Measurements of Treatment and Procedure Compliance (11.3)

Compliance with treatment and study procedures was assessed. The following categories of treatment compliance were assessed:

- Overall treatment compliance (Section 11.3.1)
- Treatment compliance for breast cancer analyses (Section 11.3.2)
- Treatment compliance for VTE analyses (Section 11.3.3)

Compliance with study procedures (specifically, mammogram, clinical breast examination, and ECG) was also assessed; results of these assessments are presented with the relevant study endpoints.

Overall Treatment Compliance (11.3.1.)

Patients may have stopped taking study drug for reasons presented in Table GGIO.10.3; however, in accordance with the study design, patients were to remain in the study for follow-up. Patients were considered to be treatment compliant if their overall treatment compliance was between 70% and 120% (inclusive).

Table GGIO.11.8 presents results for overall treatment compliance. Mean overall treatment compliance was 75.4%, and results were comparable between treatment groups. Figure GGIO.14.1 shows the overall treatment compliance on a by-visit basis.

Table GGIO.11.8. Overall Treatment Compliance (All Randomized Patients)

	Placebo (N=5057)	Ralox (N=5044)	Total (N=10101)	p-Value*
Patient considered treatment-compliant**				
No. patients***	4983	4995	9978	.621
Yes, n (%)	3532(70.88)	3518(70.43)	7050(70.66)	
No, n (%)	1451(29.12)	1477(29.57)	2928(29.34)	
Summary of overall treatment compliance (%):				
Mean	75.80	74.97	75.38	.202
Standard deviation	32.12	33.02	32.57	
Median	91.60	91.90	91.80	
Minimum	0.00	0.00	0.00	
Maximum	179.20	314.20	314.20	

*Treatment-compliant patients: p-Value is obtained from a Pearson's Chi-square test.
Mean treatment compliance: p-Value is obtained from an F-test using Type III Sum of Squares from an ANOVA model: response=therapy.
**Considered treatment-compliant if overall treatment compliance is between 70% and 120%.
***Overall treatment compliance is unavailable if all visit compliance values are unavailable.

Program: RMP.H3SSGGIO.SASPGM(MSCMCMP1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H380.GGIO.FINAL(MSTCMP)

Treatment Compliance for Breast Cancer Analyses (11.3.2)

Patients who were diagnosed with breast cancer were required to immediately and permanently discontinue study drug. Mean overall treatment compliance for the breast cancer analyses was 75.9%, and results were comparable between treatment groups.

Table xxx. Overall Treatment Compliance for Breast Cancer Analyses (All Randomized Patients)

	Placebo (N=5057)	Ralox (N=5044)	Total (N=10101)	p-Value*
Patient considered treatment-compliant for breast cancer analyses**				
No. patients***	4980	4994	9974	.329
Yes, n (%)	3579(71.87)	3545(70.99)	7124(71.43)	
No, n (%)	1401(28.13)	1449(29.01)	2850(28.57)	
Summary of overall treatment compliance for breast cancer analyses (%):				
Mean	76.43	75.30	75.87	.081
Standard deviation	31.89	32.91	32.41	
Median	92.10	92.20	92.10	
Minimum	0.00	0.00	0.00	
Maximum	179.20	314.20	314.20	

*Treatment-compliant patients: p-Value is obtained from a Pearson's Chi-square test.
Mean treatment compliance: p-Value is obtained from an F-test using Type III Sum of Squares from an ANOVA model: response=therapy.
**Considered treatment-compliant if overall treatment compliance for breast cancer analyses is between 70% and 120%.
***Overall treatment compliance for breast cancer analyses is unavailable if all visit compliance values (until visit of breast cancer diagnosis, if applicable) are unavailable.

Program: RMP.H3SSGGIO.SASPGM(MSCKCMP1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(MSTCMPBC)

Treatment Compliance for VTE Analyses (11.3.3)

Patients who were diagnosed with VTE were required to immediately and permanently discontinue study drug. Mean overall treatment compliance for the VTE analyses was 76.0%, and results were comparable between treatment groups.

Table xxx. Overall Treatment Compliance for VTE Analyses (All Randomized Patients)

	Placebo (N=5057)	Ralox (N=5044)	Total (N=10101)	p-Value*
Patient considered treatment-compliant for VTE analyses**				
No. patients***	4975	4987	9962	.729
Yes, n (%)	3566(71.68)	3559(71.37)	7125(71.52)	
No, n (%)	1409(28.32)	1428(28.63)	2837(28.48)	
Summary of overall treatment compliance for VTE analyses (%):				
Mean	76.32	75.68	76.00	.318
Standard deviation	31.90	32.70	32.30	
Median	92.00	92.30	92.20	
Minimum	0.00	0.00	0.00	
Maximum	179.20	314.20	314.20	

Abbreviations: VTE=venous thromboembolic event.
*Treatment-compliant patients: p-Value is obtained from a Pearson's Chi-square test.
Mean treatment compliance: p-Value is obtained from an F-test using Type III Sum of Squares from an ANOVA model: response=therapy.
**Considered treatment-compliant if overall treatment compliance for VTE analyses is between 70% and 120%.
***Overall treatment compliance for VTE analyses is unavailable if all visit compliance values (until visit of VTE diagnosis, if applicable) are unavailable.

Program: RMP.H3SSGGIO.SASPGM(MSCMCMP1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(MSTCMPV)

Efficacy Results and Tabulations of Individual Patient Data (11.4)

Analysis of Efficacy (11.4.1)

Primary endpoints:

- Composite coronary endpoint of coronary death, nonfatal (including silent) MI, or hospitalized ACS other than MI
- Invasive breast cancer

Analyses highlights:

- The analyses for primary and secondary endpoints used the ITT population and compared the two treatment groups in terms of time to first event, unless noted otherwise.
- All study endpoints were adjudicated and results presented in this report are based on adjudicated events, unless noted otherwise.
- In all analyses, "baseline" was defined as the last non-missing observation at or before the randomization visit (Visit 2). "Post-baseline" was defined as any observation recorded at or following Visit 3.
- Subgroup analyses were performed for patients who had non-missing values for the subgroup variable. Thus, the total number of patients analyzed is less than 10,101 for some subgroup variables.

Significance levels for various analyses

- For the final analysis of the primary endpoints, the treatment effect on the coronary primary endpoint was tested at a two-sided significance level of 0.0423; the breast cancer primary endpoint was tested at a two-sided significance level of 0.008.
- For all other analyses, the treatment effects were tested at a two-sided significance level of 0.05
- Interaction effects were tested at a significance level of 0.10.

Prespecified and post-hoc analyses:

- To evaluate results of this trial, prespecified and post-hoc analyses were conducted. Results presented in this report are based on the prespecified analyses, unless noted otherwise.

Absolute risk reduction:

- In the incidence tables, the term "absolute risk reduction" (ARR) is a column header. A negative ARR value means that there was an absolute risk increase of a given event and a positive ARR value means that there was an absolute risk reduction or decrease.

- The ARR presented in the incidence tables is calculated based on 5.3 years of follow-up and, in the text, ARR is reported based on 1 year of follow-up for 1000 patients (ie, 1000 woman-years).

Time to event analysis of combined endpoints:

- In a time-to-event analysis of a combined endpoint, only the first occurrence of any adjudicated event of the combined endpoint is included in the analysis.
- When the individual components of the endpoint are analyzed separately, the first occurrence of that specific event is included in the analysis.
- Thus, a patient may be counted in the analysis of each individual endpoint if she experiences each of the respective events. Consequently, the sum of the individual events may exceed the number of events reported for the combined endpoint. For example, the GGIO coronary primary endpoint was the first occurrence of a coronary death, nonfatal MI, or hospitalized ACS other than MI. A patient may have had an MI, and later died due to a coronary cause. Each event was counted in the individual event analyses; however, only the first event (ie, MI) was counted in the analysis of the combined primary coronary endpoint.

Breast Cancer Analyses (11.4.2)

The breast cancer analyses are presented in the following order:

- Breast cancer primary and secondary endpoints (invasive breast cancer and all breast cancer) (Section 11.4.2.1)
- Sensitivity analyses of invasive breast cancer (Section 11.4.2.2)
- Subgroup analyses of invasive breast cancer (Section 11.4.2.3)
- Tumor characteristics of breast cancer events (Section 11.4.2.4)
- Compliance with and findings from clinical breast examinations and mammograms (Section 11.4.2.5)
- Analysis for Investigator-reported breast cancers (Section 11.4.2.6)
- Follow-up treatment after diagnosis of breast cancer (Section 11.4.2.7)

Throughout this report, the term "all breast cancer" refers to all adjudicated cases of breast cancer irrespective of invasive status. The listing of all reported breast cancer cases is presented in (Appendix 16.2.6). Patients with multiple breast cancers have multiple records in the listing.

- A total of 132 breast cancer events were reported in 129 patients (76 in placebo, 53 in raloxifene) during the study period and were sent for adjudication.
- Of the 129 patients, 128 patients (76 in placebo, 52 in raloxifene) had at least one adjudicated breast cancer.
- Analyses of breast cancer were based on the 128 patients with an adjudicated breast cancer unless otherwise specified.

Four cases were excluded from the breast cancer analyses:

- Patient 078/5863 (assigned to raloxifene) had two reported breast cancers and both were adjudicated as non-invasive breast cancers. The first breast cancer was included and the second breast cancer was excluded from the analyses.
- Patient 450/1261 (assigned to placebo) had two reported breast cancers with the same diagnosis dates and both were adjudicated as invasive ER-unknown breast cancers. The case with larger tumor size was included and the other breast cancer was excluded from the analyses.
- Patient 863/1104 (assigned to placebo) had two reported breast cancers and one was adjudicated as invasive ER-positive breast cancer and the other one was not adjudicatable due insufficient information. The adjudicated breast cancer was included in the analyses.
- Patient 985/1151 (assigned to raloxifene) was reported to have breast cancer but it was not adjudicated as breast cancer due to insufficient information. The investigator palpated a mass in the patient's left breast and recommended a biopsy; however, the patient refused a biopsy. Approximately 6 months later, the patient was hospitalized, refused treatment, and subsequently died. The death was adjudicated as due to breast cancer.

Breast Cancer Primary and Secondary Endpoints: Invasive Breast Cancer and All Breast Cancer (11.4.2.1)

Table GGIO.11.11 presents results of the time-to-event analyses of breast cancers by invasiveness and ER status, and Table GGIO.11.12 presents incidence rates for breast cancers by invasiveness and ER status.

The incidence of invasive breast cancer, the breast cancer primary endpoint, was significantly decreased by 44% in the raloxifene group compared with the placebo group ($p = 0.0032$). As the protocol-specified significance level was 0.008, the breast cancer primary objective was achieved.
There were 1.50 cases of invasive breast cancer per 1000 patients per year in the raloxifene group and 2.66 cases of invasive breast cancer per 1000 patients per year in the placebo group which translated to an absolute risk reduction of 1.2 cases per 1000 woman-years in the raloxifene group. As shown in Figure GGIO.11.1, the treatment group curves began to separate after about 18 months of follow-up and remain separated throughout the remainder of the study follow-up.

Analyses of invasive breast cancer by ER status showed that most of the cases of invasive breast cancer were ER-positive. Raloxifene significantly decreased the incidence of ER-positive invasive breast cancer by 55% compared with the placebo. This translated to an absolute risk reduction of 1.2 cases of ER-positive invasive breast cancer per 1000 woman-years.
There was no significant decrease or increase in the incidence of ER-negative invasive breast cancer in patients assigned to raloxifene compared with those assigned to placebo.

There was no significant decrease or increase in the incidence of noninvasive breast cancer in patients assigned to raloxifene compared with those assigned to placebo. All 16 cases of

noninvasive breast cancer were ductal carcinoma in situ (DCIS); no cases of lobular carcinoma in situ (LCIS) were reported. The proportion of patients with a noninvasive breast cancer was greater in the raloxifene group compared with the placebo group.
There was a significant decrease in the incidence of all breast cancer (irrespective of invasiveness) by 33% in the raloxifene group compared with the placebo group. It translated to an absolute risk reduction of 1.0 cases of all breast cancer per 1000 woman-years.

Figure GGIO.11.1. Kaplan-Meier curves of invasive breast cancer for all randomized patients.

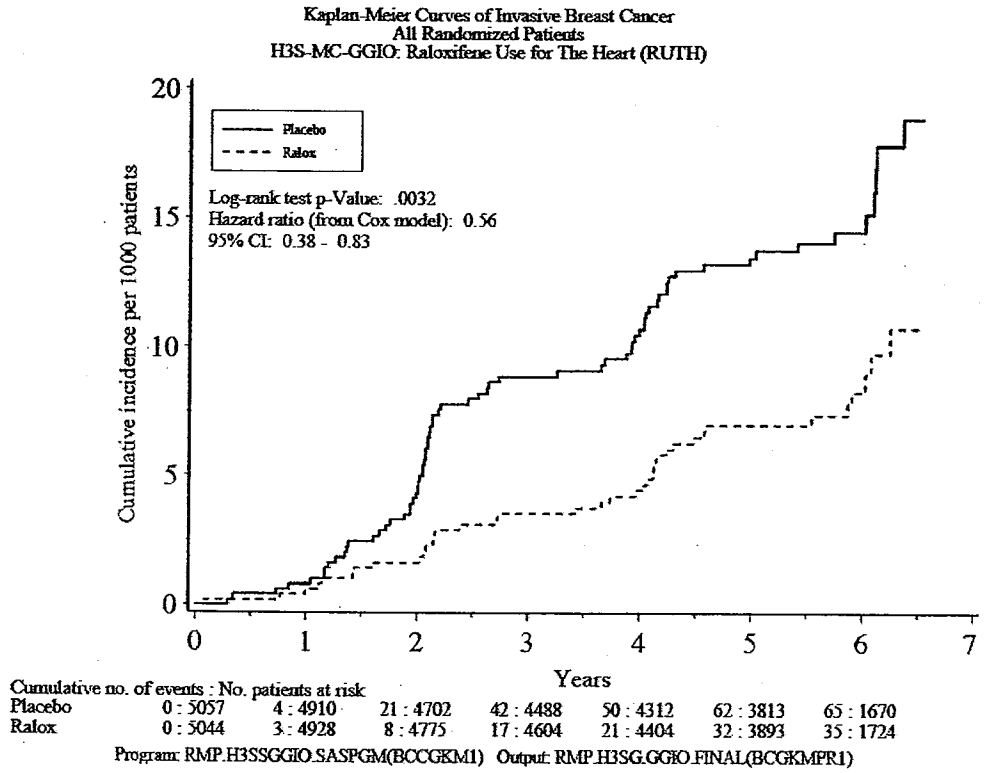


Table GGIO.11.11. Time-to-Event Analysis of Breast Cancer by Invasiveness and ER Status (All Randomized Patients)

Breast cancer category	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard ratio (95% CI)	p-Value*
Invasive cases	70(1.38)	40(0.79)	0.56(0.38, 0.83)	.0032
ER(+) cases	55(1.09)	25(0.50)	0.45(0.28, 0.72)	.0006
ER(-) cases	9(0.18)	13(0.26)	1.44(0.61, 3.36)	.3995
ER unknown cases	6(0.12)	2(0.04)	0.33(0.07, 1.63)	.1507
Noninvasive cases	5(0.10)	11(0.22)	2.17(0.75, 6.24)	.1414
DCIS	5(0.10)	11(0.22)	2.17(0.75, 6.24)	.1414
LCIS	0(0.00)	0(0.00)	N/A	N/A
Invasiveness unknown cases	1(0.02)	1(0.02)	N/A	N/A
All cases	76(1.50)	52(1.03)	0.67(0.47, 0.96)	.0270

Abbreviations: CI=confidence interval; ER=estrogen receptor; DCIS=ductal carcinoma in situ; LCIS=lobular carcinoma in situ.
*p-Value is obtained from a log-rank test. Statistical test is not performed when the total number of patients in a category is less than 5.

Program: RMP.H3SSGGIO.SASPGM(HCCTHR1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(BCTHRPR1)

Table GGIO.11.12. Incidence Rate of Breast Cancer by Invasiveness and ER Status (All Randomized Patients)

Breast cancer category	Placebo (N=5057) n (%)	Patient-years of follow-up	Incidence rate* per 1000 patients	Ralox (N=5044) n (%)	Patient-years of follow-up	Incidence rate* per 1000 patients	ARR** per 1000 patients
Invasive cases	70(1.38)	26290	2.66	40(0.79)	26695	1.50	5.85
ER(+) cases	55(1.09)	26339	2.09	25(0.50)	26722	0.94	5.67
ER(-) cases	9(0.18)	26451	0.34	13(0.26)	26763	0.49	-0.80
ER unknown cases	6(0.12)	26466	0.23	2(0.04)	26782	0.07	0.79
Noninvasive cases	5(0.10)	26467	0.19	11(0.22)	26759	0.41	-1.19
DCIS	5(0.10)	26467	0.19	11(0.22)	26759	0.41	-1.19
LCIS	0(0.00)	26483	0.00	0(0.00)	26786	0.00	0.00
Invasiveness unknown cases	1(0.02)	26482	0.04	1(0.02)	26784	0.04	0.00
All cases	76(1.50)	26273	2.89	52(1.03)	26666	1.95	4.66

Abbreviations: ER=estrogen receptor; DCIS=ductal carcinoma in situ; LCIS=lobular carcinoma in situ.
*Incidence rate is calculated as the number of patients who developed the event of interest divided by the patient-years of follow-up.
**Absolute risk reduction (ARR) is calculated by subtracting the cumulative incidence of the raloxifene arm from that of the placebo arm, where cumulative incidence is estimated using 1-exp(-I*T). I is the incidence rate, and T is the average patient-years of follow-up in each arm.

Program: RMP.H3SSGGIO.SASPGM(BCCTIR1) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(BCTIRPR)

Figure GGIO.11.2. Kaplan-Meier curves of ER-positive invasive breast cancer for all randomized patients.

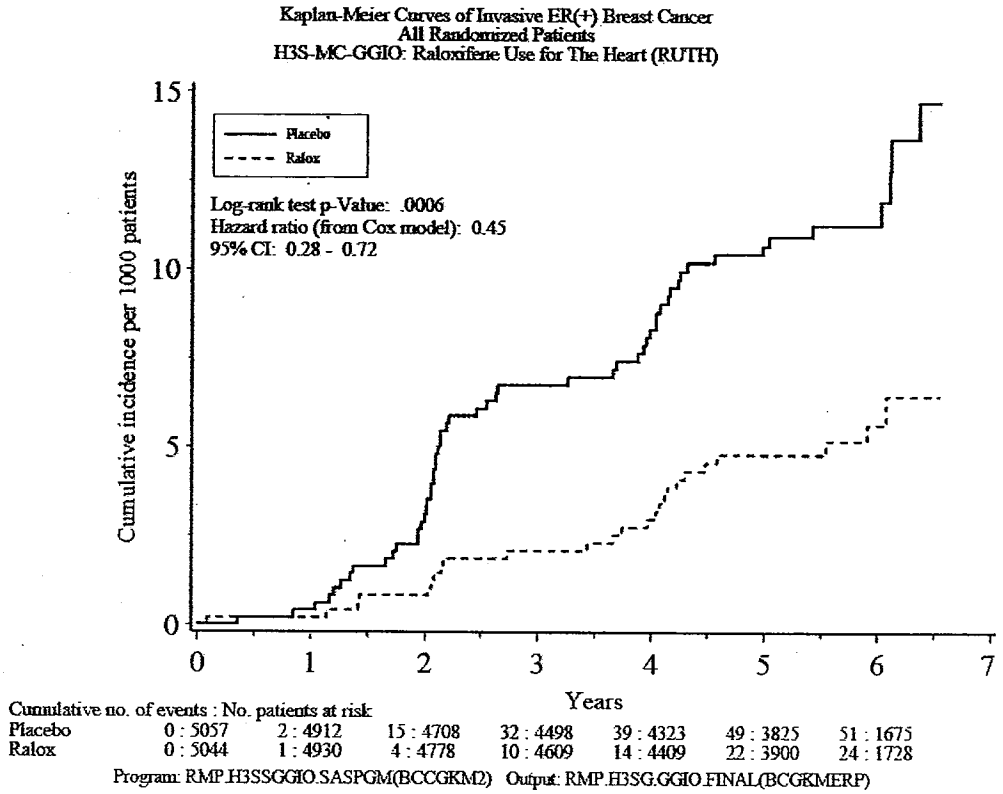
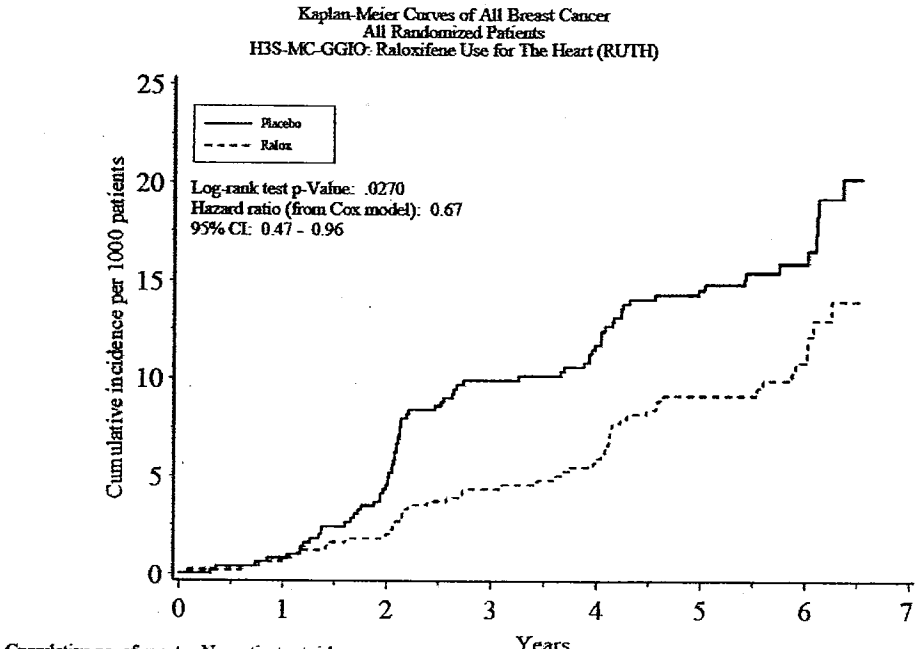


Figure GGIO.11.3. Kaplan-Meier curves of all breast cancer for all randomized patients.



Cumulative no. of events : No. patients at risk

Placebo	0 : 5057	4 : 4910	22 : 4701	47 : 4483	55 : 4307	67 : 3808	71 : 1667
Ralox	0 : 5044	4 : 4927	10 : 4773	21 : 4600	28 : 4397	42 : 3883	46 : 1720

Program: RMP.H3SSGGIO.SASPGM(BCCGKM3) Output: RMP.H3SG.GGIO.FINAL(BCGKMALL)

Sensitivity Analyses of Invasive Breast Cancer (11.4.2.2)

The following sensitivity analyses were conducted to investigate whether the observed effect of raloxifene on invasive breast cancer was robust with respect to the subsets of interest or to potential confounding factors:

- Invasive breast cancer in the PP population
- Invasive breast cancer in patients at least 60 years old
- Invasive breast cancer stratified by geographical region
- Invasive breast cancer adjusted for baseline risk factors

Each sensitivity analysis showed a significant reduction in the incidence of invasive breast cancer in patients assigned to raloxifene compared with patients assigned to placebo:

- In the subset of the per-protocol population (N=3375 raloxifene, N=3454 placebo), raloxifene significantly decreased the incidence of invasive breast cancer by 45% (hazard ratio [HR] 0.55; 95% CI, 0.35 to 0.88).
- In the subset of the patients at least 60 years old at randomization (N=4218 raloxifene, N=4213 placebo), raloxifene significantly decreased the incidence of invasive breast cancer by 43% (HR 0.57; 95% CI, 0.38 to 0.86).
- In the subset of the patients less than 60 years old at randomization (N=826 raloxifene, N=844 placebo), there were 12 patients diagnosed with invasive breast cancer (n=4 raloxifene, n=8 placebo)
- Results from the analysis stratified by geographical region showed that the effect of raloxifene on invasive breast cancer was consistent across regions and had a significant 44% reduction in the incidence of invasive breast cancer (HR 0.56; 95% CI, 0.38 to 0.83)

To determine whether the observed effects of raloxifene on the primary analyses of invasive breast cancer were confounded by baseline characteristics, analyses were performed adjusting for baseline risk factors. A baseline characteristic was considered a risk factor if it significantly affected the endpoint of interest in a univariate analysis and in the final multivariate adjusted model. The risk factors that were significant in the univariate model and remained significant in the final multivariate adjusted model in the time-to-event analysis included the following:

- Prior use of estrogen only
- Family history of breast cancer in mother, sister, or daughter
- Race (Caucasian, all other races)

After adjusting for baseline risk factors, raloxifene significantly decreased the incidence of invasive breast cancer by 40% (HR 0.60; 95% CI, 0.40 to 0.90).

