.9	0.12	0.37	(0.71;1.14)
SWITCHING EFFECT	0.04	1.04	0.17	0.83	(0.74;1.46)
GROUP BY SWITCHING EFFECT INTERACTION	0.91	2.49	0.19	< 0.0001	(1.73;3.59)
EXPOSURE	-0.002	0.99	0.0001	< 0.0001	(0.998;0.99)

@Log relative risk estimate of each parameter adjusted for baseline covariates, and the other parameters in the model.

TABLE 11. HHS Double Blind and Open Label Eight Year Follow-up: Relative Risk (RR) Estimates of Non-Cardiac Deaths

PARAMETER	LOGRR@	RR	STD.ERR	P-VALUE	95%CI
RANDOMIZED GROUPS	0.12	1.13	0.1	0.21	(0.93;1.37)
SWITCHING EFFECT	0.13	1.14	0.13	0.33	(0.88;1.46)
GROUP BY SWITCHING EFFECT INTERACTION	0.58	1.79	0.14	< 0.0001	(1.35;2.36)
EXPOSURE	-0.002	0.99	0.0001	< 0.0001	(0.998;0.99)

@Log relative risk estimate of each parameter adjusted for baseline covariates, and the other parameters in the model.

TABLE 12. HHS Double Blind and Open Label Eight Year Follow-up: Relative Risk (RR) Estimates of Non-Cardiac, Non-Cancer Deaths

PARAMETER	LOGRR@	RR	STD.ERR	P-VALUE	95%CI
RANDOMIZED GROUPS	0.06	1.06	0.13	0.67	(0.82;1.37)
SWITCHING EFFECT	0.13	1.14	0.18	0.48	(0.80;1.62)
GROUP BY SWITCHING EFFECT INTERACTION	0.91	2.49	0.19	< 0.0001	(1.71;3.65)
EXPOSURE	-0.002	0.99	0.0002	< 0.0001	(0.998;0.99)

@Log relative risk estimate of each parameter adjusted for baseline covariates, and the other parameters in the model.

TABLE 13. HHS Double Blind and Open Label Eight Year Follow-up: Relative Risk (RR) Estimates of Cancer Deaths

PARAMETER	LOGRR@	RR	STD.ERR	P-VALUE	95%CI
RANDOMIZED GROUPS	0.22	1.24	0.16	0.17	(0.91;1.69)
SWITCHING EFFECT	0.14	1.16	0.2	0.47	(0.78;1.70)
GROUP BY SWITCHING EFFECT INTERACTION	0.17	1.18	0.22	0.45	(0.77;1.83)
EXPOSURE	-0.002	0.99	0.0002	< 0.0001	(0.998;0.99)

@Log relative risk estimate of each parameter adjusted for baseline covariates, and the other parameters in the model.

TABLE 14. HHS Double Blind and Open Label Eight Year Follow-up: Relative Risk (RR) Estimates of Cancer Diagnoses

PARAMETER	LOGRR@	RR	STD.ERR	P-VALUE	95%CI
RANDOMIZED GROUPS	-0.05	0.96	0.1	0.66	(0.86;1.06)
SWITCHING EFFECT	0.2	1.22	0.14	0.17	(1.06;1.41)
GROUP BY SWITCHING EFFECT INTERACTION	0.16	1.68	0.16	0.0009	(1.00;1.37)
EXPOSURE	-0.001	0.99	0.0001	< 0.0001	(0.998;0.99)

@Log relative risk estimate of each parameter adjusted for baseline covariates, and the other parameters in the model.

TABLE 15. HHS Double Blind and Open Label Eight Year Follow-up: Relative Risk (RR) Estimate of Randomized Group Effect for Major Events

EVENT	LOGRR@	RR	STD.ERR	P-VALUE	95%CI
CARDIAC ENDPOINTS	-0.14	0.87	0.07	0.03	(0.77;0.99)
ALL CAUSE MORTALITY	+0.03	1.03	0.07	0.72	(0.89;1.19)
CARDIAC	+0.11	0.9	0.12	0.37	(0.71;1.14)
NON-CARDIAC	+0.12	1.13	0.1	0.21	(0.93;1.37)
NON-CANCER	+0.06	1.06	0.13	0.67	(0.82;1.37)
CANCER	+0.22	1.24	0.16	0.17	(0.91;1.69)
CANCER DIAGNOSES	-0.04	0.96	0.1	0.66	(0.86;1.06)

@Log relative risk with respect to the original double blind, randomized assignment to groups, adjusted for baseline covariates, switching status, interaction between randomized group assignment and switching status, and exposure to study conditions.

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