Subgroup Analyses of Invasive Breast Cancer (11.4.2.3)

The potential effects of raloxifene on the incidence of the invasive breast cancer primary endpoint were examined for predefined clinically relevant risk factors. The treatment by subgroup interaction was not significant for any subgroup with the exception of prior ovariectomy (interaction p value=0.0673). Raloxifene demonstrated similar effects regardless of age (≤65 years old or >65 years old) or 5-year predicted risk of invasive breast cancer risk (<1.66% or ≥1.66%). There were too few non-Caucasian patients to adequately assess the effect of raloxifene among subgroups by race. For patients reporting having at least one ovary, a significant reduction in the incidence of invasive breast cancer was observed for patients assigned to raloxifene compared with those assigned to placebo. However, there was no significant difference between treatment groups for patients reporting a prior ovariectomy. The sample size of the subgroup of patients reporting a prior ovariectomy was small (approximately 16% of the all randomized patients) relative to the number of patients reporting at least one intact ovary thereby limiting the interpretation of these results.

Table GGIO.11.13. Subgroup Analysis of Invasive Breast Cancer (All Randomized Patients)

Subgroup	Placebo (N=5057) N	n (%)	Ralox (N=5044) N	n (%)	Hazard ratio (95% CI)	Interaction p-Value*
Age (yrs)						.4584
<=65	1877	26(1.39)	1854	12(0.65)	0.46(0.23, 0.90)	
>65	3180	44(1.38)	3190	28(0.88)	0.62(0.39, 1.00)	
Race						.8733
Caucasian	4247	66(1.55)	4234	38(0.90)	0.57(0.38, 0.84)	
All other races	810	4(0.49)	810	2(0.25)	0.49(0.09, 2.66)	
Body mass index (kg/m2)						.3095
<=25	1230	11(0.89)	1186	9(0.76)	0.84(0.35, 2.03)	
>25 and <=30	2013	30(1.49)	2039	12(0.59)	0.38(0.20, 0.75)	
>30	1798	28(1.56)	1805	19(1.05)	0.67(0.37, 1.19)	
5-year predicted invasive breast cancer risk >= 1.66%						.4986
Yes	2061	35(1.68)	2101	23(1.09)	0.65(0.38, 1.09)	
No	2975	34(1.14)	2943	17(0.58)	0.49(0.28, 0.86)	
Family history of breast cancer						.3413
Yes	445	9(2.02)	452	8(1.77)	0.89(0.34, 2.31)	
No	4139	53(1.28)	4148	29(0.70)	0.53(0.34, 0.84)	
Prior use of estrogen only						.3400
Yes	702	14(1.99)	697	11(1.58)	0.80(0.36, 1.77)	
No	4300	55(1.28)	4292	29(0.68)	0.52(0.33, 0.81)	

Abbreviations: CI=confidence interval.
*Interaction p-Value is obtained from a Cox model: year*censor=therapy + subgroup + therapy*subgroup.

Program: RMP.H38SGGIO.SASPGM(BCCTHR2) Data: RMP.SAS.H3SK.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(BCTSSGRP)

Table GGIO.11.13. Subgroup Analysis of Invasive Breast Cancer All Randomized Patients (Concluded)

Subgroup	Placebo (N=5057) N	n (%)	Ralox (N=5044) N	n (%)	Hazard ratio (95% CI)	Interaction p-Value*
Prior use of estrogen plus progestin						.8015
Yes	323	7(2.17)	262	3(1.06)	0.49(0.13, 1.88)	
No	4641	62(1.34)	4658	37(0.79)	0.58(0.39, 0.88)	
Prior hysterectomy						.2760
Yes	1175	15(1.28)	1144	12(1.05)	0.81(0.38, 1.73)	
No	3871	55(1.42)	3896	28(0.72)	0.50(0.31, 0.78)	
Prior ovariectomy						.0673
Yes	774	9(1.16)	800	11(1.38)	1.16(0.48, 2.79)	
No	4207	60(1.43)	4185	26(0.67)	0.46(0.29, 0.72)	

Abbreviations: CI=confidence interval.
*Interaction p-Value is obtained from a Cox model: year*censor=therapy + subgroup + therapy*subgroup.

Program: RMP.H3S6GGIO.SASPGM(SCCTHR2) Data: RMP.SAS.H3SM.L.NCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SCTSHGRP)

Tumor Characteristics of Breast Cancer Events (11.4.2.4.)

Table xxx shows the tumor characteristics for diagnosed breast cancers. Breast cancer tumor characteristics were assessed and recorded by the adjudication committee based on local pathology reports and other available documentation.

- **ER status** was determined for 109 breast cancers, 83 were ER-positive.
- **Invasiveness** was ascertained for 126 tumors, 110 were determined invasive, and the majority was infiltrating ductal (70.91%) or lobular carcinomas (13.64%).
- **Lymph node status** was evaluated in 104 cases; 75 cases had 0 positive nodes.
- The most common **stage** reported was Stage I. There were two Stage IIIA cases, one Stage IIIB case, and one Stage IV case; all were reported in patients assigned to raloxifene.

Methodology to ascertain if a breast cancer was **preexisting** was described in section 9.5.1.1.

- In this study, 39 breast cancers were considered preexisting.

Table xxx. Tumor Characteristics of Breast Cancer Events Randomized Patients with Breast Cancer

	Placebo (N=76)		Ralox (N=52)		Total (N=128)	
Characteristic	n (%)	IR*	n (%)	IR*	n (%)	IR*
Estrogen receptor status						
ER(+)	57(75.00)	2.17	26(50.00)	0.98	83(64.84)	1.57
ER(-)	10(13.16)	0.38	16(30.77)	0.60	26(20.31)	0.49
Not done	5(6.58)	0.19	9(17.31)	0.34	14(10.94)	0.26
Cannot determine	4(5.26)	0.15	1(1.92)	0.04	5(3.91)	0.09
Tumor type						
Non-invasive	5(6.58)	0.19	11(21.15)	0.41	16(12.50)	0.30
Ductal carcinoma in situ	5(100.00)	0.19	11(100.00)	0.41	16(100.00)	0.30
Lobular carcinoma in situ	0(0.00)	0.00	0(0.00)	0.00	0(0.00)	0.00
Non-infiltration comedocarcinoma	0(0.00)	0.00	0(0.00)	0.00	0(0.00)	0.00
Other non-invasive	0(0.00)	0.00	0(0.00)	0.00	0(0.00)	0.00
Invasive	70(92.11)	2.66	40(76.92)	1.50	110(85.94)	2.08
Adenocarcinoma or carcinoma NOS	4(5.71)	0.15	2(5.00)	0.08	6(5.45)	0.11
Infiltrating ductal carcinoma	51(72.86)	1.94	27(67.50)	1.01	78(70.91)	1.47
Lobular carcinoma	10(14.29)	0.38	5(12.50)	0.19	15(13.64)	0.28
Medullary	0(0.00)	0.00	1(2.50)	0.04	1(0.91)	0.02
Micinous adenocarcinoma	1(1.43)	0.04	2(5.00)	0.08	3(2.73)	0.06
Papillary carcinoma	1(1.43)	0.04	1(2.50)	0.04	2(1.82)	0.04
Tubular adenocarcinoma	3(4.29)	0.11	1(2.50)	0.04	4(3.64)	0.08
Other invasive	0(0.00)	0.00	1(2.50)	0.04	1(0.91)	0.02
Cannot assess	1(1.32)	0.04	1(1.92)	0.04	2(1.56)	0.04
Tumor grade						
Well differentiated	15(19.74)	0.57	11(21.15)	0.41	26(20.31)	0.49
Moderately differentiated	35(46.05)	1.33	20(38.46)	0.75	55(42.97)	1.04
Poorly differentiated	10(13.16)	0.38	16(30.77)	0.60	26(20.31)	0.49
Undifferentiated	0(0.00)	0.00	0(0.00)	0.00	0(0.00)	0.00
Unknown	16(21.05)	0.61	5(9.62)	0.19	21(16.41)	0.40

*Incidence per 1000 patient-years: 26273 follow up patient-years in Placebo, 26666 in Ralox.
Program: RMP.H3SSGGIO.SASPGM(SCCTTUM1) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SCCTTUM1)

Characteristic	Placebo (N=76) n (%)	IR*	Ralox (N=52) n (%)	IR*	Total (N=128) n (%)	IR*
Tumor stage						
Lymph nodes evaluated						
Yes	63(82.89)	1.40	41(78.85)	1.54	104(81.25)	1.96
0 positive nodes	43(68.25)	1.64	32(78.05)	1.20	75(72.12)	1.42
1-3 positive nodes	12(19.05)	0.46	7(17.07)	0.26	19(18.27)	0.36
>=4 positive nodes	8(12.70)	0.30	2(4.88)	0.08	10(9.62)	0.19
No	12(15.79)	0.46	10(19.23)	0.38	22(17.19)	0.42
Unknown	1(1.32)	0.04	1(1.92)	0.04	2(1.56)	0.04
Stage 0	5(6.58)	0.19	11(21.15)	0.41	16(12.50)	0.30
Stage I	37(48.68)	1.41	19(36.54)	0.71	56(43.75)	1.06
Stage IIA	19(25.00)	0.72	9(17.31)	0.34	28(21.88)	0.53
Stage IIB	4(5.26)	0.15	4(7.69)	0.15	8(6.25)	0.15
Stage IIIA	0(0.00)	0.00	2(3.85)	0.08	2(1.56)	0.04
Stage IIIB	0(0.00)	0.00	1(1.92)	0.04	1(0.78)	0.02
Stage IV	1(1.32)	0.04	1(1.92)	0.04	2(1.56)	0.04
Cannot be determined	10(13.16)	0.38	5(9.62)	0.19	15(11.72)	0.28
Tumor size** (cm)						
<=1.0	19(25.00)	0.72	17(32.69)	0.64	36(28.13)	0.68
>1.0 and <=2.0	37(48.68)	1.41	13(25.00)	0.49	50(39.06)	0.94
>2.0 and <=3.0	10(13.16)	0.38	13(25.00)	0.49	23(17.97)	0.43
>3.0	5(6.58)	0.19	3(5.77)	0.11	8(6.25)	0.15
Unknown	5(6.58)	0.19	6(11.54)	0.23	11(8.59)	0.21
Pre-existing breast cancer						
Yes	24(31.58)	0.91	15(28.85)	0.56	39(30.47)	0.74
No	48(63.16)	1.83	21(59.62)	1.16	79(61.72)	1.49
Cannot be determined	4(5.26)	0.15	6(11.54)	0.23	10(7.81)	0.19

*Incidence per 1000 patient-years: 26273 follow up patient-years in Placebo, 26666 in Ralox.
**Tumor size is the maximum of the length, the width or the breadth of a tumor.

Program: RMP.H38SQGIO.SASPGM(SCCTTUM1) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H38O.GGIO.FINAL(SCCTTUM1)

Compliance with and Findings from Clinical Breast Examinations and Mammograms (11.4.2.5.)

Clinical breast exams were scheduled at randomization and every 2 years thereafter.
Almost all patients were compliant with clinical breast exams at baseline (99.17%).
Compliance with clinical breast exams was consistent between treatment groups at all the visits where the breast exams were scheduled (see the table below).
Findings from clinical breast exams were classified as normal for at least 95% of patients at each scheduled time point and the classification of findings as normal or abnormal did not differ significantly between treatment groups (Table GGIO.11.16).

Table xxx. Clinical Breast Examination Compliance (All Randomized Patients)

Years in study (Visit)	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Baseline (2)				
Eligible patients**	5057	5044	10101	
Clinical breast exams performed	5015(99.17)	5002(99.17)	10017(99.17)	.991
2 years (7)				
Eligible patients**	4699	4771	9470	
Clinical breast exams performed	4274(90.96)	4370(91.60)	8644(91.28)	.270
4 years (11)				
Eligible patients**	4336	4404	8740	
Clinical breast exams performed	3824(88.19)	3888(88.28)	7712(88.24)	.894
6 years (15)				
Eligible patients**	1010	1009	2019	
Clinical breast exams performed	867(85.84)	861(85.33)	1728(85.59)	.744

*p-Value is obtained from a Pearson's Chi-square test.
**A patient is considered eligible for a clinical breast exam through the last visit at which study information regarding the patient is available.

Program: RMP.H3SSGGIO.SASPGM(SCCTBCMP)
Data: RMP.SAS.H3SM.L.MOGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(SCTBCMP)

Table xxx. Clinical Breast Examination Findings by Visit (All Randomized Patients)

Years in study (Visit)	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Baseline (2)				
Clinical breast exams performed	5015	5002	10017	.6497
Normal	4785(95.41)	4782(95.60)	9567(95.51)	
Abnormal	230(4.59)	220(4.40)	450(4.49)	
Not clinically significant	214(93.04)	202(91.82)	416(92.44)	
Clinically significant	16(6.96)	18(8.18)	34(7.56)	
2 years (7)				
Clinical breast exams performed	4274	4370	8644	.4528
Normal	4141(96.89)	4246(97.16)	8387(97.03)	
Abnormal	133(3.11)	124(2.84)	257(2.97)	
Not clinically significant	118(88.72)	105(84.68)	223(86.77)	
Clinically significant	15(11.28)	19(15.32)	34(13.23)	
4 years (11)				
Clinical breast exams performed	3824	3888	7712	.3780
Normal	3710(97.02)	3785(97.35)	7495(97.19)	
Abnormal	114(2.98)	103(2.65)	217(2.81)	
Not clinically significant	105(92.11)	90(87.38)	195(89.86)	
Clinically significant	9(7.89)	13(12.62)	22(10.14)	
6 years (15)				
Clinical breast exams performed	867	861	1728	.9858
Normal	854(98.50)	848(98.49)	1702(98.50)	
Abnormal	13(1.50)	13(1.51)	26(1.50)	
Not clinically significant	11(84.62)	9(69.23)	20(76.92)	
Clinically significant	2(15.38)	4(30.77)	6(23.08)	

*p-Value for testing normal versus abnormal is obtained from a Pearson's Chi-square test.

Program: RMP.H3SGGIO.SASPGM(BCCTBFND)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(BCTBFND)

Mammograms were scheduled at randomization and every 2 years thereafter. Almost all patients were compliant with mammograms at baseline (99.96%). Compliance with mammograms was consistent between treatment groups at all times (Table GGIO.11.17).
Findings from mammograms were classified as normal for at least 95% of patients at each scheduled time point and the classification of findings as normal or abnormal did not differ significantly between treatment groups (Table GGIO.11.18). One patient (294/1220) in the placebo group had a baseline mammogram showing a clinically significant abnormality; a malignancy was diagnosed. This patient was inadvertently randomized (Appendix 16.2.2).

Mammograms performed as part of study conclusion (ie, final visit) were only classified by the investigator as either showing no significant abnormality or a clinically significant abnormality without any further categorization as to the presence or absence of a malignancy (Table GGIO.11.18).
There was no significant difference between treatment groups in the post-baseline mammogram assessment in patients whose baseline mammogram readings indicated no significant abnormality (Table GGIO.11.19).

Table GGIO.11.17. Mammogram Compliance (All Randomized Patients)

Years in study (Visit)	Placebo (N=5057) n	(%)	Ralox (N=5044) n	(%)	Total (N=10101) n	(%)	p-Value*
Baseline (2)							
Eligible patients (a)	5057		5044		10101		
Mammograms performed	5055	(99.96)	5042	(99.96)	10097	(99.96)	N/A
2 years (7)							
Eligible patients (a)	4699		4771		9470		
Mammograms performed	4311	(91.74)	4405	(92.33)	8716	(92.04)	.292
4 years (11)							
Eligible patients (a)	4336		4404		8740		
Mammograms performed	3799	(87.62)	3858	(87.60)	7657	(87.61)	.985
6 years (15)							
Eligible patients (a)	1010		1009		2019		
Mammograms performed	813	(80.50)	798	(79.09)	1611	(79.79)	.431
Study conclusion (Final visit)							
Eligible patients (b)	1856		1933		3789		
Mammograms performed	1383	(74.52)	1456	(75.32)	2839	(74.93)	.566
Other**							
Mammograms performed	17		22		39		

*p-Value is obtained from a Pearson's Chi-square test if total>=10, Fisher's exact test if 5<=total<10, and N/A otherwise.
**Performed as part of final visit procedures for patients who withdrew consent prior to study conclusion.
(a) A patient is considered eligible for a mammogram through the last visit at which study information regarding the patient is available.
(b) A patient is considered eligible for a mammogram at study conclusion if at least two years had elapsed since the previous mammogram.

Program: RMP.H3SGGIO.SASPGM(HCCMMCF)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(HCTMCMP)

Table GGIO.11.18. Mammogram Findings by Visit (All Randomized Patients)

Years in study (Visit)	Placebo (N=5057) n	(%)	Ralox (N=5044) n	(%)	Total (N=10101) n	(%)	p-Value*
Baseline (2)							
Mammograms performed	5055		5042		10097		.2514
No significant abnormality	4825	(95.45)	4788	(94.96)	9613	(95.21)	
Clinically significant abnormality	230	(4.55)	254	(5.04)	484	(4.79)	
No malignancy	229	(99.57)	253	(99.61)	482	(99.59)	
Malignancy diagnosed	1	(0.43)	0	(0.00)	1	(0.21)	
2 years (7)							
Mammograms performed	4311		4405		8716		.2280
No significant abnormality	4135	(95.92)	4247	(96.41)	8382	(96.17)	
Clinically significant abnormality	176	(4.08)	158	(3.59)	334	(3.83)	
No malignancy	147	(83.52)	144	(91.14)	291	(87.13)	
Malignancy diagnosed	29	(16.48)	10	(6.33)	39	(11.68)	
4 years (11)							
Mammograms performed	3799		3858		7657		.5213
No significant abnormality	3672	(96.66)	3739	(96.92)	7411	(96.79)	
Clinically significant abnormality	127	(3.34)	119	(3.08)	246	(3.21)	
No malignancy	110	(86.61)	103	(86.55)	213	(86.59)	
Malignancy diagnosed	14	(11.02)	12	(10.08)	26	(10.57)	
6 years (15)							
Mammograms performed	813		798		1611		.9489
No significant abnormality	790	(97.17)	775	(97.12)	1565	(97.14)	
Clinically significant abnormality	23	(2.83)	23	(2.88)	46	(2.86)	
No malignancy	20	(86.96)	21	(91.30)	41	(89.13)	
Malignancy diagnosed	2	(8.70)	2	(8.70)	4	(8.70)	
Study conclusion (Final visit)							
Mammograms performed	1383		1456		2839		.1006
No significant abnormality	1357	(98.12)	1415	(97.18)	2772	(97.64)	
Clinically significant abnormality	26	(1.88)	41	(2.82)	67	(2.36)	
Other**							
Mammograms performed	17		22		39		N/A
No significant abnormality	17	(100.00)	21	(95.45)	38	(97.44)	
Clinically significant abnormality	0	(0.00)	1	(4.55)	1	(2.56)	

*p-Value is obtained from a Pearson's Chi-square test if total>=10, Fisher's exact test if 5<=total<10, and N/A otherwise.
**Performed as part of final visit procedures for patients who withdrew consent prior to study conclusion.

Program: RMP.H3SGGIO.SASPGM(HCCMMCF)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(HCTMFWD)

Table GGIO.11.19. Post-baseline Mammogram Findings (Randomized Patients with Baseline Mammograms Indicating No Significant Abnormality)

Most serious postbaseline mammogram finding**	Placebo (N=4226) n (%)	Ralox (N=4295) n (%)	Total (N=8521) n (%)	p-Value*
No significant abnormality	3983(94.21)	4066(94.67)	8049(94.44)	
Clinically significant abnormality	245(5.79)	229(5.33)	474(5.56)	.3511
No malignancy	188(76.73)	174(75.98)	362(76.37)	
Malignancy diagnosed	41(16.73)	22(9.61)	63(13.29)	

*p-Value for testing 'clinical significant abnormality' vs 'no significant abnormality' is obtained from a Pearson's Chi-square test.
**An abnormal mammogram resulting in the diagnosis of a malignancy is considered the most serious finding, followed by an abnormal mammogram resulting in a diagnosis other than malignancy, and finally a mammogram with no significant abnormality.

Program: RMP.H3SSGGIO.SASPGM(BCCTMCON)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(BCTMCONV)

Analysis for Investigator-Reported Breast Cancers (11.4.2.6.)

There were 129 patients reported as being diagnosed with breast cancer; this includes Patient 985/1151, who was assigned to raloxifene and had an investigator-reported breast cancer that was not adjudicated as such.

- Raloxifene significantly decreased the incidence of all investigator-reported breast cancers by 31% (HR 0.69; 95% CI, 0.48 to 0.97) (Table GGIO.14.17).

Follow-up Treatment after Diagnosis of Breast Cancer (11.4.2.7.)

For patients who had an investigator-reported breast cancer, treatment information was collected at each 6-month visit after the diagnosis and was classified according to treatment type (Table GGIO.11.20).

- Among the 129 patients with an investigator-reported breast cancer, more than half (70/129, 54.3%) reported treatment after their diagnosis, 35.7% (46/129) reported no treatment, and 10.1% (13/129) reported no information regarding follow-up treatment.
- The most common treatments administered for breast cancer were tamoxifen and radiation therapy.

Table GGIO.11.20. Summary of Follow-up Treatment after Diagnosis with Breast Cancer (Investigator-Reported, Randomized Patients with Breast Cancer)

Treatment information*	Placebo (N=76) n (%)	Ralox (N=53) n (%)
Yes	46(60.53)	24(45.28)
Tamoxifen	29(38.16)	11(20.75)
Chemotherapy	12(15.79)	7(13.21)
Radiation therapy	28(36.84)	11(20.75)
Other	11(14.47)	7(13.21)
No	25(32.89)	21(39.62)
Missing	5(6.58)	8(15.09)

*Patient received treatment at some time following breast cancer diagnosis.

Program: RMP.H3SSGGIO.SASPGM(BCCTFU)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(BCTMED)

Coronary Primary Endpoint (11.4.3.)

The analyses of the coronary primary endpoint events are presented in the following order in this section:

- Coronary primary and secondary endpoints: composite and individual events (Section 11.4.3.1)
- Sensitivity analyses of the coronary primary endpoint (Section 11.4.3.2),
- Subgroup analyses of the coronary primary endpoint (Section 11.4.3.3).
- ECG compliance and findings (Section 11.4.3.4)
- Other analyses of the coronary primary endpoint (Section 11.4.3.5)

A total of 1595 primary coronary events in 1221 patients were **reported** by investigators (Table GGIO.14.18). The analyses reported in this document are based on 1086 patients with **adjudicated** coronary events (Table GGIO.11.21), unless otherwise specified.

Details of the primary coronary endpoint events:

- **Coronary death:** A total of 468 patients were **reported** to have died from coronary causes during the study period (243 in placebo, 225 in raloxifene) (Table GGIO.14.18); 526 deaths were **adjudicated** as due to coronary causes (273 in placebo, 253 in raloxifene) (Table GGIO.11.21).
  - Analyses of coronary deaths were based on the 526 patients with adjudicated coronary deaths, unless otherwise specified.
- **Nonfatal MIs:** A total of 472 patients (241 in placebo, 231 in raloxifene) were **reported** to have had at least one nonfatal MI during the study period (Table GGIO.14.18). A total of 391 patients (208 in placebo, 183 in raloxifene) had at least one **adjudicated** nonfatal MI (Table GGIO.11.21).
  - Analyses of nonfatal MIs were based on the 391 patients with adjudicated nonfatal MIs, unless otherwise specified.
- Hospitalized ACS other than MI: A total of 450 patients (247 in placebo, 203 in raloxifene) were **reported** to have had at least one hospitalized ACS during the study period (Table GGIO.14.18). A total of 354 patients (185 in placebo, 169 in raloxifene) had a least one **adjudicated** hospitalized ACS (Table GGIO.11.21).
  - Analyses of hospitalized ACS were based on the 354 patients with adjudicated hospitalized ACS, unless otherwise specified.

Coronary Primary and Secondary Endpoints: Composite and Individual Events (11.4.3.1.)

Table GGIO.11.21 presents results of the time-to-event analyses of the coronary primary endpoint and the individual coronary events, and Table GGIO.11.22 presents incidence rates for the coronary primary endpoint and the individual coronary events.

- There was no significant increase or decrease in incidence of the coronary primary endpoint of combined coronary death, nonfatal MI, or hospitalized ACS other than MI in the raloxifene group compared with the placebo group (Figure GGIO.11.4).
- Thus, the coronary primary objective was not achieved at the protocol-specified significance level of 0.0423.

The cumulative incidence curves for the combined coronary primary endpoint show no evidence for an early increase in risk of CHD events in the raloxifene group (Figure GGIO.11.4).

There was no significant increase or decrease in the incidence of any of the individual events of the coronary primary endpoint in the raloxifene group compared with the placebo group (Table GGIO.11.21, Figure GGIO.11.5, Figure GGIO.11.6, and Figure GGIO.11.7). Caution should be used in interpreting the results of the time-to-event analyses for the individual events of hospitalized ACS or MI as a patient may have had an MI before a hospitalized ACS or had a hospitalized ACS before an MI.
Consequently, the time-to-event analysis for hospitalized ACS or MI combined is more informative. No between treatment group differences were observed for hospitalized ACS or MI combined (Table GGIO.11.21).

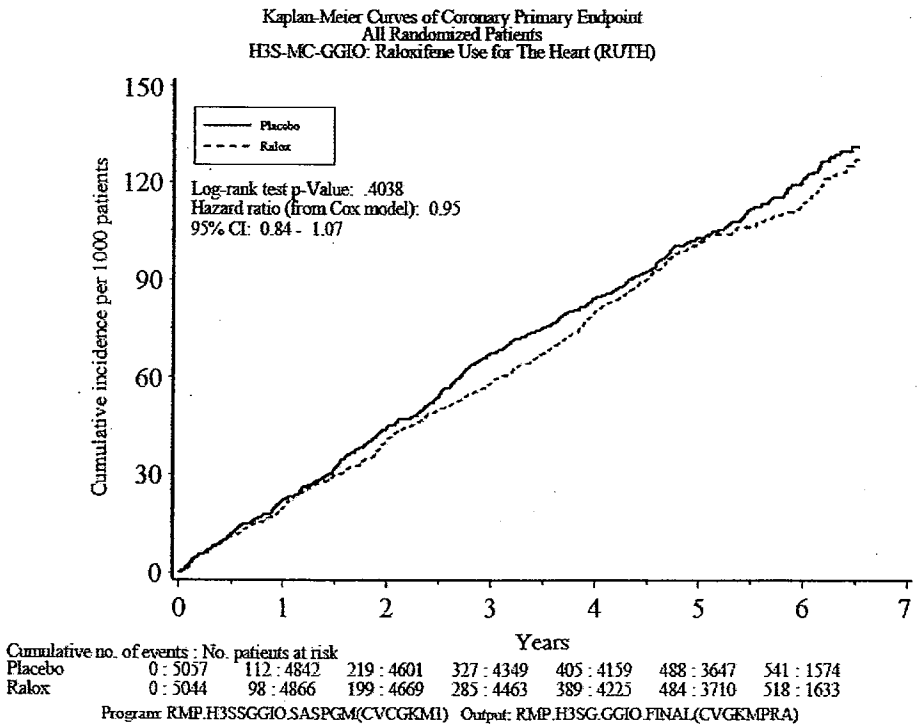


Figure GGIO.11.4. Kaplan-Meier curves of coronary primary endpoint for all randomized patients.

Table GGIO.11.21. Time-to-Event Analysis of Coronary Primary Endpoint and Coronary Events (All Randomized Patients)

Coronary endpoint	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard ratio (95% CI)	p-Value*
Coronary primary endpoint	553(10.94)	533(10.57)	0.95(0.84, 1.07)	.4028
Coronary death	273(5.40)	253(5.02)	0.92(0.77, 1.09)	.3139
Nonfatal MI**	208(4.11)	183(3.63)	0.87(0.71, 1.06)	.1629
Criterion I	40(19.23)	40(21.86)		
Criterion II	90(43.27)	60(32.79)		
Criterion III	56(26.92)	54(29.51)		
Criterion IV (silent MI)	9(4.33)	24(13.11)		
Criterion V	13(6.25)	5(2.73)		
Hospitalized ACS other than MI	185(3.66)	169(3.35)	0.90(0.73, 1.11)	.3385
Nonfatal MI** or hospitalized ACS other than MI	360(7.12)	326(6.46)	0.89(0.77, 1.04)	.1410
Coronary death or nonfatal MI**	416(8.23)	400(7.93)	0.95(0.83, 1.09)	.4538

Abbreviations: CI=confidence interval; MI=myocardial infarction; ACS=acute coronary syndrome.
*p-Value is obtained from a log-rank test.
**Nonfatal MI includes silent MI.

Program: RMP.H3SSGGIO.SASPGM(CVCTHR1) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRPRA)

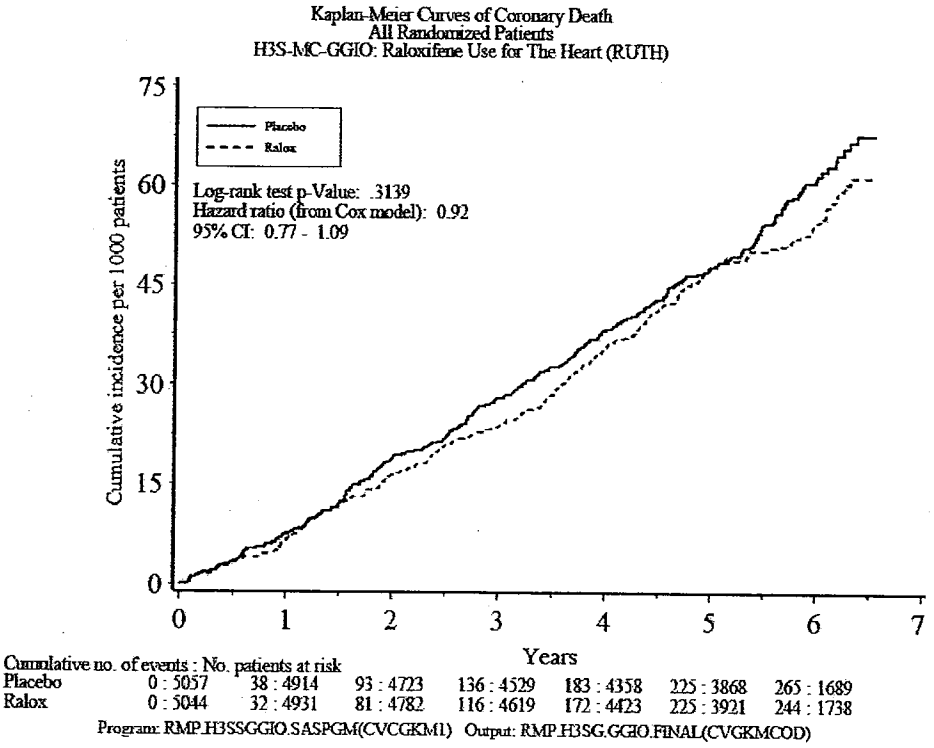


Figure GGIO.11.5. Kaplan-Meier curves of coronary death for all randomized patients.

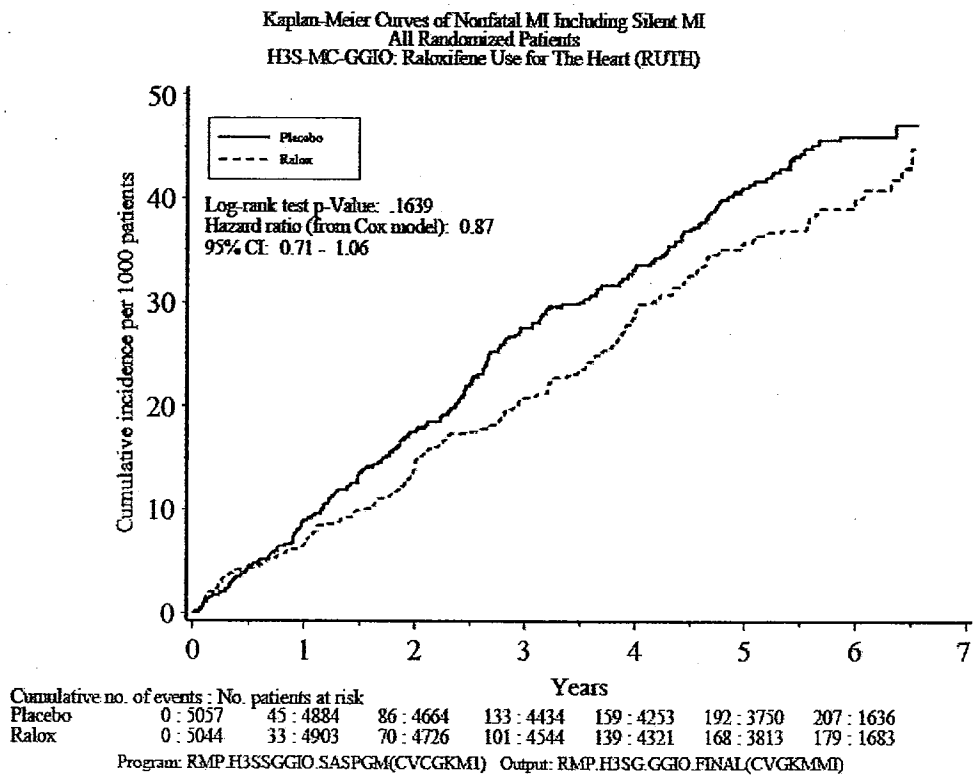


Figure GGIO.11.6. Kaplan-Meier curves of nonfatal (including silent) MI for all randomized patients.

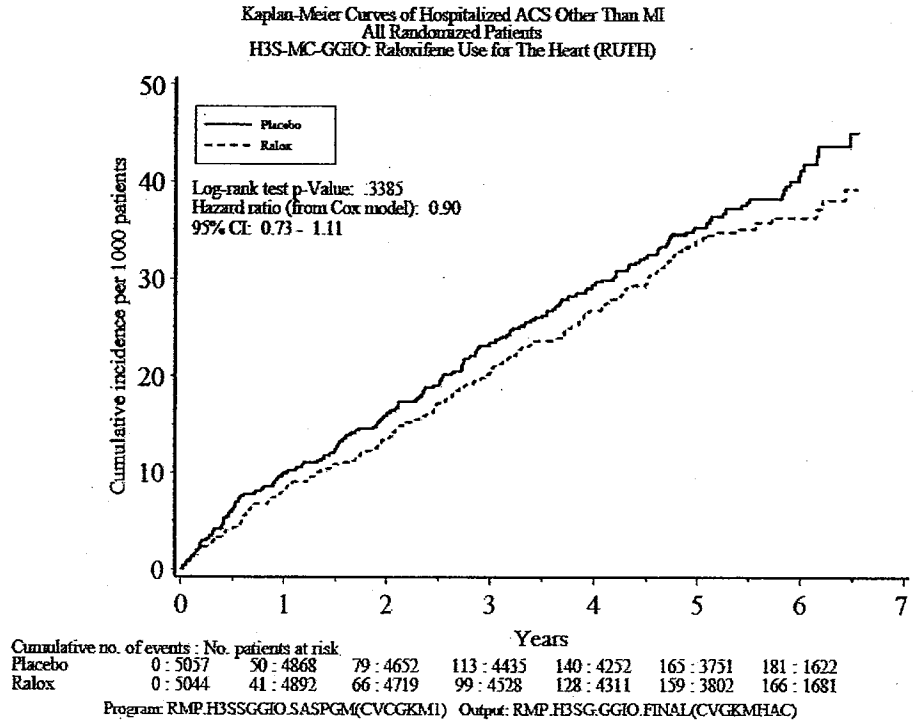


Figure GGIO.11.7. Kaplan-Meier curves of hospitalized ACS other than MI for all randomized patients.

Table GGIO.11.22. Incidence Rate of Coronary Primary Endpoint and Coronary Events (All Randomized Patients)

Coronary endpoint	Placebo (N=5057) n (%)	Patient-years of follow-up	Incidence rate* per 1000 patients	Ralox (N=5044) n (%)	Patient-years of follow-up	Incidence rate* per 1000 patients	ARR** per 1000 patients
Coronary primary endpoint	553 (10.94)	25570	21.62	533 (10.57)	25930	20.55	3.31
Coronary death	273 (5.40)	26403	10.31	253 (5.02)	26706	9.45	3.63
Nonfatal MI including silent MI	208 (4.11)	26027	7.99	183 (3.63)	26268	6.94	4.67
Hospitalized ACS other than MI	185 (3.66)	25982	7.12	169 (3.35)	26301	6.43	2.97

Abbreviations: MI-myocardial infarction; ACS-acute coronary syndrome.
*Incidence rate is calculated as the number of patients who developed the event of interest divided by the patient-years of follow-up.
**Absolute risk reduction (ARR) is calculated by subtracting the cumulative incidence of the raloxifene arm from that of the placebo arm, where cumulative incidence is estimated using 1-exp(-I*T), I is the incidence rate, and T is the average patient-years of follow-up in each arm.

Program: RMP.H3SGGIO.SASPGM(CVCTIR1) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTIRPR)

Sensitivity Analyses of the Coronary Primary Endpoint (11.4.3.2.)

The following sensitivity analyses were conducted to investigate whether the observed effect of raloxifene on the coronary primary endpoint was robust with respect to the subsets of interest or potential confounding factors:

- An analysis of the coronary primary endpoint in the **per protocol (PP) population**, **primary prevention population**, and **secondary prevention population**
- An analysis of the coronary primary endpoint stratified **by country**
- An analysis of the coronary primary endpoint **adjusted for baseline risk factors**

- Consistent with results from the analysis on the ITT population, there was no significant increase or decrease in the incidence of the coronary primary endpoint in patients assigned to raloxifene compared to patients assigned to placebo, in the PP population (Table GGIO.14.19, Figure GGIO.14.4), the primary prevention population (Table GGIO.14.20, Figure GGIO.14.5), or the secondary prevention population (Table GGIO.14.21, Figure GGIO.14.6).
- There was no significant increase or decrease in the incidence of the coronary primary endpoint stratified by country (Table GGIO.14.22).

To determine whether the observed effects of raloxifene in the primary analysis of time-to-event were confounded by baseline characteristics, analyses were performed adjusting for **baseline risk factors**.

- A baseline characteristic was considered a risk factor if it significantly affected the endpoint of interest in a univariate analysis and in the final multivariate adjusted model.
- The following risk factors were significant in the univariate model and remained significant in the final multivariate adjusted model in the time-to-event analysis:
  - ACE inhibitor or angiotensin receptor blocker use at baseline
  - Age (≤65, >65 and <70, ≥70)
  - Aspirin use at baseline
  - Calcium channel blocker use at baseline
  - Cardiovascular risk score at baseline (≤5, >5 and ≤9, >9)
  - Diuretic use at baseline
  - Lower extremity arterial disease at baseline
  - Diabetes mellitus at baseline
  - Prior myocardial infarction
  - HMG-CoA reductase inhibitor use at baseline

After adjusting for baseline risk factors, there was no significant increase or decrease in the incidence of the coronary primary endpoint between treatment groups (Table GGIO.14.23).

Subgroup Analyses of the Coronary Primary Endpoint (11.4.3.3.)

The potential effects of raloxifene on the incidence of the coronary primary endpoint were examined for predefined clinically relevant risk factors (Table GGIO.9.4). The treatment-by-subgroup interaction was not significant for any subgroup, indicating that raloxifene did not

affect the incidence of the coronary primary endpoint in the subgroups analyzed (Table GGIO.11.23).

Table GGIO.11.23. Subgroup Analysis of Coronary Primary Endpoint (All Randomized Patients)

Subgroup	Placebo (N=5057) N	Placebo (N=5057) n (%)	Ralox (N=5044) N	Ralox (N=5044) n (%)	Hazard ratio (95% CI)	Interaction p-Value*
Age (yrs)						.2868
AGE<=65	1858	183(9.85)	1841	156(8.47)	0.84(0.68, 1.04)	
65<AGE<70	1219	114(9.35)	1252	130(10.38)	1.09(0.85, 1.40)	
AGE>=70	1980	256(12.93)	1951	247(12.66)	0.97(0.81, 1.16)	
Race						.8070
Caucasian	4247	461(10.85)	4234	441(10.42)	0.94(0.83, 1.06)	
All other races	810	92(11.36)	810	92(11.36)	0.98(0.74, 1.31)	
Body mass index (kg/m2) at baseline						.8149
<=25	1230	138(11.22)	1186	136(11.47)	1.01(0.80, 1.29)	
>25 and <=30	2013	212(10.53)	2029	203(9.96)	0.93(0.76, 1.12)	
>30	1798	202(11.23)	1805	192(10.64)	0.93(0.76, 1.13)	
Prior myocardial infarction						.8501
Yes	1468	245(16.69)	1482	235(15.86)	0.94(0.78, 1.13)	
No	3589	308(8.58)	3562	298(8.37)	0.96(0.82, 1.12)	
Prior angina pectoris with documented coronary disease						.2211
Yes	1638	222(13.55)	1703	203(11.92)	0.86(0.71, 1.04)	
No	3419	331(9.68)	3341	330(9.88)	1.00(0.86, 1.17)	
Prior coronary artery bypass surgery or catheter based coronary revascularization						.8595
Yes	1464	172(11.75)	1580	176(11.14)	0.93(0.76, 1.15)	
No	3593	381(10.60)	3464	357(10.31)	0.96(0.83, 1.10)	

Abbreviations: CI=confidence interval.
*Interaction p-Value is obtained from a Cox model: year*censor-therapy + subgroup + therapy*subgroup.

Program: EMP.H3SSGGIO.SASPGM(CVCTHR2) Data: EMP.SAS.H3SH.L.MCGGIOSA.FINAL.MAIN Output: EMP.H3SO.GGIO.FINAL(CVTSBGRP)

Subgroup	Placebo (N=5057) N	Placebo (N=5057) n (%)	Ralox (N=5044) N	Ralox (N=5044) n (%)	Hazard ratio (95% CI)	Interaction p-Value*
Lower extremity arterial disease at baseline						.9505
Yes	540	72(13.33)	543	70(12.89)	0.94(0.68, 1.31)	
No	4516	481(10.65)	4501	463(10.29)	0.95(0.84, 1.08)	
Diabetes mellitus at baseline						.3196
Yes	1309	286(12.39)	2298	262(11.40)	0.89(0.76, 1.06)	
No	2734	264(9.66)	2736	269(9.83)	1.01(0.85, 1.20)	
Current smoker at baseline						.6290
Yes	649	61(9.40)	607	51(8.40)	0.87(0.60, 1.26)	
No	4408	492(11.16)	4437	482(10.86)	0.96(0.85, 1.09)	
Hypertension at baseline						.9236
Yes	3935	438(11.13)	3928	421(10.72)	0.95(0.83, 1.08)	
No	1121	115(10.26)	1115	111(9.96)	0.96(0.74, 1.25)	
Hyperlipidemia at baseline						.9424
Yes	3701	400(10.81)	3680	385(10.46)	0.95(0.82, 1.09)	
No	1330	150(11.28)	1342	145(10.80)	0.96(0.76, 1.20)	
Cardiovascular risk score at baseline						.2261
<=5	1836	114(6.21)	1835	116(6.32)	1.01(0.78, 1.31)	
>5 and <=9	1757	218(12.41)	1712	224(13.08)	1.04(0.86, 1.25)	
>9	1464	221(15.10)	1497	193(12.89)	0.83(0.68, 1.01)	

Abbreviations: CI=confidence interval.
*Interaction p-Value is obtained from a Cox model: year*censor-therapy + subgroup + therapy*subgroup.

Program: EMP.H3SSGGIO.SASPGM(CVCTHR2) Data: EMP.SAS.H3SH.L.MCGGIOSA.FINAL.MAIN Output: EMP.H3SO.GGIO.FINAL(CVTSBGRP)

Subgroup	Placebo (N=5057) N	n (%)	Relox (N=5044) N	n (%)	Hazard ratio (95% CI)	Interaction p-Value*
HMG-CoA reductase inhibitor use at baseline						.8023
Yes	2361	238(10.08)	2382	236(9.91)	0.97(0.81, 1.16)	
No	2670	312(11.72)	2631	295(11.21)	0.94(0.80, 1.10)	
Aspirin use at baseline						.5920
Yes	2865	369(12.88)	2846	346(12.16)	0.93(0.80, 1.08)	
No	2166	182(8.40)	2167	185(8.54)	1.00(0.81, 1.22)	
Beta-blocker use at baseline						.7212
Yes	2262	277(11.72)	2431	271(11.15)	0.93(0.79, 1.10)	
No	2668	274(10.27)	2582	260(10.07)	0.97(0.82, 1.15)	
Calcium channel blocker use at baseline						.5236
Yes	1800	240(13.33)	1779	221(12.42)	0.91(0.76, 1.09)	
No	3231	311(9.63)	3234	310(9.59)	0.98(0.84, 1.15)	
ACE inhibitor or angiotensin receptor blocker use at baseline						.8144
Yes	2424	304(12.54)	2469	302(12.23)	0.96(0.82, 1.13)	
No	2607	247(9.47)	2544	229(9.00)	0.93(0.78, 1.12)	
Diuretic use at baseline						.2753
Yes	1956	278(14.21)	2036	262(12.87)	0.88(0.74, 1.04)	
No	3075	273(8.88)	2977	269(9.04)	1.01(0.85, 1.19)	

Abbreviations: CI=confidence interval; HMG-CoA=hydroxymethylglutaryl-coenzyme A; ACE=angiotensin converting enzyme.
*Interaction p-Value is obtained from a Cox model: year*censor=therapy + subgroup + therapy*subgroup.

Program: RMP.H3SSGGIO.SASPGM(CVCTHR2) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTSBGRP)

ECG Compliance and Findings (11.4.3.4.)

Electrocardiograms were scheduled at baseline, Year 2, Year 4, and the final visit, if not performed in the 3 months prior to the final visit. Almost all patients had an ECG tracing performed at baseline (99.88%). Compliance with ECGs was consistent between treatment groups at all scheduled times (Table GGIO.11.24).

At baseline, 40.73% of patients had an abnormal ECG but this did not differ significantly between treatment groups. Of those patients with an abnormal ECG at baseline, significantly more raloxifene assigned patients had an ECG showing atrial fibrillation or flutter as compared to placebo-assigned patients.
At Year 4 and the final visit, significantly more placebo-assigned patients had abnormal ECG readings compared to raloxifene-assigned patients (Table GGIO.11.25).

For patients with a normal baseline ECG, significantly more placebo-assigned patients developed **a subsequent abnormal ECG** than raloxifene-assigned patients; the proportion of patients in the placebo group with pathologic ST-T depression was significantly greater than in the raloxifene group (Table GGIO.11.26).

Table GGIO.11.24. ECG Compliance (All Randomized Patients)

Years in study (Visit)	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Baseline (2)				
Eligible patients (a)	5057	5044	10101	
ECGs performed	5052(99.92)	5036(99.84)	10089(99.88)	.246
ECG evaluation forms received	5053(99.92)	5034(99.80)	10087(99.86)	.108
2 years (7)				
Eligible patients (a)	4693	4763	9456	
ECGs performed	4350(92.69)	4431(93.03)	8781(92.86)	.523
ECG evaluation forms received	4341(92.50)	4419(92.78)	8760(92.64)	.604
4 years (11)				
Eligible patients (a)	4326	4401	8727	
ECGs performed	3890(89.92)	3967(90.14)	7857(90.03)	.735
ECG evaluation forms received	3877(89.62)	3952(89.80)	7829(89.71)	.786
Study conclusion (Final visit)				
Eligible patients (b)	3979	4060	8039	
ECGs performed	3548(89.17)	3593(88.50)	7141(88.83)	.340
ECG evaluation forms received	3430(86.20)	3482(85.76)	6911(85.98)	.571
Other**				
ECGs performed	104	79	183	
ECG evaluation forms received	42(40.38)	40(50.63)	82(44.81)	

*p-Value is obtained from a Pearson's Chi-square test.
**Patient either had an ECG performed at an unscheduled visit, or completed a final visit prior to study conclusion and had an ECG performed as part of those visit procedures.
(a) A patient is considered eligible for an ECG through the last visit at which study information regarding the patient is available.
(b) A patient is considered eligible for an ECG at study completion if more than three months had elapsed since the previous study ECG.

Program: RMP.H3SGGIO.SASPGM(CVCTCMP1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTECMP)

Table GGIO.11.25. ECG Findings by Visit (All Randomized Patients)

Years in study (Visit)	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Baseline (2)				
ECG evaluation forms received	5053	5034	10087	
Tracing not assessable	87(1.72)	91(1.81)	178(1.76)	
Tracing assessable	4966(98.28)	4943(98.19)	9909(98.24)	
Normal	2914(58.68)	2959(59.86)	5873(59.27)	
Abnormal	2052(41.32)	1984(40.14)	4036(40.73)	.2306
Definite Q-wave MI	571(27.83)	545(27.47)	1116(27.65)	.4356
Pathologic ST-T depression	387(18.86)	400(20.16)	787(19.50)	.6029
Conduction disturbances	720(35.09)	678(34.17)	1398(34.64)	.2467
Atrial fibrillation or flutter	96(4.68)	128(6.45)	224(5.55)	.0291
Ventricular hypertrophy	679(33.09)	637(32.11)	1316(32.61)	.2335
2 years (7)				
ECG evaluation forms received	4341	4419	8760	
Tracing not assessable	90(2.07)	97(2.20)	187(2.13)	
Tracing assessable	4251(97.93)	4322(97.80)	8573(97.87)	
Normal	2473(58.17)	2598(60.11)	5071(59.15)	
Abnormal	1778(41.83)	1724(39.89)	3502(40.85)	.0682
Definite Q-wave MI	492(27.67)	482(27.96)	974(27.81)	.7681
Pathologic ST-T depression	336(18.90)	340(19.72)	676(19.30)	.8462
Conduction disturbances	665(37.40)	604(35.03)	1269(36.24)	.0747
Atrial fibrillation or flutter	103(5.79)	131(7.60)	234(6.68)	.0612
Ventricular hypertrophy	512(28.80)	518(30.05)	1030(29.41)	.8097
4 years (11)				
ECG evaluation forms received	3877	3952	7829	
Tracing not assessable	94(2.42)	102(2.58)	196(2.50)	
Tracing assessable	3783(97.58)	3850(97.42)	7633(97.50)	
Normal	2167(57.28)	2307(59.92)	4474(58.61)	
Abnormal	1616(42.72)	1543(40.08)	3159(41.39)	.0192
Definite Q-wave MI	438(27.10)	436(28.26)	874(27.67)	.9753
Pathologic ST-T depression	308(19.06)	278(18.02)	586(18.55)	.2132
Conduction disturbances	634(39.23)	591(38.30)	1225(38.78)	.2067
Atrial fibrillation or flutter	109(6.75)	113(7.32)	222(7.03)	.7712
Ventricular hypertrophy	435(26.92)	438(28.39)	873(27.64)	.8839
Study conclusion (Final visit)				
ECG evaluation forms received	3430	3482	6912	
Tracing not assessable	107(3.12)	98(2.81)	205(2.97)	
Tracing assessable	3323(96.88)	3384(97.19)	6707(97.03)	
Normal	1800(54.17)	1947(57.54)	3747(55.87)	
Abnormal	1523(45.83)	1437(42.46)	2960(44.13)	.0055
Definite Q-wave MI	373(24.49)	355(24.70)	728(24.59)	.5115
Pathologic ST-T depression	309(20.29)	270(18.79)	579(19.56)	.1015
Conduction disturbances	613(40.25)	557(38.76)	1170(39.53)	.0902
Atrial fibrillation or flutter	124(8.14)	128(8.91)	252(8.51)	.7826
Ventricular hypertrophy	415(27.25)	425(29.58)	840(28.38)	.6897

*p-Value is obtained from a Pearson's Chi-square test.

Program: RMP.H3SSGGIO.SASPGM(CVCTECG3)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: EMP.H3SO.GGIO.FINAL(CVTECGV5)

Table GGIO.11.26. Abnormal Post-baseline ECG Findings (Randomized Patients with Normal Baseline ECGs)

	Placebo (N=2124) n (%)	Ralox (N=2959) n (%)	Total (N=5873) n (%)	p-Value*
Abnormal postbaseline ECG findings	624(21.41)	562(18.99)	1186(20.19)	.0208
Definite Q-wave MI	18(2.88)	21(3.74)	39(3.29)	.6643
Pathologic ST-T depression	264(42.31)	217(38.61)	481(40.56)	.0159
Conduction disturbances	254(40.71)	233(41.46)	487(41.06)	.2419
Atrial fibrillation or flutter	59(9.46)	42(7.47)	101(8.52)	.0744
Ventricular hypertrophy	113(18.11)	108(19.22)	221(18.63)	.6463

*p-Value is obtained from a Pearson's Chi-square test.

Program: RMP.H3SSGGIO.SASPGM(CVCTECG1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTECGAR)

Analyses were also performed among patients in the primary and secondary prevention populations who had ECGs classified as normal at baseline.

In the **primary prevention population**, a significantly greater proportion of patients in the placebo group compared to those in the raloxifene group with a normal baseline ECG were identified as having an abnormal post-baseline ECG; the proportion of patients in the placebo group with atrial fibrillation or flutter was significantly greater than in the raloxifene group (Table GGIO.11.27).

In the **secondary prevention population**, there was no difference between treatment groups in the proportion of women with a normal baseline ECG who had a post-baseline abnormal ECG; significantly more patients in the placebo group had a post-baseline ECG showing pathologic ST-T segment depression compared to the raloxifene group (Table GGIO.11.28).

Table GGIO.11.27. Abnormal Post-baseline ECG Findings (Primary Prevention Population Patients with Normal Baseline ECGs)

	Placebo (N=1713) n (%)	Ralox (N=1699) n (%)	Total (N=3412) n (%)	p-Value*
Abnormal postbaseline ECG findings	328(19.15)	265(15.60)	593(17.38)	.0062
Definite Q-wave MI	9(2.74)	9(3.40)	18(3.04)	.9861
Pathologic ST-T depression	108(32.93)	94(35.47)	202(34.06)	.3394
Conduction disturbances	145(44.21)	121(45.66)	266(44.86)	.1435
Atrial fibrillation or flutter	33(10.06)	17(6.42)	50(8.43)	.0244
Ventricular hypertrophy	69(21.04)	51(19.25)	120(20.24)	.1037

*p-Value is obtained from a Pearson's Chi-square test.

Program: RMP.H3SSGGIO.SASPGM(CVCTECG1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTECGAP)

Table GGIO.11.28. Abnormal Post-baseline ECG Findings (Secondary Prevention Population Patients with Normal Baseline ECGs)

	Placebo (N=1201) n (%)	Ralox (N=1260) n (%)	Total (N=2461) n (%)	p-Value*
Abnormal postbaseline ECG findings	296(24.65)	297(23.57)	593(24.10)	.5332
Definite Q-wave MI	9(3.04)	12(4.04)	21(3.54)	.5842
Pathologic ST-T depression	156(52.70)	123(41.41)	279(47.05)	.0116
Conduction disturbances	109(36.82)	112(37.71)	221(37.27)	.8712
Atrial fibrillation or flutter	26(8.78)	25(8.42)	51(8.60)	.7531
Ventricular hypertrophy	44(14.86)	57(19.19)	101(17.03)	.2823

*p-Value is obtained from a Pearson's Chi-square test.

Program: RMP.H3SGGIO.SASPGM(CVCTECG1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTECGAS)

Other Analyses of the Coronary Primary Endpoint (11.4.3.5.)

Some patients experienced more than one coronary event during the study. Analyses of the patients who had multiple coronary events were performed to assess potential differences between treatment groups in terms of **time to the most serious coronary event**, to assess whether raloxifene **reduced the recurrence of events**, and to assess whether raloxifene **prolonged the average time between coronary events** for a given patient. Among the 3 coronary primary endpoint events, coronary death was considered the most serious, and hospitalized ACS other than MI was considered the least serious.
There were no significant differences between treatment groups in terms of:

- The **time to the most serious coronary event**
- The **number of patients** experiencing more than one coronary event (recurrent events)
- The average **time elapsed between** initial and subsequent coronary events (Table GGIO.11.29, Figure GGIO.14.7).

Table GGIO.11.29. Time-to-Event Analysis of Multiple Coronary Primary Endpoint Events (All Randomized Patients)

Coronary endpoint	Placebo (N=5057) n (%)	Raloxifene (N=5044) n (%)	Hazard ratio (95% CI)	p-Value*	Mean years between events** Placebo	Raloxifene
Most serious coronary event***	553(10.94)	537(10.65)	0.95(0.84, 1.07)	.3999		
Recurrent coronary event						
First event	553(10.94)	533(10.57)	0.95(0.84, 1.07)	.4038		
Second event	122(2.41)	92(1.82)	0.80(0.61, 1.05)	.1042	0.81	0.94
Third event	28(0.55)	17(0.34)	0.61(0.33, 1.12)	.1085	1.00	0.66
Fourth event	7(0.14)	2(0.04)	0.24(0.05, 1.17)	.0767	0.67	0.77
Fifth event	2(0.04)	1(0.02)	N/A	N/A	0.28	0.23
Sixth event	0(0.00)	1(0.02)	N/A	N/A	0.00	0.09

Abbreviations: CI=confidence interval.
*p-Value is obtained from a log-rank test for most serious event, from a PWP-GT model for recurrent events.
**Mean years between the first and second events, the second and third events, the third and the fourth events, and the fourth and fifth events for each treatment arm.
***Coronary death is considered the most serious event, followed by nonfatal MI, with hospitalized ACS other than MI being considered the least serious.

Program: RMP.H3SGGIO.SASPGM(CVCTHR3) Data: RMP.SAS.H3SM.L.ECGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRMUL)

Lag-time analysis

In the protocol design, a raloxifene treatment benefit lag of 9 months for the coronary primary endpoint was assumed. Thus, a lag-time analysis was performed to assess differences between the two time periods consisting of the first 9 months after randomization and the time thereafter.

- There were no differences between treatment groups in the two time periods assessed (Table GGIO.14.24).

Other Secondary Endpoints (11.4.4.)

Statistical analyses of secondary endpoints are presented in the following order:

- Combined cardiovascular endpoints (Section 11.4.4.1)
- Stroke (Section 11.4.4.2)
- VTE (Section 11.4.4.3)
- All-cause mortality (Section 11.4.4.4)
- Revascularization and amputations (Section 11.4.4.5)
- Fracture (Section 11.4.4.6)
- All-cause hospitalization (Section 11.4.4.7)

Combined Cardiovascular Endpoints (11.4.4.1.)

The effect of raloxifene on the incidences of the following combined CV endpoint events was assessed (Table GGIO.11.30):

- CV death, nonfatal (including silent) MI, hospitalized ACS other than MI, or stroke.
- CV death, nonfatal (including silent) MI, hospitalized ACS other than MI, stroke, or myocardial revascularization.

There was no significant difference between the raloxifene and placebo groups in the incidences of either of these cardiovascular endpoint event combinations.

Table GGIO.11.30. Time-to-Event Analysis of Cardiovascular Endpoint Combinations (All Randomized Patients)

Cardiovascular endpoint combination	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard Ratio (95% CI)	p-Value*
Cardiovascular death, nonfatal MI, hospitalized ACS other than MI, or stroke	767(15.17)	789(15.64)	1.02(0.92, 1.12)	.7504
Cardiovascular death, nonfatal MI, hospitalized ACS other than MI, stroke, or myocardial revascularization	1041(20.59)	1067(21.15)	1.01(0.93, 1.10)	.8021

Abbreviations: CI-confidence interval; ACS-acute coronary syndrome; MI-myocardial infarction.
*p-Value is obtained from a log-rank test.

Program: RMP.H3SGGIO.SASPGM(CVCICMB1) Data: RMP.SAS.H3SM.L.NCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRCMB)

Stroke (11.4.4.2.)

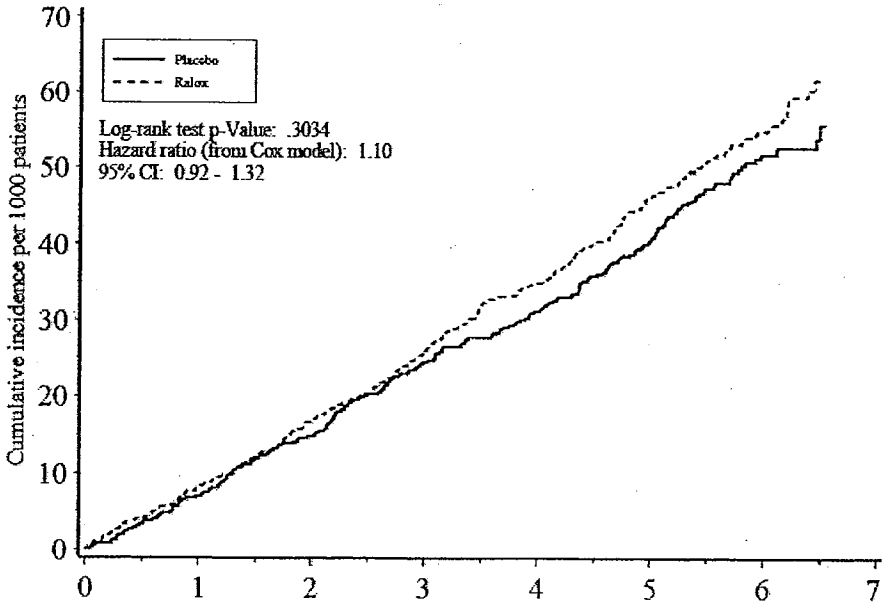
Effect of raloxifene on the incidence of all strokes was evaluated in prespecified and post-hoc analyses.

- A total of 539 patients (260 in placebo, 279 in raloxifene) were **reported** to have had at least one stroke during the study period. In these 539 patients, 473 patients (224 in placebo, 249 in raloxifene) had at least one **adjudicated** stroke.
  - All stroke analyses were based on the 473 patients with an adjudicated stroke, unless otherwise specified.

Analysis of Stroke Endpoint (11.4.4.2.1.)

Table GGIO.11.31 presents results of the **time-to-event analyses** of all strokes, and of hemorrhagic and ischemic strokes by pathogenesis; and Table GGIO.11.32 presents the post-hoc analyses of **incidence rates** for all strokes and each subtype.

- There was no significant increase or decrease in the incidence of all strokes (Table GGIO.11.31; Figure GGIO.11.8, Figure GGIO.14.8) or any stroke subtype in the raloxifene group compared with the placebo group.
- In post-hoc analyses, there were no significant differences between treatment groups for hemorrhagic or ischemic strokes categorized according to pathogenesis (Table GGIO.11.31).



Cumulative no. of events : No. patients at risk							
Placebo	0 : 5057	35 : 4889	73 : 4670	118 : 4447	148 : 4263	187 : 3762	221 : 1627
Ralox	0 : 5044	40 : 4897	82 : 4719	124 : 4535	167 : 4326	216 : 3799	242 : 1680

Program: RMP.H3SSGGIO.SASPGM(CVCMSTRK) Output: RMP.H3SG.GGIO.FINAL(CVGKMSTK)

Figure GGIO.11.8. Kaplan-Meier curves of all strokes for all randomized patients.

Table GGIO.11.31. Time-to-Event Analysis of Stroke Endpoint (All Randomized Patients)

Stroke category	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard ratio (95% CI)	p-Value*
All stroke	224(4.43)	249(4.94)	1.10(0.92, 1.32)	.3034
Haemorrhagic stroke	30(0.59)	18(0.36)	0.59(0.33, 1.06)	.0742
Primary intracerebral	17(0.34)	11(0.22)	0.64(0.30, 1.36)	.2401
Primary subarachnoid haemorrhage	6(0.12)	3(0.06)	0.49(0.13, 1.97)	.3074
Haemorrhagic transformation of ischaemic	7(0.14)	3(0.06)	0.42(0.11, 1.64)	.1985
Undetermined	0(0.00)	1(0.02)	N/A	N/A
Ischaemic stroke	171(3.38)	198(3.93)	1.15(0.93, 1.41)	.1903
Atheroma	11(0.22)	18(0.36)	1.62(0.77, 3.43)	.2018
Lacune	8(0.16)	8(0.16)	0.99(0.37, 2.63)	.9813
Cardioembolism	11(0.22)	10(0.20)	0.90(0.38, 2.12)	.8114
Other documented cause	3(0.06)	4(0.08)	1.31(0.29, 5.87)	.7192
Undetermined	141(2.79)	164(3.25)	1.15(0.92, 1.44)	.2226
Undetermined	30(0.59)	39(0.77)	1.28(0.80, 2.07)	.3015

Abbreviations: CI=confidence interval.
*p-Value is obtained from a log-rank test. Statistical test is not performed when the total number of patients in a category is less than 5.

Program: RMP.H3SSGGIO.SASPGM(CVCTHRT0) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRT0)

Table GGIO.11.32. Incidence Rate of Strokes (Post-hoc Analysis, All Randomized Patients)

Stroke endpoint	Placebo (N=5057) n (%)	Patient-years of follow-up	Incidence rate* per 1000 patients	Ralox (N=5044) n (%)	Patient-years of follow-up	Incidence rate* per 1000 patients	ARR** per 1000 patients
All stroke	224(4.43)	26053	8.60	249(4.94)	26329	9.46	-4.84
Haemorrhagic stroke	30(0.59)	26445	1.13	18(0.36)	26767	0.67	2.35
Ischaemic stroke	171(3.38)	26134	6.54	198(3.93)	26389	7.50	-5.24
Undetermined	30(0.59)	26438	1.13	39(0.77)	26739	1.46	-1.79

*Incidence rate is calculated as the number of patients who developed the event of interest divided by the patient-years of follow-up.
**Absolute risk reduction (ARR) is calculated by subtracting the cumulative incidence of the raloxifene arm from that of the placebo arm, where cumulative incidence is estimated using 1-exp(-I*T), I is the incidence rate, and T is the average patient-years of follow-up in each arm.

Program: RMP.H3SSGGIO.SASPGM(CVCTIRST) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTIRST1)

Sensitivity Analyses of Stroke (11.4.4.2.2.)

A sensitivity analysis of stroke was performed for the PP population (N=3348 raloxifene, N=3407 placebo).

- There was no significant difference between treatment groups in the incidence of all strokes in the PP population (Table GGIO.14.25, Figure GGIO.14.9).

Subgroup Analyses of Stroke (11.4.4.2.3.)

The potential effect of raloxifene on the incidence of all strokes was examined for predefined clinically relevant risk factors (Table GGIO.9.5).

- The treatment by subgroup interaction was not significant for any of the variables assessed, with the exception of smoking (Table GGIO.11.33).

The proportion of patients in the placebo group who did not smoke and had a stroke (4.7%) was greater than the proportion of patients who did smoke and had a stroke (2.3%). Post-hoc analysis showed this difference was statistically significant (p=0.005) (Table GGIO.14.26). This observation is inconsistent with epidemiologic data regarding the association between **smoking and stroke risk** and was therefore, deemed not clinically relevant.

Although the **CV risk score at baseline** was significantly different between treatment groups, the effect of raloxifene on the incidence of all strokes did not differ by CV risk score categories; thereby supporting the prior conclusion that the imbalance in baseline CV risk score was not clinically relevant.

Hypertension at baseline was considered to be present in any patient who reported having hypertension and taking antihypertensive medications or any patient whose systolic blood pressure was >160 mmHg or diastolic blood pressure was >95 mmHg on at least two measurements prior to randomization (Appendix 16.1.1, Protocol GGIO[d], Section 3.4.2.1). The effect of raloxifene on the incidence of all strokes did not differ by the hypertensive subgroup using the baseline definition. Post-hoc subgroup analyses were performed using differing cut-points of baseline systolic (≤140, >140 to <160, and ≥160 mmHg) and diastolic (≤80, >80 to <90, and ≥90 mmHg) blood pressure. The treatment by subgroup interaction was not significant for either of these subgroups (Table GGIO.11.40).

Hyperlipidemia at baseline was considered to be present in any patient who reported taking lipid-lowering medications, in any patient whose fasting LDL-C was >160 mg/dL (4.14 mmol/L), or in any patient whose fasting HDL-C was <45 mg/dL (1.16 mmol/L) with fasting triglycerides >250 mg/dL (2.82 mmol/L).The effect of raloxifene on the incidence of all strokes did not differ by the hyperlipidemia subgroup using the baseline definition. Post-hoc subgroup analyses were performed using different cut-points of baseline levels of total cholesterol (≤200, >200 to <240, ≥240 mg/dL), LDL-C (≤100, >100 to <130, ≥130 mg/dL), and triglycerides (<150, ≥150 mg/dL). The treatment by subgroup interaction was not significant for any of these subgroups (Table GGIO.11.40).

Table GGIO.11.33. Subgroup Analysis of All Strokes (All Randomized Patients)

Subgroup	Placebo (N=5057) N	n (%)	Ralox (N=5044) N	n (%)	Hazard ratio (95% CI)	Interaction p-Value*
Age (yrs)						.7457
<=65	1858	58(3.12)	1841	61(3.31)	1.04(0.72, 1.48)	
>65 and <70	1219	55(4.51)	1252	71(5.67)	1.24(0.87, 1.76)	
>=70	1960	111(5.61)	1951	117(6.00)	1.07(0.82, 1.38)	
Race						.6697
Caucasian	4247	183(4.31)	4234	207(4.89)	1.12(0.92, 1.37)	
All other races	810	41(5.06)	810	42(5.19)	1.01(0.66, 1.55)	
Region						.6937
North America	518	22(4.27)	514	30(5.84)	1.36(0.79, 2.36)	
Latin/South America	683	25(3.66)	687	22(3.20)	0.85(0.48, 1.50)	
Western Europe	2343	106(4.52)	2336	105(4.49)	0.99(0.75, 1.29)	
Eastern Europe	1186	51(4.41)	1154	69(5.98)	1.32(0.92, 1.89)	
Africa	109	4(3.67)	106	4(3.77)	1.02(0.25, 4.07)	
Asia Pacific	251	16(6.37)	247	19(7.69)	1.22(0.63, 2.37)	
Body mass index (kg/m2) at baseline						.6909
<=25	1230	53(4.31)	1186	49(4.13)	0.95(0.64, 1.40)	
>25 and <=30	2013	92(4.57)	2039	108(5.30)	1.14(0.86, 1.50)	
>30	1798	78(4.34)	1805	92(5.10)	1.16(0.86, 1.57)	
Primary prevention population						.4461
Yes	2561	113(4.41)	2606	115(4.59)	1.02(0.79, 1.32)	
No	2496	111(4.45)	2528	134(5.26)	1.18(0.91, 1.51)	
Lower extremity arterial disease at baseline						.3645
Yes	540	29(5.37)	542	39(7.18)	1.35(0.84, 2.19)	
No	4516	195(4.32)	4501	210(4.67)	1.06(0.87, 1.29)	

Abbreviations: CI=confidence interval;
*Interaction p-Value is obtained from a Cox model: year*censor-therapy + subgroup + therapy*subgroup.

Program: RMP.H3SGGIO.SASPGM(CVCTSTK8) Data: RMP.SAS.H3SM.L.MCGGIO8A.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRST3)

Subgroup	Placebo (N=5057) N	n (%)	Ralox (N=5044) N	n (%)	Hazard ratio (95% CI)	Interaction p-Value*
Diabetes mellitus at baseline						.6847
Yes	2309	129(5.59)	2298	140(6.09)	1.06(0.83, 1.35)	
No	2734	95(3.47)	2736	109(3.98)	1.14(0.87, 1.51)	
Current smoker at baseline						.0937
Yes	649	15(2.31)	607	26(4.28)	1.84(0.98, 3.48)	
No	4408	209(4.74)	4437	223(5.03)	1.04(0.86, 1.26)	
Hypertension at baseline						.8587
Yes	3935	185(4.70)	3918	204(5.19)	1.09(0.89, 1.33)	
No	1121	39(3.48)	1115	45(4.04)	1.14(0.74, 1.75)	
Hyperlipidemia at baseline						.5303
Yes	3701	158(4.27)	3680	170(4.62)	1.06(0.86, 1.32)	
No	1330	64(4.81)	1342	78(5.81)	1.21(0.87, 1.68)	
Cardiovascular risk score at baseline						.7450
<=5	1036	62(3.38)	1035	64(3.49)	1.01(0.72, 1.44)	
>5 and <=9	1757	83(4.72)	1712	98(5.72)	1.20(0.90, 1.61)	
>9	1464	79(5.40)	1497	87(5.81)	1.06(0.79, 1.44)	
History of atrial fibrillation						.0565
Yes	229	25(10.92)	253	32(12.65)	1.14(0.68, 1.92)	
No	4828	199(4.12)	4791	217(4.53)	1.08(0.89, 1.31)	
HMG-CoA reductase inhibitor use at baseline						.6419
Yes	2361	88(3.73)	2382	104(4.37)	1.16(0.87, 1.54)	
No	2670	136(5.09)	2631	145(5.51)	1.06(0.84, 1.34)	

Abbreviations: CI-confidence interval; HMG-CoA-hydroxymethylglutaryl-coenzyme A;
*Interaction p-Value is obtained from a Cox model: year*censor-therapy + subgroup + therapy*subgroup.

Program: RMP.H3SGGIO.SASPGM(CVCTSTK8) Data: RMP.SAS.H3SM.L.MCGGIO8A.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRST3)

Subgroup	Placebo (N=5057) N	n (%)	Ralox (N=5044) N	n (%)	Hazard ratio (95% CI)	Interaction p-Value*
Warfarin use at baseline						.4208
Yes	195	9(4.62)	221	16(7.24)	1.52(0.67, 3.44)	
No	4836	115(4.45)	4791	233(4.86)	1.08(0.90, 1.30)	
Aspirin use at baseline						.6912
Yes	2865	132(4.61)	2846	150(5.27)	1.13(0.90, 1.43)	
No	1166	92(4.24)	2167	99(4.57)	1.05(0.79, 1.40)	
Non-aspirin antiplatelet use at baseline						.6065
Yes	142	7(4.93)	156	11(7.05)	1.40(0.54, 3.62)	
No	4889	217(4.44)	4857	238(4.90)	1.09(0.91, 1.31)	
Beta-blocker use at baseline						.6139
Yes	2363	107(4.53)	2421	129(5.33)	1.15(0.89, 1.49)	
No	2668	117(4.39)	2582	120(4.65)	1.05(0.81, 1.35)	
Calcium channel blocker use at baseline						.7890
Yes	1900	84(4.67)	1779	96(5.40)	1.14(0.85, 1.52)	
No	3231	140(4.33)	3224	153(4.73)	1.08(0.86, 1.36)	
ACE inhibitor or angiotensin receptor blocker use at baseline						.4746
Yes	2424	117(4.83)	2469	125(5.06)	1.03(0.80, 1.32)	
No	2607	107(4.10)	2544	124(4.87)	1.17(0.91, 1.52)	
Diuretic use at baseline						.1613
Yes	1956	104(5.32)	2036	105(5.16)	0.95(0.72, 1.24)	
No	3075	120(3.90)	2977	144(4.84)	1.23(0.96, 1.57)	

Abbreviations: CI=confidence interval; ACE=angiotensin converting enzyme.
*Interaction p-Value is obtained from a Cox model: year*censor+therapy + subgroup + therapy*subgroup.

Program: RMP.H3SSGGIO.SASPGM(CVCTSTK5) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRST3)

Venous Thromboembolism (11.4.4.3.)

The effect of raloxifene on the incidences of all VTEs and various types of VTE was evaluated in a prespecified analysis. A post-hoc analysis of time to event for VTE by year was also performed.

- A total of 215 patients (88 in placebo, 127 in raloxifene) were **reported** to have at least one VTE during the study period. In these 215 patients, 174 patients (71 in placebo, 103 in raloxifene) had at least one **adjudicated** VTE.
    - Analyses of VTEs were based on the 174 patients with an adjudicated VTE, unless otherwise specified.

11.4.4.3.1. Analysis of VTE Endpoint

Table GGIO.11.34 presents results of the **time-to-event** analyses of the VTE endpoint, and Table GGIO.11.35 presents the **incidence rates** for the VTE endpoint.

- A significant 44% increase in the incidence of **VTE** was seen in the raloxifene-assigned patients compared to placebo-assigned patients (Figure GGIO.11.9, Table GGIO.11.34).
    - This translated to an absolute risk increase of 1.2 VTEs per 1000 woman-years (Table GGIO.11.35).
- A significant 44% increase in the incidence of **PE or DVT combined** was seen in the raloxifene-assigned patients compared to placebo-assigned patients (Table GGIO.11.34, Figure GGIO.11.10).
    - This translated to an absolute risk increase of 1.1 PE or DVT combined per 1000 woman-years (Table GGIO.11.35).

Kaplan-Meier curves were generated separately for all DVTs (Figure GGIO.14.10) and all PEs (Figure GGIO.14.11).

- In a cumulative time–to-event post-hoc analysis of VTEs, the incidence of VTE did not differ significantly between treatment groups at the end of Year 1. However, at the end of Year 2, the incidence of VTE was significantly greater in the raloxifene group compared with the placebo group and this finding persisted until the end of the trial (Table GGIO.11.36).

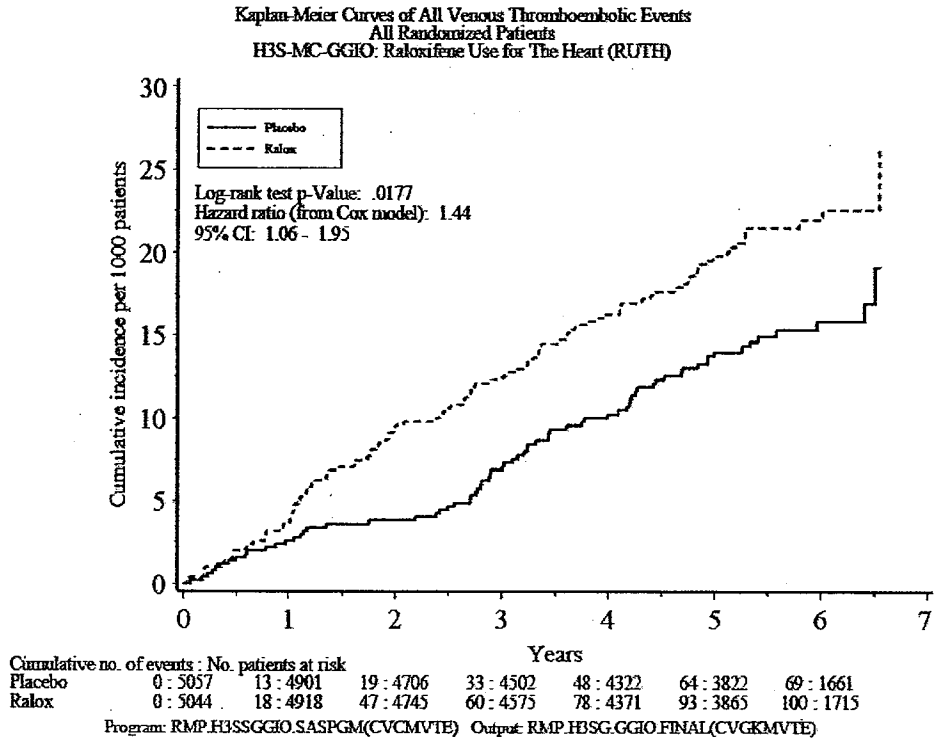


Figure GGIO.11.9. Kaplan-Meier curves of all venous thromboembolic events for all randomized patients.

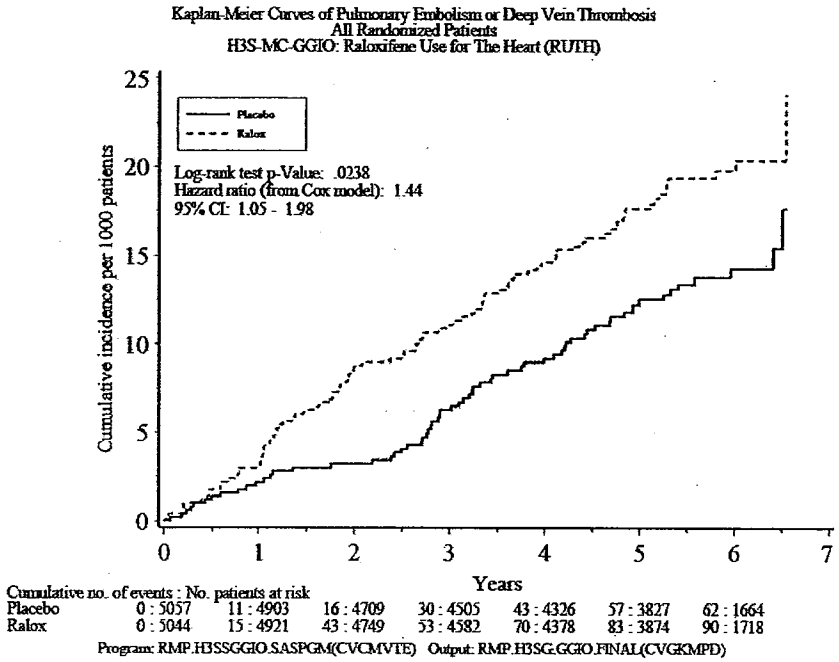


Figure GGIO.11.10. Kaplan-Meier curves of deep vein thrombosis or pulmonary embolism for all randomized patients.

Table GGIO.11.34. Time-to-Event Analysis of VTE Endpoint (All Randomized Patients)

VTE endpoint classification	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard Ratio (95% CI)	p-Value*
All VTEs	71(1.40)	103(2.04)	1.44(1.06, 1.95)	.0177
PE or DVT	64(1.27)	93(1.84)	1.44(1.05, 1.98)	.0238
Pulmonary embolism	24(0.47)	36(0.71)	1.49(0.89, 2.49)	.1289
Deep vein thrombosis	47(0.93)	65(1.29)	1.37(0.94, 1.99)	.1001
Intracranial thrombosis	6(0.12)	8(0.16)	1.32(0.46, 3.80)	.6063
Other	1(0.02)	2(0.04)	N/A	N/A

Abbreviations: CI=confidence interval; VTE=venous thromboembolic event; PE=pulmonary embolism; DVT=deep vein thrombosis.
*p-Value is obtained from a log-rank test. Statistical test is not performed when the total number of patients in a category is less than 5.

Program: EMP.H3SSGGIO.SASPGM(CVCMVTE)
Data: EMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: EMP.H3SO.GGIO.FINAL(CVTHRVT1)

Table GGIO.11.35. Incidence Rate of VTE Endpoint (All Randomized Patients)

VTE endpoint classification	Placebo (N=5057) n (%)	Patient-years of follow-up	Incidence rate* per 1000 patients	Ralox (N=5044) n (%)	Patient-years of follow-up	Incidence rate* per 1000 patients	ARR** per 1000 patients
All VTEs	71(1.40)	26316	2.70	103(2.04)	26557	3.88	-6.27
PE or DVT	64(1.27)	26327	2.43	93(1.84)	26589	3.50	-5.69
Pulmonary embolism	24(0.47)	26442	0.91	36(0.71)	26717	1.35	-2.38
Deep vein thrombosis	47(0.93)	26361	1.78	65(1.29)	26639	2.44	-3.65
Intracranial thrombosis	6(0.12)	26462	0.23	8(0.16)	26761	0.30	-0.40
Other	1(0.02)	26483	0.04	2(0.04)	26779	0.07	-0.20

Abbreviations: VTE=venous thromboembolic event; PE=pulmonary embolism; DVT=deep vein thrombosis.
*Incidence rate is calculated as the number of patients who developed the event of interest divided by the patient-years of follow-up.
**Absolute risk reduction (ARR) is calculated by subtracting the cumulative incidence of the raloxifene arm from that of the placebo arm, where cumulative incidence is estimated using 1-exp(-I*T), I is the incidence rate, and T is the average patient-years of follow-up in each arm.

Program: EMP.H3SSGGIO.SASPGM(CVCMVTE) Data: EMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: EMP.H3SO.GGIO.FINAL(CVTIRVT1)

Table GGIO.11.36. Time-to-Event Analysis of VTE by Year (Post-hoc Analysis, All Randomized Patients)

VTE	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard ratio (95% CI)	p-Value*
1 year	13(0.26)	18(0.36)	1.39(0.68, 2.83)	.3687
2 year	19(0.38)	47(0.93)	2.46(1.45, 4.20)	.0006
3 year	33(0.65)	60(1.19)	1.81(1.18, 2.76)	.0056
4 year	48(0.95)	78(1.55)	1.61(1.13, 2.31)	.0086
5 year	64(1.27)	93(1.84)	1.44(1.05, 1.98)	.0239
6 year	69(1.36)	100(1.98)	1.44(1.06, 1.95)	.0201
7 year	71(1.40)	103(2.04)	1.44(1.06, 1.95)	.0177

*p-Value is obtained from a log-rank test. Statistical test is not performed when the total number of patients in a category is less than 5.

Program: EMP.H3SSGGIO.SASPGM(SFCTHRV4)
Data: EMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: EMP.H3SO.GGIO.FINAL(SFTHRV4)

Sensitivity Analysis of VTE (11.4.4.3.2.)

Sensitivity analyses of VTE were performed for the PP, primary prevention, and secondary prevention populations.

- In the **PP population**, the incidence of VTE was greater in the raloxifene group compared with the placebo group, although this finding was not statistically significant (Table GGIO.14.27, Table GGIO.14.28).
- In the **primary prevention population** (N=2506 raloxifene, N=2561 placebo), raloxifene use was associated with a significantly increased incidence of VTE (HR 1.88; 95% CI, 1.20 to 2.95) and incidence of PE or DVT combined (HR 2.15; 95% CI, 1.32 to 3.49) compared to placebo (Table GGIO.14.29, Table GGIO.14.30).
- In the **secondary prevention population** (ie, patients with CHD), there was no difference in the incidence of VTE between treatment groups (Table GGIO.14.31, Table GGIO.14.32).

All-Cause Mortality (11.4.4.4.)

Results for the prespecified and post-hoc analyses of mortality are presented in this section.

Analysis of Mortality Endpoint (11.4.4.4.1.)

Table GGIO.11.37 presents results of the **time-to-event analysis** of the all-cause mortality endpoint, and Table GGIO.11.38 presents post-hoc analyses of **incidence rates** for all deaths and the individual causes of death.

- A total of 1149 patients died during the trial; 11.8% of those were randomized to placebo and 11.0% to raloxifene.
- There was no significant difference between treatment groups in the **incidence of all deaths** (Figure GGIO.11.11).

Deaths were classified into **CV** and **non-CV** causes or cause of death **unavailable** (Table GGIO.11.37).

- There was no between treatment group difference in the incidence of **deaths due to CV causes overall** (Figure GGIO.11.12).
- There was a significant, 20% decrease in the incidence of **deaths due to non-CV causes** in the raloxifene group compared with the placebo group. No specific disease category, which included deaths due to cancer, explained this finding. The clinical relevance of this observation is unknown.
    - There was **no difference** between the raloxifene and placebo groups in the incidence of **death due to cancer.**
        - Two patients (<0.1%) died due to breast cancer, as determined by the death adjudication committee; both patients were in the raloxifene group. One patient (985/1151) was reported to have had a breast cancer but it was not adjudicated as such; however, her cause of death was adjudicated as being due to breast cancer (Section 11.4.2). The other patient (728/1041) had an adjudicated breast cancer (Stage IIIB) and died within 2 years after diagnosis with the cause of death being adjudicated as due to breast cancer.

Cardiovascular deaths were classified into **coronary** and **non-coronary** causes.

- There was no significant difference between treatment groups for coronary deaths or non-coronary deaths (Table GGIO.11.37).
    - Three additional coronary deaths (1 in placebo, 2 in raloxifene) were included in the analysis for all cause mortality (ie, 529 events) (Table GGIO.11.37) than in the analysis for the individual primary coronary endpoint event of coronary death (ie, 526 events) (Table GGIO.11.21). These 3 deaths were deemed unadjudicatable but were classified as coronary deaths by the adjudication committee. Only adjudicated coronary deaths were included in the analysis of the

primary coronary endpoint and the individual components; hence the discrepancy in these numbers.

In those patients for whom cause of death was classified as due to a **CV, non-coronary** etiology, 98 deaths were due to a **cerebrovascular etiology**. All cerebrovascular deaths were due to stroke.

- There was a significant increase in the incidence of death due to stroke in patients assigned to raloxifene compared with those assigned to placebo.
- The incidence of death due to stroke was 2.2 per 1000 women per year for raloxifene versus 1.5 per 1000 women per year for placebo. Absolute risk increase in death due to stroke of 0.7 per 1000 woman-years.

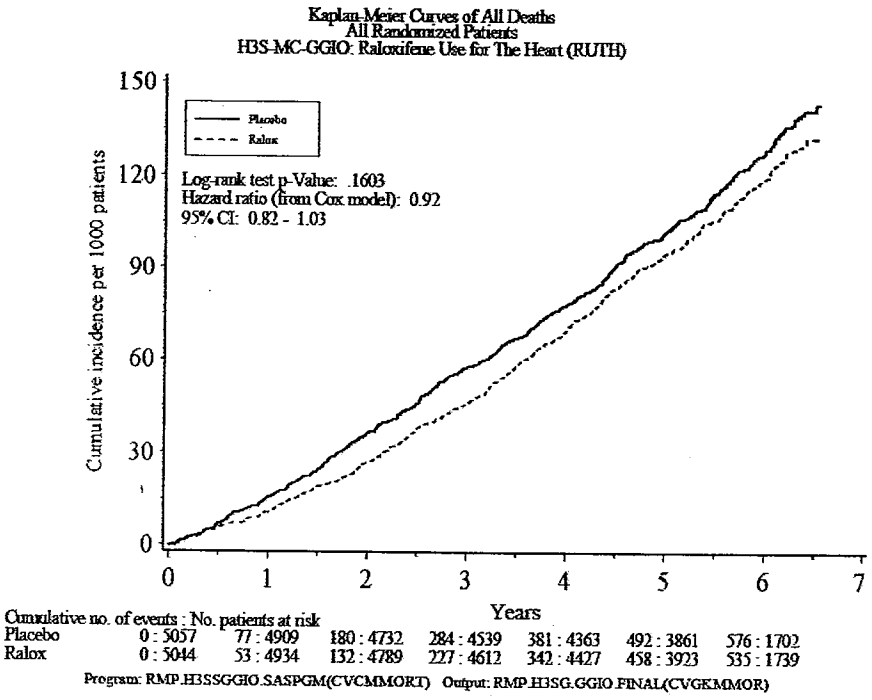


Figure GGIO.11.11. Kaplan-Meier curves of all deaths for all randomized patients.

Table GGIO.11.37. Time-to-Event Analysis of All-Cause Mortality Endpoint (All Randomized Patients)

Mortality endpoint classification	Placebo (N=5057) n(%)	Ralox (N=5044) n(%)	Hazard Ratio (95% CI)	p-Value*
All deaths	595(11.77)	554(10.98)	0.92(0.82, 1.03)	.1601
Cardiovascular death	355(7.02)	362(7.18)	1.01(0.87, 1.17)	.9129
Coronary death	274(5.42)	255(5.06)	0.92(0.78, 1.09)	.2401
Acute MI	45(0.89)	33(0.65)	0.73(0.46, 1.14)	.1614
Sudden death	137(2.71)	128(2.54)	0.92(0.73, 1.18)	.5198
Unwitnessed death	4(0.08)	3(0.06)	0.74(0.17, 3.32)	.6962
Heart failure with history of CAD	59(1.17)	57(1.13)	0.96(0.66, 1.37)	.8045
Related to undergoing a CAP	11(0.22)	9(0.18)	0.81(0.34, 1.96)	.6395
Specific cause of coronary death unavailable	16(0.26)	25(0.50)	1.37(0.75, 2.51)	.3069
Non-coronary death	81(1.60)	107(2.12)	1.31(0.98, 1.74)	.0697
Cerebrovascular disease (stroke or other cause)	39(0.77)	59(1.17)	1.49(1.00, 2.24)	.0499
Aortic, mesenteric, renal, or lower limb PVD	11(0.22)	15(0.30)	1.35(0.62, 2.93)	.4517
Related to undergoing an NCAP	1(0.02)	2(0.04)	N/A	N/A
Venous thromboembolic event	5(0.10)	10(0.20)	1.98(0.68, 5.79)	.2032
Endocarditis/myocarditis	1(0.02)	0(0.00)	N/A	N/A
Valvular disease	6(0.12)	7(0.14)	1.15(0.39, 3.42)	.8000
Other non-coronary death	8(0.16)	5(0.10)	0.62(0.20, 1.88)	.3903
Specific cause of non-coronary death unavailable	10(0.20)	9(0.18)	0.89(0.36, 2.19)	.7973
Non-cardiovascular death	231(4.57)	188(3.73)	0.80(0.66, 0.96)	.0264
Cancer	103(2.04)	97(1.92)	0.93(0.70, 1.23)	.6050
Breast cancer	0(0.00)	2(0.04)	N/A	N/A
Other cancer	103(2.04)	95(1.88)	0.91(0.69, 1.20)	.5099
Accidental/Suicide/Homicide	6(0.12)	8(0.16)	1.32(0.46, 3.79)	.6099
Other non-cardiovascular death	97(1.92)	61(1.21)	0.62(0.45, 0.86)	.0033
Specific cause of non-cardiovascular death unavailable	25(0.49)	22(0.44)	0.88(0.49, 1.55)	.6493
Cause of death unavailable	9(0.18)	4(0.08)	0.44(0.14, 1.43)	.1595

Abbreviations: CI=confidence interval; MI=myocardial infarction; CAD=coronary artery disease; CAP=coronary arterial procedure; PVD=peripheral vascular disease. NCAP=non-coronary arterial procedure.
*p-Value is obtained from a log-rank test. Statistical test is not performed when the total number of patients in a category is less than 5.

Program: RMP.H3SSGGIO.SASPGM(CVCMMORT) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHEMOR)

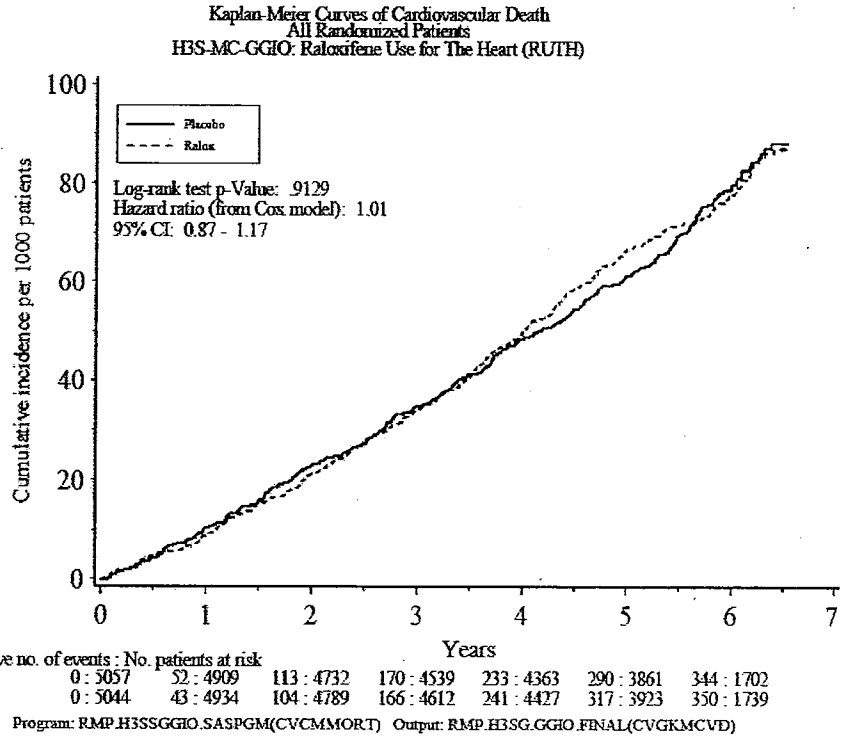


Figure GGIO.11.12. Kaplan-Meier curves of cardiovascular death for all randomized patients.

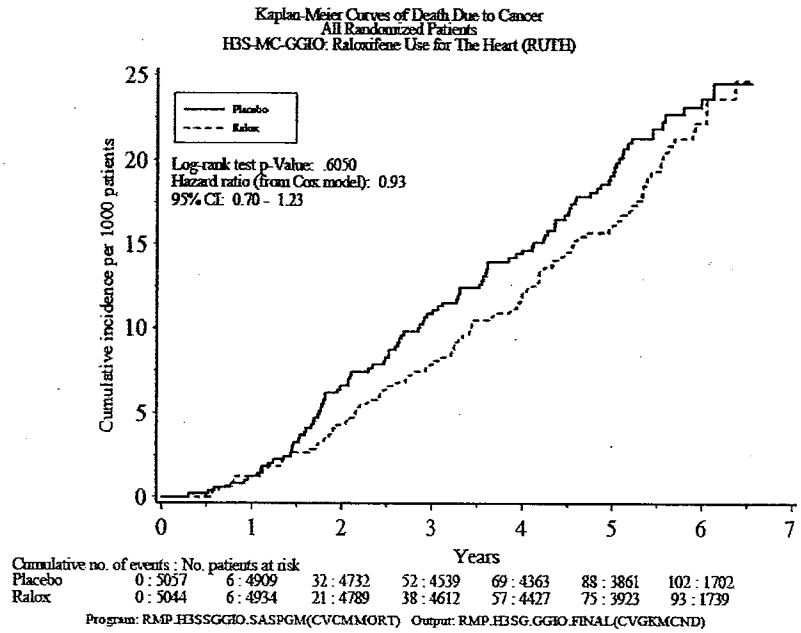


Figure GGIO.11.13. Kaplan-Meier curves of death due to cancer for all randomized patients.

Table GGIO.11.38. Incidence Rate of All-Cause Mortality Endpoint (Post-hoc Analysis, All Randomized Patients)

Coronary endpoint	Placebo (N=5057) n (%)	Patient-years of follow-up	IR* per 1000 patients	Raloxifene (N=5044) n (%)	Patient-years of follow-up	IR* per 1000 patients	ARR** per 1000 patients
All deaths	595(11.77)	26499	22.45	556(10.90)	26784	20.68	6.98
Cardiovascular death	355(7.02)	26499	13.40	362(7.18)	26784	13.52	-1.46
Coronary death	274(5.42)	26499	10.34	255(5.06)	26784	9.52	3.44
Acute MI	45(0.89)	26499	1.70	33(0.65)	26784	1.23	2.34
Sudden death	137(2.71)	26499	5.17	128(2.54)	26784	4.78	1.67
Unwitnessed death	4(0.08)	26499	0.15	3(0.06)	26784	0.11	0.20
Heart failure with CAD	59(1.17)	26499	2.23	57(1.13)	26784	2.13	0.36
Related to undergoing a CAP	11(0.22)	26499	0.42	9(0.18)	26784	0.34	0.39
Coronary Cause Unavailable	18(0.36)	26499	0.68	25(0.50)	26784	0.93	-1.39
Non-coronary death	81(1.60)	26499	3.06	107(2.13)	26784	3.99	-5.20
Cerebrovascular disease	39(0.77)	26499	1.47	59(1.17)	26784	2.20	-3.95
Aortic,mesenteric,renal	11(0.22)	26499	0.42	15(0.30)	26784	0.56	-0.80
Related to undergoing an NCAP	1(0.02)	26499	0.04	2(0.04)	26784	0.07	-0.20
Venous thromboembolic event	5(0.10)	26499	0.19	10(0.20)	26784	0.37	-0.99
Endocarditis/myocarditis	1(0.02)	26499	0.04	0(0.00)	26784	0.00	0.20
Valvular disease	6(0.12)	26499	0.23	7(0.14)	26784	0.26	-0.20
Other non-coronary	8(0.16)	26499	0.30	5(0.10)	26784	0.19	0.59
Non-CO Cause Unavailable	10(0.20)	26499	0.38	9(0.18)	26784	0.34	0.19

Abbreviations: MI-myocardial infarction; CAD-coronary artery disease; CAP-coronary arterial procedure.
*Incidence rate is calculated as the number of patients who developed the event of interest divided by the patient-years of follow-up.
**Absolute risk reduction (ARR) is calculated by subtracting the cumulative incidence of the raloxifene arm from that of the placebo arm, where cumulative incidence is estimated using 1-exp(-I*T), I is the incidence rate, and T is the average patient-years of follow-up in each arm.

Program: RMP.H3SGGIO.SASPGM(CVCTIRD) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTIRD)

Coronary endpoint	Placebo (N=5057) n (%)	Patient-years of follow-up	IR* per 1000 patients	Raloxifene (N=5044) n (%)	Patient-years of follow-up	IR* per 1000 patients	ARR** per 1000 patients
Non-cardiovascular death	231(4.57)	26499	8.72	188(3.73)	26784	7.02	8.07
Cancer	103(2.04)	26499	3.89	97(1.92)	26784	3.62	1.11
Breast cancer	0(0.00)	26499	0.00	2(0.04)	26784	0.07	-0.40
Other cancer	103(2.04)	26499	3.89	95(1.88)	26784	3.55	1.50
Accidental/Suicide/Homicide	6(0.11)	26499	0.23	8(0.16)	26784	0.30	-0.40
Other Non-cardiovascular	97(1.92)	26499	3.66	61(1.21)	26784	2.28	6.98
Non-CV Cause Unavailable	25(0.49)	26499	0.94	22(0.44)	26784	0.82	0.58
Cause of death unavailable	9(0.18)	26499	0.34	4(0.08)	26784	0.15	0.99

Abbreviations: MI-myocardial infarction; CAD-coronary artery disease; CAP-coronary arterial procedure.
*Incidence rate is calculated as the number of patients who developed the event of interest divided by the patient-years of follow-up.
**Absolute risk reduction (ARR) is calculated by subtracting the cumulative incidence of the raloxifene arm from that of the placebo arm, where cumulative incidence is estimated using 1-exp(-I*T), I is the incidence rate, and T is the average patient-years of follow-up in each arm.

Program: RMP.H3SGGIO.SASPGM(CVCTIRD) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTIRD)

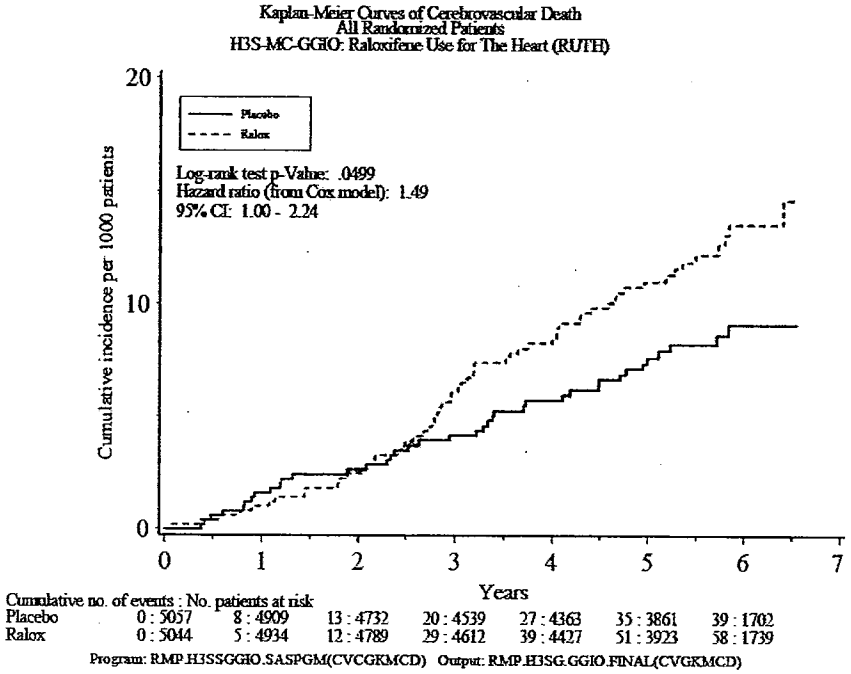


Figure GGIO.11.14. Kaplan-Meier curves of cerebrovascular death for all randomized patients.

Exploratory Analyses of Stroke and Death Due to Stroke (11.4.4.4.2.)

The observation of an increase in the incidence of death due to stroke in the raloxifene group compared to the placebo group is perplexing: there was no significant increase in the incidence of all strokes in the raloxifene group, and no significant increase in the incidence of death due to stroke has been observed in previous raloxifene clinical trials. In an attempt to better understand the clinical significance of this finding, exploratory analyses were performed for all strokes and deaths due to stroke.

Baseline Characteristics (11.4.4.4.2.1.)

Baseline demographics and **CV risk factors** for patients who had a stroke and for patients who died due to a stroke were compared between treatment groups.

Of the **473 patients who experienced a stroke**, there were no treatment group differences in the **baseline demographics**, except for *heart rate* and *exposure to secondary smoke*, both of which were significantly higher in the patients assigned to raloxifene (Table GGIO.14.33). The magnitudes of these differences are small and were not deemed clinically relevant.

There were no treatment group differences in the **baseline CV risk factors** for the 473 patients who experienced a stroke (Table GGIO.14.34). Figure GGIO.11.15 and Figure GGIO.11.16 show the proportion of all randomized patients with a pertinent baseline co-morbid condition or co-medication who had a stroke.

There were no treatment group differences in the **baseline demographics** (Table GGIO.14.35) or **CV risk factors** (Table GGIO.14.36) for the **98 patients who died due to a stroke**. Figure GGIO.11.17 and Figure GGIO.11.18 show the proportion of all randomized patients with a pertinent baseline co-morbid condition or co-medication who died due to a stroke.

CV risk factors for patients experiencing a stroke and for patients who died due to a stroke were compared to the respective characteristics for all randomized women (Table GGIO.11.39).

- A greater proportion of patients who had a stroke or died due to a stroke were 70 years of age or older, or had diabetes mellitus, lower extremity arterial disease, hypertension, a prior MI, atrial fibrillation, stroke, or TIA (Table GGIO.11.39). Although not assessed statistically, these findings suggest the patients who had a stroke or died due to a stroke might have had a higher attributable CV risk compared with the entire cohort of all randomized women.

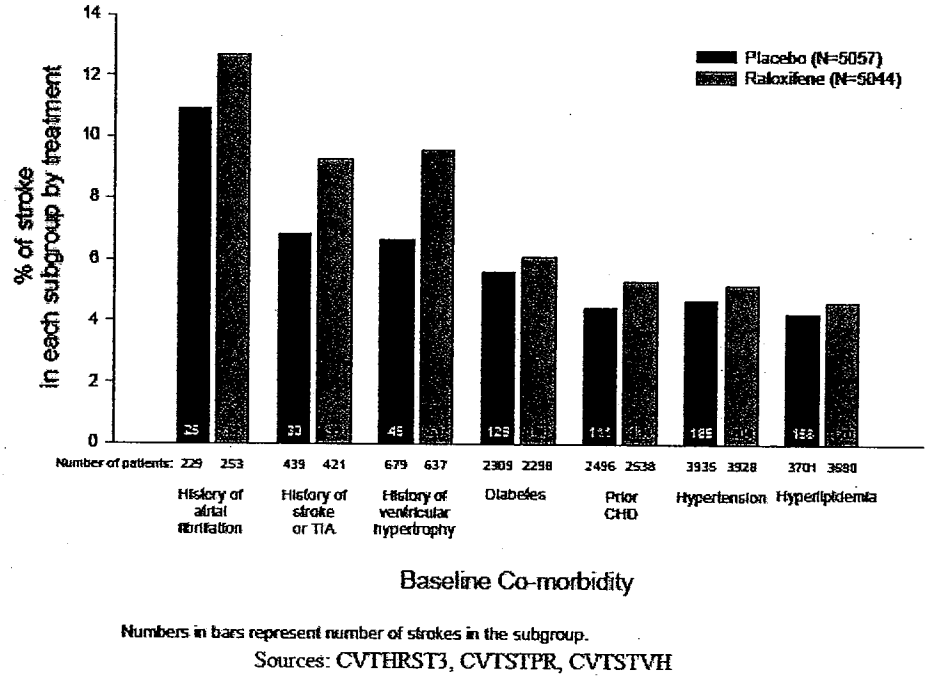
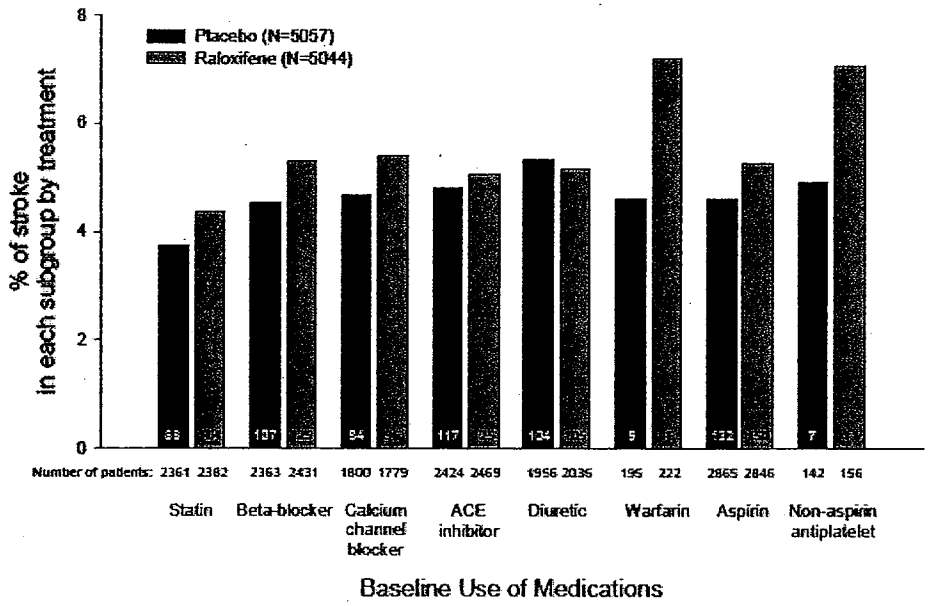
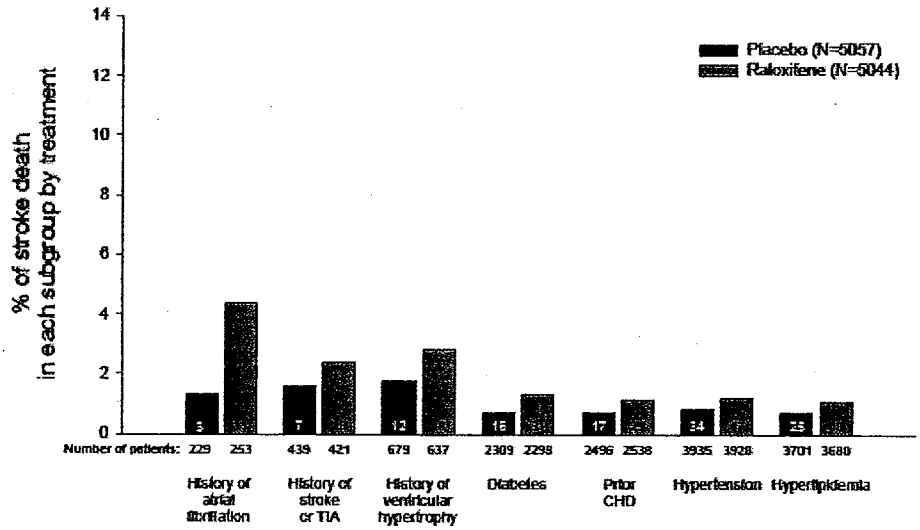


Figure GGIO.11.15. Incidence of stroke by baseline co-morbidity for all randomized patients (post-hoc analysis)



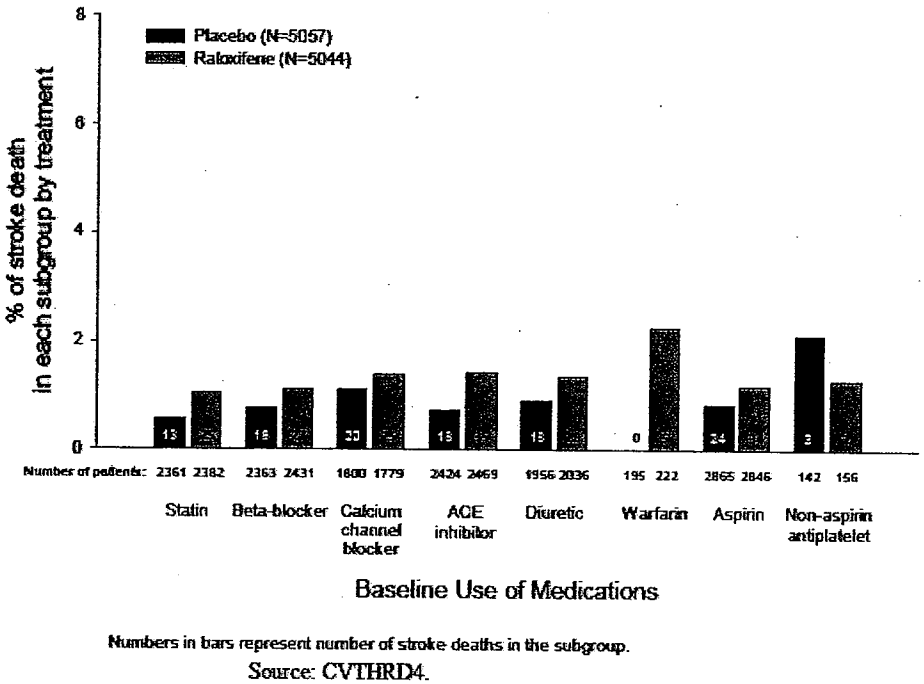
Numbers in bars represent number of strokes in the subgroup.
Source: CVTHRST3.

Figure GGIO.11.16. Incidence of stroke by baseline medication use for all randomized patients (post-hoc analysis)



Numbers in bars represent number of stroke deaths in the subgroup.
Source: CVTHRD4, CVTSTDPR, CVTSTDVH

Figure GGIO.11.17. Incidence of death due to stroke by baseline co-morbidity for all randomized patients (post-hoc analysis)



Numbers in bars represent number of stroke deaths in the subgroup.
Source: CVTHRD4.

Figure GGIO.11.18. Incidence of death due to stroke by baseline medication use for all randomized patients (post-hoc analysis)

Table GGIO.11.39. Baseline CV Risk Assessment for All Randomized Patients, Patients with a Stroke, and Patients Dying from a Stroke (Post-Hoc Analysis)

Characteristic	All Patients (N=10101)	Patients with a Stroke (N=473)	Patients Dying from a Stroke (N=98)
Mean age, yrs	67.5	69.5	71.4
Age ≥70 yrs, %	38.9	48.2	61.2
CV risk score, mean	7.83	8.54	8.29
Current smoker, %	12.4	8.7	8.2
Diabetes mellitus, %	45.7	56.9	48.0
Lower extremity arterial disease, %	10.7	14.4	19.4
Hyperlipidemia, %	73.4	69.8	67.0
Hypertension, %	77.9	82.2	82.7
Prior myocardial infarction, %	29.2	33.0	36.7
Prior coronary artery bypass graft, %	16.4	15.6	16.3
Prior catheter-based revascularization, %	19.0	19.6	14.5
Prior angina with documented CHD, %	33.1	34.3	25.5
History of atrial fibrillation, %[a]	4.8	12.1	14.3
Prior stroke or TIA, %[a]	8.5	14.6	17.3

Abbreviations: CHD = coronary heart disease; CV = cardiovascular; TIA = transient ischemic attack

[a] History of atrial fibrillation and prior stroke or TIA was ascertained from historical or secondary diagnoses reported at baseline. Data reported for these characteristics were adapted from CVTHRD4, CVTHRST3, CVTSTDPR, CVTDST3

Sources: MSTBLDEM, CVTBLRSK, MSTBLS2, MSTBLS4, MSTBLK2, MSTBLK4.

Subgroup Analyses (11.4.4.4.2.2.)

Subgroup analyses of all strokes and deaths due to stroke were performed to evaluate whether baseline demographics, co-morbidities, or co-medications might affect response to treatment with raloxifene.

The following table lists the 20 clinically relevant risk factors which were prespecified for the subgroup analyses of all strokes. Post-hoc analyses of deaths due to stroke were performed for these same subgroups.

Table GGIO.11.33. Subgroup Analysis of All Strokes (All Randomized Patients)

Subgroup	Placebo (N=8057) N	n (%)	Raloxifene (N=8044) N	n (%)	Hazard ratio (95% CI)	Interaction p-Value*
Age (yrs)						.7457
<=65	1858	68(3.12)	1861	61(3.31)	1.04(0.72, 1.48)	
>65 and <70	1219	55(4.51)	1252	71(5.67)	1.24(0.87, 1.76)	
>=70	1980	111(5.61)	1951	117(6.00)	1.07(0.82, 1.38)	
Race						.6697
Caucasian	4267	183(4.31)	4234	207(4.89)	1.12(0.92, 1.37)	
All other races	810	41(5.06)	810	42(5.19)	1.01(0.66, 1.55)	
Region						.6937
North America	515	22(4.27)	514	30(5.84)	1.36(0.79, 2.36)	
Latin/South America	683	25(3.66)	687	22(3.20)	0.85(0.48, 1.50)	
Western Europe	2343	106(4.52)	2336	105(4.49)	0.99(0.75, 1.29)	
Eastern Europe	1156	51(4.41)	1154	69(5.98)	1.32(0.92, 1.89)	
Africa	109	4(3.67)	106	4(3.77)	1.02(0.25, 4.07)	
Asia Pacific	251	16(6.37)	247	19(7.69)	1.21(0.63, 2.37)	
Body mass index (Kg/m2) at baseline						.6909
<=25	1230	53(4.31)	1196	49(4.13)	0.95(0.64, 1.40)	
>25 and <=30	2013	92(4.57)	2039	108(5.30)	1.14(0.86, 1.50)	
>30	1798	78(4.34)	1805	92(5.10)	1.14(0.86, 1.57)	
Primary prevention population						.4461
Yes	2561	113(4.41)	2506	116(4.59)	1.02(0.79, 1.32)	
No	2496	111(4.45)	2538	134(5.28)	1.18(0.91, 1.51)	
Lower extremity arterial disease at baseline						.3645
Yes	540	29(5.37)	543	39(7.18)	1.35(0.84, 2.19)	
No	4516	195(4.32)	4501	210(4.67)	1.06(0.87, 1.29)	
Diabetes mellitus at baseline						.6847
Yes	2309	129(5.59)	2298	140(6.09)	1.06(0.83, 1.35)	
No	2734	95(3.47)	2736	109(3.98)	1.14(0.87, 1.51)	
Current smoker at baseline						.0937
Yes	649	15(2.31)	607	26(4.28)	1.84(0.98, 3.48)	
No	4408	209(4.74)	4437	223(5.03)	1.06(0.86, 1.26)	
Hypertension at baseline						.8597
Yes	3935	185(4.70)	3928	204(5.19)	1.09(0.89, 1.33)	
No	1121	39(3.48)	1115	45(4.04)	1.14(0.74, 1.75)	
Hyperlipidemia at baseline						.5303
Yes	3701	158(4.27)	3680	170(4.62)	1.06(0.86, 1.32)	
No	1330	64(4.81)	1342	78(5.81)	1.21(0.87, 1.68)	
Cardiovascular risk score at baseline						.7450
<=5	1836	62(3.38)	1835	64(3.49)	1.01(0.72, 1.44)	
>5 and <=9	1757	83(4.72)	1712	98(5.72)	1.20(0.90, 1.61)	
>9	1464	79(5.40)	1497	87(5.81)	1.06(0.79, 1.44)	
History of atrial fibrillation						.8565
Yes	229	25(10.92)	253	32(12.65)	1.14(0.68, 1.92)	
No	4828	199(4.12)	4791	217(4.53)	1.08(0.89, 1.31)	
HMG-CoA reductase inhibitor use at baseline						.6419
Yes	2361	88(3.73)	2382	104(4.37)	1.16(0.87, 1.54)	
No	2670	136(5.09)	2631	145(5.51)	1.06(0.84, 1.34)	

Warfarin use at baseline					.4208
Yes	195	9(4.62)	222	16(7.21)	1.52(0.67, 3.44)
No	4436	215(4.85)	4791	233(4.86)	1.06(0.90, 1.30)
Aspirin use at baseline					.6912
Yes	2865	132(4.61)	2846	150(5.27)	1.13(0.90, 1.43)
No	2166	92(4.25)	2167	99(4.57)	1.05(0.79, 1.40)
Non-aspirin antiplatelet use at baseline					.6065
Yes	142	7(4.93)	156	11(7.05)	1.40(0.54, 3.62)
No	4889	217(4.44)	4857	238(4.90)	1.09(0.91, 1.31)
Beta-blocker use at baseline					.6139
Yes	2262	107(4.53)	2431	129(5.31)	1.15(0.89, 1.49)
No	2668	117(4.39)	2582	120(4.65)	1.05(0.81, 1.35)
Calcium channel blocker use at baseline					.7890
Yes	1800	84(4.67)	1779	96(5.40)	1.14(0.85, 1.52)
No	3231	140(4.33)	3234	153(4.73)	1.08(0.86, 1.36)
ACE inhibitor or angiotensin receptor blocker use at baseline					.4746
Yes	2424	117(4.83)	2469	125(5.06)	1.03(0.80, 1.33)
No	2607	107(4.10)	2544	124(4.87)	1.27(0.91, 1.52)
Diuretic use at baseline					.1613
Yes	1956	104(5.32)	2036	105(5.16)	0.95(0.72, 1.24)
No	3075	120(3.90)	2977	144(4.84)	1.23(0.96, 1.57)

Abbreviations: CI=confidence interval, ACE=angiotensin converting enzyme.
*Interaction p-Value is obtained from a Cox model: year*censor-therapy + subgroup + therapy*subgroup.

Program: RMP.H38SGGIO.SASPGM(CVCTSTES) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRST3)

In addition, post-hoc analyses of all strokes and deaths due to stroke were performed for the following subgroups (Table GGIO.9.7, Table GGIO.9.8):

- Systolic BP at baseline (≤160, >160 mmHg)
- Mean pulse pressure at baseline (≤60, >60 mmHg)
- Congestive heart failure at baseline
- Ventricular hypertrophy on baseline ECG
- History of stroke or TIA

For the prespecified subgroup analyses of all strokes, the treatment by subgroup interaction was not significant for any of the variables assessed, with the exception of smoking.
For the post-hoc subgroup analyses of all strokes, the treatment by subgroup interaction was not significant for any of the variables assessed.

Table GGIO.11.40. Subgroup Analysis of Stroke (Post-Hoc Analysis, All Randomized Patients)

Subgroup Category—conditions at baseline	Placebo N=5057			Raloxifene N=5044			HR (95%CI)	Interaction p-value[a]
	N	n	%	N	n	%		
Systolic BP (mmHg)								0.7602
≤160	4076	167	4.10	4091	190	4.64	1.12 (0.91, 1.38)	
>160	981	57	5.81	953	59	6.19	1.05 (0.73, 1.51)	
Systolic BP (mmHg)								0.3210
≤140	2433	84	3.45	2412	109	4.52	1.29 (0.97, 1.71)	
>140 and <160	1273	62	4.87	1279	58	4.53	0.92 (0.64, 1.32)	
≥160	1351	78	5.77	1353	82	6.06	1.04 (0.76, 1.41)	
Diastolic BP (mmHg)								0.5929
≤80	2817	127	4.51	2809	132	4.70	1.02 (0.80, 1.31)	
>80 and <90	747	37	4.95	771	42	5.45	1.07 (0.69, 1.67)	
≥90	1492	60	4.02	1464	75	5.12	1.27 (0.91, 1.79)	
Mean Pulse Pressure (mmHg)								0.2391
≤60	2637	95	3.60	2599	117	4.50	1.24 (0.94, 1.62)	
>60	2420	129	5.33	2445	132	5.40	0.99 (0.78, 1.27)	
LDL (mg/dL)								0.8938
≤100	1188	59	4.97	1219	65	5.33	1.07 (0.75, 1.52)	
>100 and <130	1364	57	4.18	1317	66	5.01	1.18 (0.83, 1.69)	
≥130	1472	73	4.96	1474	79	5.36	1.06 (0.77, 1.46)	
Total cholesterol (mg/dL)								0.4295
≤200	1772	77	4.35	1836	83	4.52	1.02 (0.75, 1.39)	
>200 and <240	1815	75	4.13	1746	94	5.38	1.30 (0.96, 1.76)	
≥240	1404	68	4.84	1382	68	4.92	1.00 (0.71, 1.39)	
Triglycerides (mg/dL)								0.3192
≤150	2941	131	4.45	2944	134	4.55	1.02 (0.80, 1.30)	
≥150	2050	89	4.34	2020	111	5.50	1.23 (0.93, 1.63)	
CHF[b]								0.2743
Yes	255	17	6.67	282	29	10.28	1.50 (0.82, 2.73)	
No	4802	207	4.31	4762	220	4.62	1.06 (0.87, 1.28)	
Ventricular hypertrophy[c]								0.1636
Yes	679	45	6.63	637	61	9.58	1.40 (0.95, 2.06)	
No	4287	176	4.11	4306	184	4.27	1.03 (0.84, 1.27)	
Prior stroke or TIA[d]								0.3564
Yes	439	30	6.83	421	39	9.26	1.36 (0.84, 2.18)	
No	4618	194	4.20	4623	210	4.54	1.07 (0.88, 1.30)	

Abbreviations: BP = blood pressure, CI = confidence interval, HR = hazard ratio, LDL = low-density lipoprotein, N = number of patients with condition at baseline, n = number of patients with condition at baseline and experiencing a stroke event.

[a] Interaction p-value is obtained from a Cox model: year×censor = therapy + subgroup + therapy×subgroup.

[b] Congestive heart failure was defined as follows: patient reported either a secondary condition or an historical diagnosis with a MedDRA high-level term of 1) heart failure NEC, 2) heart failure signs and symptoms, 3) right ventricular failure, or 4) left ventricular failure.

[c] Based on baseline ECG.

[d] Prior stroke or TIA was defined as follows: patient reported either a secondary condition or an historical diagnosis with a MedDRA high-level term of 1) central nervous system hemorrhage and cerebrovascular accident, 2) transient cerebrovascular event, or 3) central nervous system vascular disorder NEC.

Sources: CVTSUS3, CVTSUB1, CVTSTHF, CVTSTVH, CVTSTPR.

In the post-hoc subgroup analyses for all deaths due to stroke, the treatment by subgroup interaction was not significant for any of the variables assessed, with the exception of baseline pulse pressure (p=0.0797) and systolic blood pressure (p=0.0761) (Table GGIO.11.41). In both of these analyses, the proportion of patients assigned raloxifene who had a mean baseline pulse pressure ≤60 mmHg or a mean baseline systolic blood pressure ≤160 mmHg and died due to a stroke was significantly greater than those patients assigned placebo. Given that high blood

pressure is a stroke risk factor, these paradoxical findings are not consistent with epidemiologic data and therefore were considered not clinically meaningful.

Table GGIO.11.41. Subgroup Analysis of Death due to Stroke (Post-Hoc Analysis, All Randomized Patients)

Subgroup Category—conditions at baseline	Placebo N=5057			Raloxifene N=5044			HR (95%CI)	Interaction p-value[a]
	N	n	(%)	N	n	(%)		
Age (years)								0.8917
≤65	1858	7	(0.38)	1841	9	(0.49)	1.27 (0.47, 3.41)	
>65 and <70	1219	9	(0.74)	1252	13	(1.04)	1.38 (0.59, 3.24)	
≥70	1980	23	(1.16)	1951	37	(1.90)	1.62 (0.96, 2.73)	
Race								0.8547
Caucasian	4247	33	(0.78)	4234	49	(1.16)	1.47 (0.95, 2.29)	
Other	810	6	(0.74)	810	10	(1.23)	1.63 (0.59, 4.48)	
Region								0.6358
North America	515	1	(0.19)	514	6	(1.17)	5.97 (0.72, 49.55)	
Latin/South America	683	7	(1.02)	687	5	(0.73)	0.69 (0.22, 2.16)	
Western Europe	2343	17	(0.73)	2336	21	(0.90)	1.24 (0.65, 2.34)	
Eastern Europe	1156	14	(1.21)	1154	22	(1.91)	1.53 (0.78, 2.98)	
Africa	109	0	(0.00)	106	3	(2.83)	N/A	
Asia Pacific	251	0	(0.00)	247	2	(0.81)	N/A	
Body mass index (kg/m^2)								0.8002
≤25	1230	12	(0.98)	1186	14	(1.18)	1.19 (0.55, 2.58)	
>25 and ≤30	2013	15	(0.75)	2039	25	(1.23)	1.61 (0.85, 3.06)	
>30	1798	12	(0.67)	1805	20	(1.11)	1.65 (0.80, 3.37)	
Primary prevention population								0.6399
Yes	2561	22	(0.86)	2506	30	(1.20)	1.37 (0.79, 2.37)	
No	2496	17	(0.68)	2538	29	(1.14)	1.66 (0.91, 3.02)	
Lower extremity arterial disease								0.8284
Yes	540	8	(1.48)	543	11	(2.03)	1.37 (0.55, 3.40)	
No	4516	31	(0.69)	4501	48	(1.07)	1.53 (0.97, 2.40)	
Diabetes mellitus								0.2817
Yes	2309	16	(0.69)	2298	31	(1.35)	1.90 (1.04, 3.47)	
No	2734	23	(0.84)	2736	28	(1.02)	1.21 (0.70, 2.10)	
Current smoker								0.8045
Yes	649	3	(0.46)	607	5	(0.82)	1.77 (0.42, 7.41)	
No	4408	36	(0.82)	4437	54	(1.22)	1.47 (0.96, 2.24)	
Hypertension								0.3409
Yes	3935	34	(0.86)	3928	47	(1.20)	1.37 (0.88, 2.12)	
No	1121	5	(0.45)	1115	12	(1.08)	2.37 (0.83, 6.72)	
Hyperlipidemia								0.6164
Yes	3701	25	(0.68)	3680	40	(1.09)	1.58 (0.96, 2.61)	
No	1330	14	(1.05)	1342	18	(1.34)	1.27 (0.63, 2.55)	
Cardiovascular risk score								0.7351
≤5	1836	11	(0.60)	1835	13	(0.71)	1.16 (0.52, 2.59)	
>5 and ≤9	1757	17	(0.97)	1712	29	(1.69)	1.73 (0.95, 3.15)	
>9	1464	11	(0.75)	1497	17	(1.14)	1.49 (0.70, 3.19)	

Subgroup Category—conditions at baseline	Placebo N=5057			Raloxifene N=5044			HR (95%CI)	Interaction p-value[a]
	N	n	(%)	N	n	(%)		
History of atrial fibrillation								0.1875
Yes	229	3	(1.31)	253	11	(4.35)	3.28 (0.91,11.74)	
No	4828	36	(0.75)	4791	48	(1.00)	1.32 (0.86, 2.04)	
HMG-CoA reductase inhibitor use								0.3903
Yes	2361	13	(0.55)	2382	25	(1.05)	1.89 (0.96, 3.68)	
No	2670	26	(0.97)	2631	34	(1.29)	1.30 (0.78, 2.17)	
Warfarin use								0.9794
Yes	195	0	(0.00)	222	5	(2.25)	N/A	
No	4836	39	(0.81)	4791	54	(1.13)	1.38 (0.91, 2.08)	
Aspirin use								0.7210
Yes	2865	24	(0.84)	2846	34	(1.19)	1.41 (0.83, 2.37)	
No	2166	15	(0.69)	2167	25	(1.15)	1.64 (0.86, 3.10)	
Non-aspirin antiplatelet use								0.2987
Yes	142	3	(2.11)	156	2	(1.28)	0.59 (0.10, 3.55)	
No	4889	36	(0.74)	4857	57	(1.17)	1.57 (1.03, 2.38)	
Beta-blocker use								0.8314
Yes	2363	18	(0.76)	2431	27	(1.11)	1.43 (0.79, 2.59)	
No	2668	21	(0.79)	2582	32	(1.24)	1.56 (0.90, 2.71)	
Calcium channel blocker use								0.3906
Yes	1800	20	(1.11)	1779	25	(1.41)	1.24 (0.69, 2.23)	
No	3231	19	(0.59)	3234	34	(1.05)	1.77 (1.01, 3.10)	
ACE inhibitor or angiotensin receptor blocker use								0.2418
Yes	2424	18	(0.74)	2469	35	(1.42)	1.88 (1.06, 3.32)	
No	2607	21	(0.81)	2544	24	(0.94)	1.15 (0.64, 2.07)	
Diuretic use								0.9452
Yes	1956	18	(0.92)	2036	28	(1.38)	1.46 (0.81, 2.65)	
No	3075	21	(0.68)	2977	31	(1.04)	1.51 (0.87, 2.62)	
Systolic BP								0.0761
≤160 mmHg	4076	26	(0.64)	4091	49	(1.20)	1.85 (1.15, 2.98)	
>160 mmHg	981	13	(1.33)	953	10	(1.05)	0.78 (0.34, 1.78)	
Pulse Pressure								0.0797
≤60	2637	15	0.57	2599	33	1.27	2.20 (1.20, 4.06)	
>60	2420	24	0.99	2445	26	1.06	1.05 (0.61, 1.84)	
Ventricular hypertrophy[b]								0.9008
Yes	679	12	(1.77)	637	18	(2.83)	1.54 (0.74, 3.20)	
No	4287	27	(0.63)	4306	40	(0.93)	1.46 (0.89, 2.38)	

Subgroup Category—conditions at baseline	Placebo N=5057			Raloxifene N=5044			HR (95%CI)	Interaction p-value[a]
	N	n	(%)	N	n	(%)		
Congestive heart failure[c]								0.5955
Yes	255	5	(1.96)	282	11	(3.90)	1.91 (0.66, 5.51)	
No	4802	34	(0.71)	4762	48	(1.01)	1.40 (0.90, 2.18)	
Prior history of stroke or TIA[d]								0.9599
Yes	439	7	(1.59)	421	10	(2.38)	1.47 (0.56, 3.85)	
No	4618	32	(0.69)	4623	49	(1.06)	1.51 (0.97, 2.35)	

Abbreviations: BP = blood pressure; CHF = congestive heart failure; CI = confidence interval; TIA = transient ischemic attack.

[a] Interaction p-value is obtained from a Cox model: year×censor = therapy + subgroup + therapy×subgroup.

[b] Based on baseline ECG.

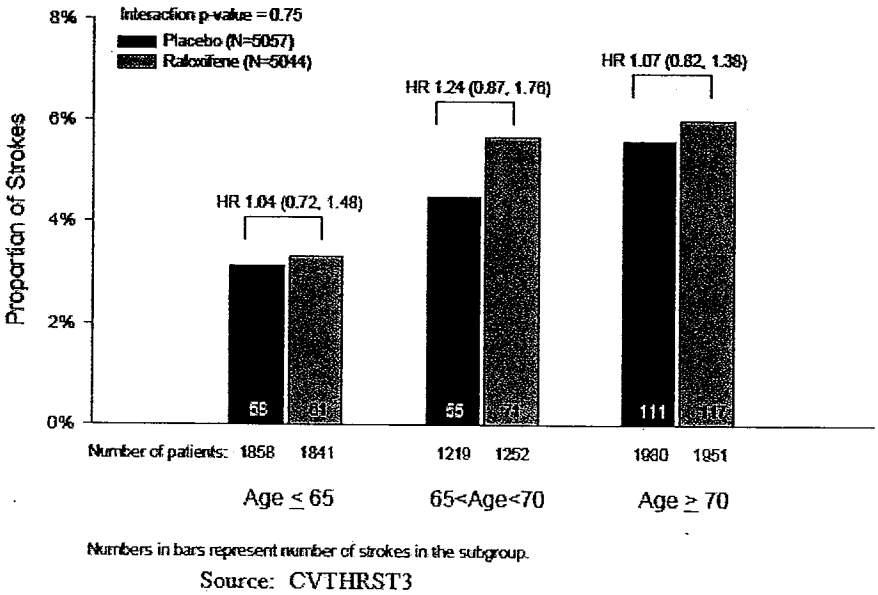
[c] Congestive heart failure was defined as follows: patient reported either a secondary condition or an historical diagnosis with a MedDRA high-level term of 1) heart failure NEC, 2) heart failure signs and symptoms, 3) right ventricular failure, or 4) left ventricular failure.

[d] Prior stroke or TIA was defined as follows: patient reported either a secondary condition or an historical diagnosis with a MedDRA high-level term of 1) central nervous system hemorrhage and cerebrovascular accident, 2) transient cerebrovascular event, or 3) central nervous system vascular disorder NEC.

Sources: CVTHRD4, CVTSUB2, CVTSTDHF, CVTSTDVH, CVTSTDPR, CVTSUB4.

To determine if *the risk of stroke* or *death due to stroke* increased with age, comparisons between treatment groups were assessed in three age categories.

- The **proportion of patients** who had a stroke (Figure GGIO.11.19) or died due to a stroke (Figure GGIO.11.20) was observed to **increase with age**; but these changes were not statistically evaluated.
- The proportion of patients who had a stroke or died due to a stroke was **greater in the raloxifene group than in the placebo group for each age category**, although there were **no significant differences** between treatment groups for any one age category.
- There was **no significant interaction** between raloxifene and the subgroup of age for all strokes or deaths due to stroke.



Source: CVTHRST3

Figure GGIO.11.19. All strokes by age categories, all randomized patients (post hoc analysis).

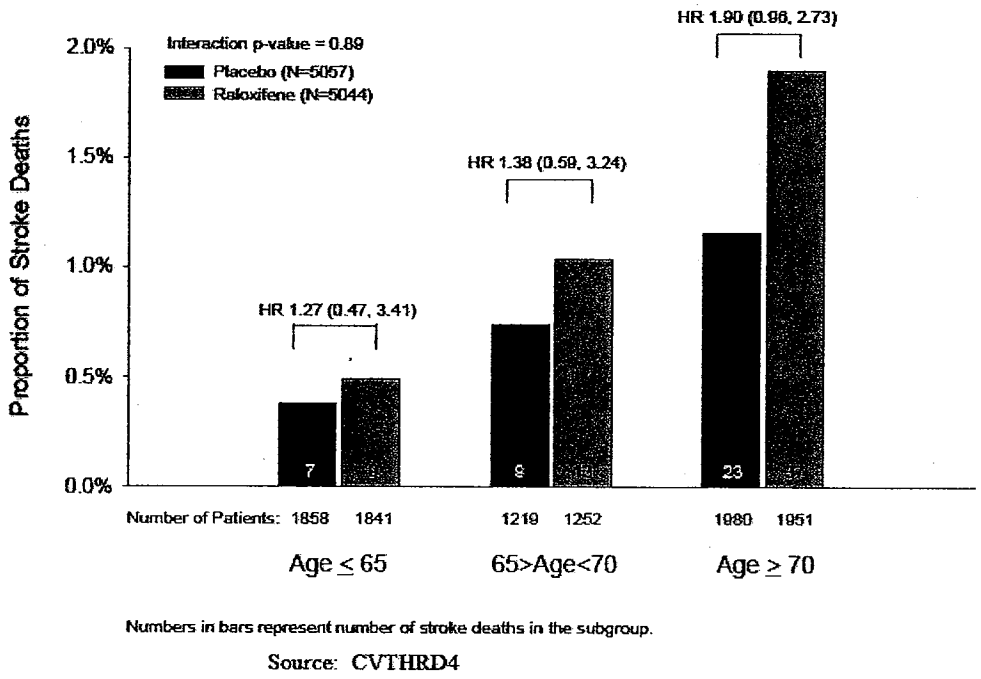


Figure GGIO.11.20. Deaths due to stroke by age category, all randomized patients (post-hoc analysis).

Risk Onset (11.4.4.4.2.3.)

Examination of the Kaplan-Meier curves for deaths due to stroke (Figure GGIO.11.14) showed that the treatment group curves began to separate around Year 3. To further investigate this observation, analyses of all strokes and deaths due to stroke were performed from the time of randomization to the end of the study on a yearly basis.

- The **cumulative time-to-event analysis of all strokes** showed no significant difference between treatment groups from the time of randomization until the end of the study, based on examination on *a yearly basis* (Table GGIO.11.42).
- In the **cumulative time-to-event analysis of deaths due to stroke**, there was no significant treatment effect on stroke mortality at the end of Year 1 or Year 2; however, an increase in incidence in the raloxifene group was seen at the end of the third year of follow-up and this increased incidence persisted until the end of the study. The between-treatment group difference did not become significant until Year 7 (Table GGIO.11.43).

Table GGIO.11.42. Time-to-Event Analysis of Stroke by Year (All Randomized Patients, post-hoc analysis, cumulative)

Stroke	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard ratio (95% CI)	p-Value*
1 year	35(0.69)	40(0.79)	1.14(0.73, 1.80)	.5596
2 year	73(1.44)	82(1.63)	1.12(0.82, 1.54)	.4806
3 year	118(2.33)	124(2.46)	1.04(0.81, 1.34)	.7440
4 year	148(2.93)	167(3.31)	1.12(0.90, 1.39)	.3253
5 year	187(3.70)	216(4.28)	1.14(0.94, 1.39)	.1815
6 year	221(4.37)	242(4.80)	1.08(0.90, 1.30)	.3936
7 year	224(4.43)	249(4.94)	1.10(0.92, 1.32)	.3034

*p-Value is obtained from a log-rank test.
Program: RMP.H3SSGGIO.SASPGM(CVCTHRTY) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRTY)

Table GGIO.11.43. Time–to-Event Analysis of Stroke Death by Year (All Randomized Patients, post-hoc analysis, cumulative)

Stroke	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard ratio (95% CI)	p-Value*
1 year	8(0.16)	5(0.10)	0.62(0.20, 1.91)	.4038
2 year	13(0.26)	12(0.24)	0.92(0.42, 2.01)	.8331
3 year	20(0.40)	29(0.57)	1.44(0.81, 2.54)	.2103
4 year	27(0.53)	39(0.77)	1.43(0.87, 2.33)	.1519
5 year	35(0.69)	51(1.01)	1.44(0.94, 2.21)	.0950
6 year	39(0.77)	58(1.15)	1.47(0.98, 2.20)	.0616
7 year	39(0.77)	59(1.17)	1.49(1.00, 2.24)	.0499

*p-Value is obtained from a log-rank test.
Program: RMP.H3SSGGIO.SASPGM(CVCTHRDY) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRDY)

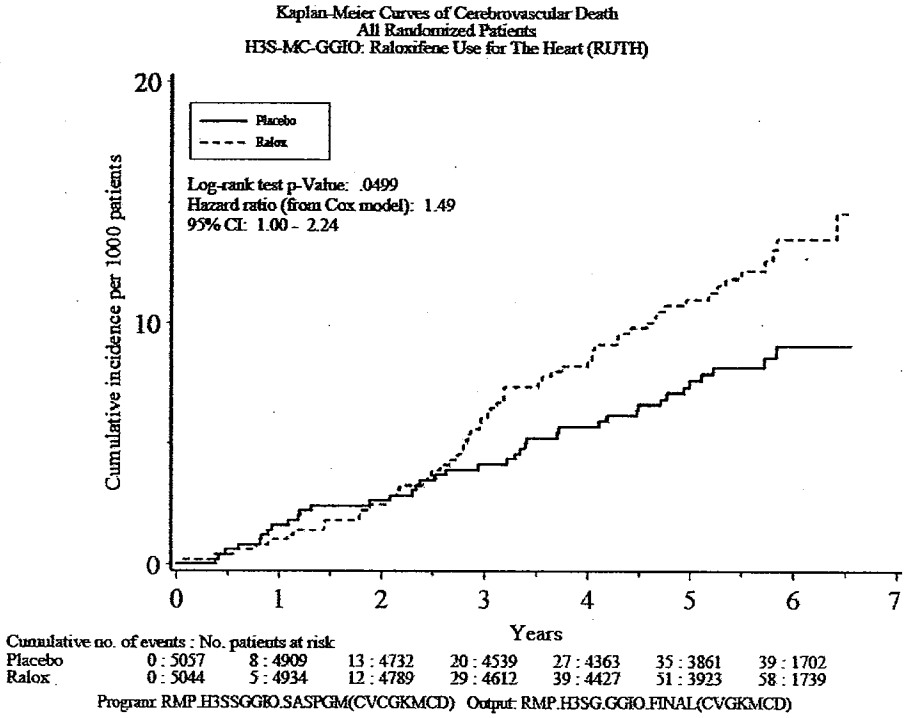


Figure GGIO.11.14. Kaplan-Meier curves of cerebrovascular death for all randomized patients.

Analysis of Deaths Due to Stroke by Stroke Subtypes (11.4.4.4.2.4.)

Analysis of stroke by subtype was a prespecified analysis. There was no significant difference between treatment groups for ischemic or hemorrhagic strokes (or cerebrovascular events which had clinical features suggestive of a stroke but for which the specific type could not be determined by adjudication). Most strokes were classified as ischemic.

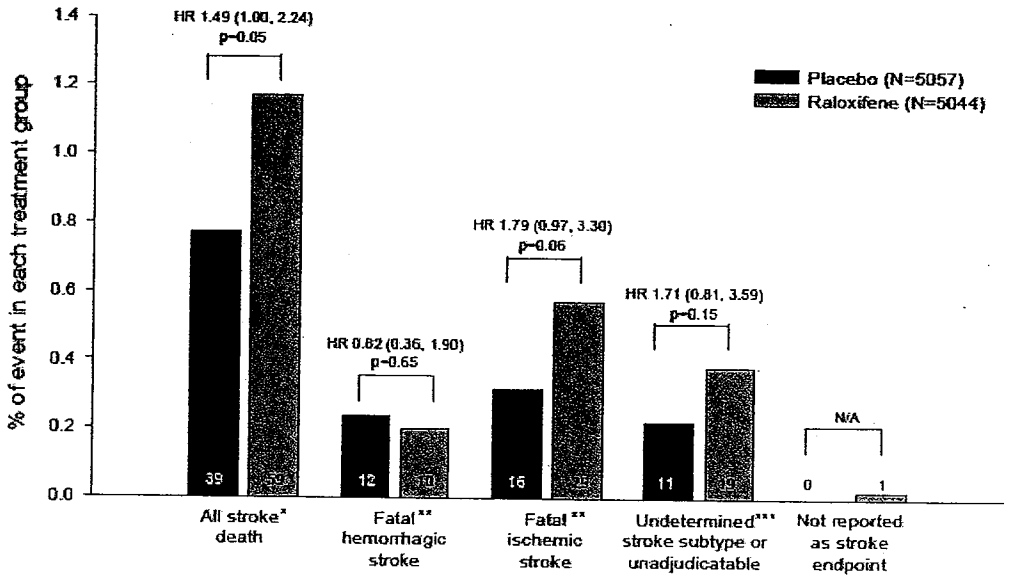
To further evaluate the observed increase in the incidence of *death due to stroke* in the raloxifene group, an analysis of the types of strokes leading to death was performed.

Because of the adjudication processes utilized in this trial, the limitations of this analysis must be noted. The committee adjudicating reported strokes was independent of the committee adjudicating deaths and assigning causality. An investigator may have reported a death due to a stroke and a stroke as trial endpoints. Available clinical documentation of the stroke was submitted to the stroke committee for review and determination if the prespecified criteria for stroke were met. If a reported stroke was adjudicated as such, the committee was asked to classify the type of stroke. A death, on the other hand, was adjudicated by a different committee, and cause of death was assigned based on available clinical information, death certificate, or autopsy report. No criteria were prespecified in the protocol defining a death due to a cerebrovascular cause.
Consequently, a reported stroke may not have been adjudicated as such, but the cause of death may have been attributed to a cerebrovascular cause. Only the stroke committee prospectively classified strokes as ischemic or hemorrhagic in origin; the committee adjudicating deaths did not classify a death due to a cerebrovascular cause as ischemic or hemorrhagic. Another limitation in interpreting the stroke mortality finding is that stroke severity was not collected for nonfatal strokes reported.

To ascertain whether deaths due to stroke were ischemic or hemorrhagic in origin, a retrospective assessment of the last adjudicated stroke for each patient who died due to a stroke was conducted. However, given the above caveats, the last adjudicated stroke was not always the stroke resulting in death. Nine patients died due to a stroke (4 in placebo, 5 in raloxifene), but the stroke resulting in death was not adjudicated as such by the stroke committee. For one of the patients assigned to raloxifene who died due to a stroke, the investigator did not report the stroke as an endpoint; thus, this stroke was reported only as an AE and was not reviewed by the stroke committee. Consequently, this assessment was conducted for 35 patients in the placebo group and 54 patients in the raloxifene group who had an adjudicated stroke prior to death.

Figure GGIO.11.21 shows deaths due to stroke classified by stroke subtype based on retrospective assessment of the last adjudicated stroke for each patient who died due to a stroke.

- The highest proportion of patients who died due to a stroke had a prior adjudicated ischemic stroke. Although not significantly different, the proportion of patients who had a fatal ischemic stroke was greater in the raloxifene group than the placebo group.
- The proportion of patients who had a fatal hemorrhagic stroke was similar between treatment groups.
- For 30 deaths due to stroke, the type of stroke could not be determined or the stroke was deemed unadjudicatable. There was no significant difference between treatment groups in this later category.



* Based on death adjudication form.
** Determined by the adjudication status of the last investigator reported stroke.
Numbers in bars represent number of events of interest in the group.
*** Undetermined stroke subtype = clinical features suggestive of a stroke but subtype unknown.
Unadjudicatable = not enough information to be adjudicated as a stroke.

Source: CVTHRD6, CVTHRMOR

Figure GGIO.11.21. Deaths due to stroke by stroke subtype, all randomized patients (post-hoc analysis).

Time-to-Event Analyses Adjusted for Baseline Risk Factors (11.4.4.4.2.5.)

To determine whether the observed effects of raloxifene in the prespecified analyses of all strokes and deaths due to stroke were confounded by baseline characteristics, analyses were performed adjusting for baseline risk factors. A baseline characteristic was considered a risk factor if it significantly affected the endpoint of interest in a univariate analysis and in the final multivariate adjusted model. The 20 prespecified variables used in the subgroup analyses of all strokes were considered potential risk factors for stroke and death due to stroke.

In the **time-to-event analysis of all strokes**, the risk factors that were significant in the univariate model and remained significant in the final multivariate adjusted model included the following:

- Age (≤65, >65 and <70, ≥70 years)
- Lower extremity arterial disease
- Diabetes mellitus
- Hypertension
- CV risk score (≤5, >5 and ≤9, >9)
- History of atrial fibrillation
- Statin use

In the **multivariate adjusted model**, there was no significant difference between treatment groups for all strokes. This result is consistent with the prespecified primary analysis of the secondary endpoint of all strokes.

Table GGIO.11.44. Time-to-Event Analysis of Stroke *Adjusted for Baseline Risk Characteristics* (Post-hoc Analysis, All Randomized Patients)

	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard ratio* (95% CI)	p-Value*
Stroke	224(4.43)	249(4.94)	1.08(0.91, 1.30)	.3783

Abbreviations: CI=confidence interval.
*Hazard ratio and p-Value are obtained from a Cox model, adjusting for the following characteristics:
Age (<=65, >65 and <70, >=70)
Lower extremity arterial disease at baseline
Diabetes mellitus at baseline
Hypertension at baseline
Cardiovascular risk score at baseline (<=5, >5 and <=9, >9)
History of artrial fibrillation
HMG-CoA reductase inhibitor use at baseline

Program: RMP.H3SSGGIO.SASPGM(CVCTHRKA) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3S0.GGIO.FINAL(CVTHRKA)

In the **time-to-event analysis of deaths due to stroke**, the risk factors that were significant in the univariate model and remained significant in the final multivariate adjusted model included the following:

- Age (≤65, >65 and <70, ≥70 years)
- Lower extremity arterial disease
- History of atrial fibrillation

The result of the **multivariate adjusted model** is consistent with the prespecified primary analysis of deaths due to stroke.

Table GGIO.11.45. Time-to-Event Analysis of Deaths Due to Stroke *Adjusted for Baseline Risk Characteristics* (Post-hoc Analysis, All Randomized Patients)

	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard ratio* (95% CI)	p-value*
Stroke Death	39(0.77)	59(1.17)	1.48(0.99, 2.22)	.0571

Abbreviations: CI=confidence interval.
*Hazard ratio and p-Value are obtained from a Cox model, adjusting for the following characteristics:
Age (<=65, >65 and <70, >=70)
Lower extremity arterial disease at baseline
History of artrial fibrillation

Program: RMP.H3SGGIO.SASPGM(CVCTHRSD) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHRSD)

Summary of Exploratory Analyses of All Strokes and Deaths Due to Stroke (11.4.4.4.2.6.)

Since the statistical significance of the increased incidence of death due to stroke was relatively weak (p=0.0499), this observation may be due to chance or may be real. Exploratory analyses were performed for all strokes and deaths due to stroke to better understand the potential clinical significance of this observation.

- None of the baseline characteristics of the patients who experienced a stroke or died due to a stroke suggested a differential response to treatment with raloxifene.
- The increase in the incidence of death due to stroke in the raloxifene group was evidenced after Year 3 of the trial and persisted thereafter, becoming significant in Year 7.
- The majority of adjudicated strokes were ischemic in origin and the majority of patients who died due to a stroke had a prior ischemic stroke, adjudicated as such.
- Results from these analyses indicated that no single risk factor could be identified from statistical modeling that would predict which patient treated with raloxifene might experience a stroke and subsequently die from it.

Revascularization and Amputation (11.4.4.5.)

Table GGIO.11.46, Figure GGIO.14.12, and Figure GGIO.14.13 present the results of analyses for revascularizations and amputations.

- Raloxifene did not significantly increase or decrease the incidence of all revascularizations or any type of revascularizations nor was there any significant difference in non-traumatic lower extremity amputations.

Table GGIO.11.46. Time-to-Event Analysis of Revascularization and Amputation (All Randomized Patients)

Revascularization/amputation endpoint	Placebo (N=5057) n(%)	Raloxifene (N=5044) n(%)	Hazard Ratio (95% CI)	p-Value*
All revascularizations	615(12.16)	611(12.11)	0.99(0.88, 1.10)	.7269
Myocardial revascularizations	467(9.23)	459(9.10)	0.97(0.85, 1.10)	.6260
Percutaneous coronary intervention	321(6.35)	320(6.34)	0.98(0.84, 1.15)	.8276
Coronary artery bypass graft	164(3.24)	149(2.95)	0.90(0.72, 1.12)	.3387
Other myocardial revascularization	3(0.06)	3(0.06)	0.99(0.20, 4.89)	.9964
Non-coronary arterial revascularizations	177(3.50)	187(3.71)	1.05(0.85, 1.29)	.6654
Carotid district	47(0.93)	38(0.75)	0.80(0.52, 1.22)	.2997
Lower extremity	112(2.21)	119(2.36)	1.05(0.81, 1.36)	.6967
Other non-coronary arterial revascularization	31(0.61)	41(0.81)	1.31(0.82, 2.08)	.2587
Non-traumatic lower extremity amputation	44(0.87)	41(0.81)	0.92(0.60, 1.41)	.7004
Above knee	17(0.34)	13(0.26)	0.75(0.37, 1.55)	.4416
Below knee	16(0.32)	9(0.18)	0.56(0.25, 1.26)	.1519
Foot/toe	25(0.49)	23(0.46)	0.91(0.52, 1.60)	.7395
Other non-traumatic lower extremity amputation	3(0.06)	1(0.02)	N/A	N/A

Abbreviations: CI-confidence interval.
*p-Value is obtained from a log-rank test. Statistical test is not performed when the total number of patients in a category is less than 5.

Program: RMP.H3SSGGIO.SASPGM(CVCMEKV) Data: RMP.SAS.H3SH.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(CVTHERRV)

Fracture (11.4.4.6.)

According to the study design, scheduled vertebral radiographs were not obtained. Use of other bone-active medications concomitantly with study medication was permitted. Table GGIO.11.47 presents results of the **time-to-event analysis** of fractures, and Table GGIO.11.48 presents post-hoc analyses of **incidence rates** for fractures.

- The incidence of clinical vertebral fracture was significantly decreased by 35% in the raloxifene group compared with the placebo group (Table GGIO.11.47 and Figure GGIO.11.22).
- Post-hoc analysis showed that raloxifene was associated with an absolute risk decrease of 1.3 clinical vertebral fractures per 1000 woman-years (Table GGIO.11.48).
- There was no significant increase or decrease in the incidences of non-vertebral fractures or hip/femur or wrist fractures in the raloxifene group compared with the placebo group (Table GGIO.11.47; Figure GGIO.14.14 to Figure GGIO.14.18).

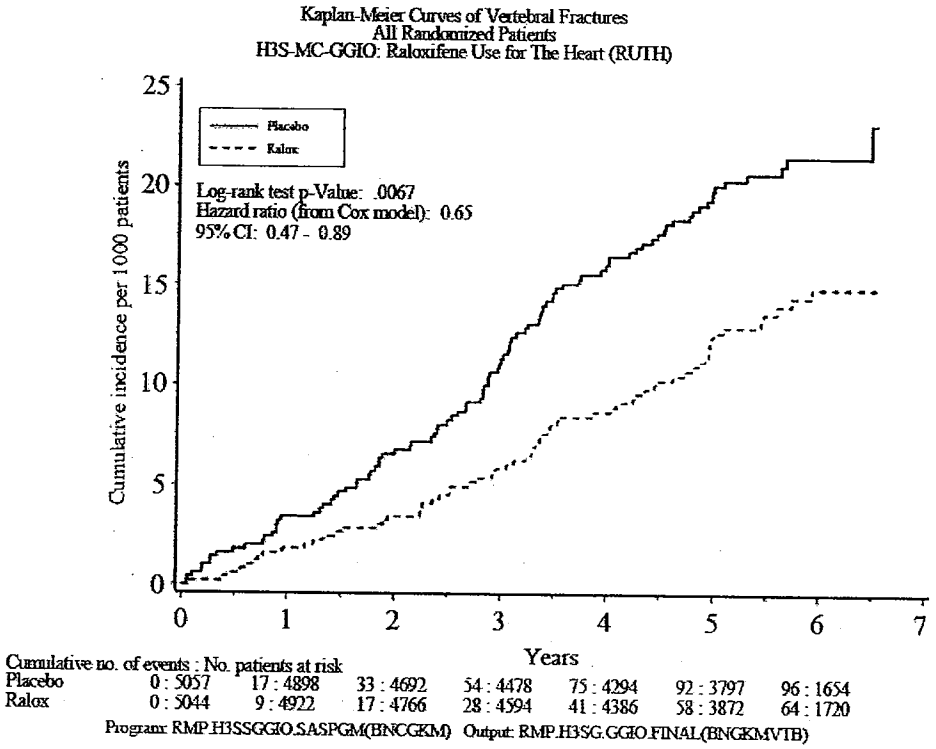


Figure GGIO.11.22. Kaplan-Meier curve of vertebral fractures.

Table GGIO.11.47. Time-to-Event Analysis of Fracture Endpoint (All Randomized Patients)

Fracture site	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Hazard Ratio (95% CI)	p-Value*
Nonvertebral** including ankle	438(8.66)	428(8.49)	0.96(0.84, 1.10)	.5871
Nonvertebral** excluding ankle	400(7.91)	384(7.61)	0.95(0.82, 1.09)	.4465
Hip/femur or wrist	211(4.17)	192(3.81)	0.90(0.74, 1.09)	.2845
Hip/femur	103(2.04)	89(1.76)	0.85(0.64, 1.13)	.2669
Wrist	111(2.19)	107(2.12)	0.95(0.73, 1.24)	.7285
Vertebral	97(1.92)	64(1.27)	0.65(0.47, 0.89)	.0067

Abbreviations: CI=confidence interval;
*p-Value is obtained from a log-rank test.
**Nonvertebral is defined by the combined fracture sites of arm/forearm/elbow, clavicle/scapula/shoulder, wrist, ribs/sternum, pelvis/sacrum, hip/femur, and tibia/fibula/patella.

Program: RMP.H3SSGGIO.SASPGM(RMCTHR1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(RMTHRFRX)

Table GGIO.11.48. Incidence Rate of Fracture Endpoint (Post-hoc Analysis, All Randomized Patients)

Fracture site	Placebo (N=5057) n (%)	Patient-years of follow-up	IR* per 1000 patients	Ralox (N=5044) n (%)	Patient-years of follow-up	IR* per 1000 patients	ARR** per 1000 patients
Nonvertebral** including ankle	438(8.66)	25363	17.27	428(8.49)	25701	16.65	1.41
Nonvertebral** excluding ankle	400(7.91)	25485	15.70	384(7.61)	25816	14.87	2.75
Hip/femur or wrist	211(4.17)	26024	8.11	192(3.81)	26319	7.30	3.52
Hip/femur	103(2.04)	26298	3.92	89(1.76)	26626	3.34	2.47
Wrist	111(2.19)	26205	4.24	107(2.12)	26475	4.04	0.72
Vertebral	97(1.92)	26223	3.70	64(1.27)	26641	2.40	6.39

*Incidence rate is calculated as the number of patients who developed the event of interest divided by the patient-years of follow-up.
**Absolute risk reduction (ARR) is calculated by subtracting the cumulative incidence of the raloxifene arm from that of the placebo arm, where cumulative incidence is estimated using 1-exp(-I*T), I is the incidence rate, and T is the average patient-years of follow-up in each arm.

Program: RMP.H3SSGGIO.SASPGM(RMCTIRA) Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(RMTIRA)

All-Cause Hospitalization (11.4.4.7.)

Table GGIO.11.49 presents the number and proportion of patients who were hospitalized for any reason during the course of the study.

- Significantly fewer patients in the raloxifene group had one or more **hospitalizations for any cause** compared with the placebo group.
- Significantly more patients in the raloxifene group compared with the placebo group were **hospitalized due to VTE**. This finding was not unexpected given that a greater proportion of patients assigned raloxifene experienced a VTE compared with those patients assigned placebo.
- Significantly more patients in the placebo group were **hospitalized for "other" reasons** compared with the raloxifene group; the clinical relevance of this finding in unknown.

In the original protocol, **hospitalization due to unstable angina** was a secondary endpoint. This secondary endpoint was **changed to hospitalized ACS** (combined hospitalized ACS other than MI and nonfatal MI) by Protocol Amendment (c).

- Prior to this protocol amendment, hospitalization due to unstable angina was collected on a separate adjudication form. Following the protocol amendment, hospitalization due to unstable angina was no longer collected. Through the period of follow-up in which this data was collected, 1.3% of patients in the placebo group and 1.2% in the raloxifene group were hospitalized due to unstable angina.

Table GGIO.11.49. All-Cause Hospitalization Endpoint (All Randomized Patients)

Hospitalization endpoint reason	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
All hospitalizations	2743(54.24)	2599(51.53)	5342(52.89)	.006
Myocardial infarction	193(3.82)	181(3.59)	374(3.70)	.544
Venous thromboembolic event	36(0.71)	57(1.13)	93(0.92)	.028
Revascularization or amputation	239(4.73)	254(5.04)	493(4.88)	.470
Stroke	171(3.38)	183(3.63)	354(3.50)	.500
Fracture	192(3.80)	171(3.39)	363(3.59)	.272
Breast cancer	26(0.51)	17(0.34)	43(0.43)	.172
Hospitalized ACS other than MI	230(4.55)	191(3.79)	421(4.17)	.056
Other reason for hospitalization	2395(47.36)	2271(45.02)	4666(46.19)	.019
Reason for hospitalization unavailable**	0(0.00)	1(0.02)	1(0.01)	N/A

Abbreviations: CI=confidence interval; ACS=acute coronary syndrome; MI=myocardial infarction.
*p-Value is obtained from a Pearson's Chi-square test. Statistical test is not performed when the total number of patients in a category is less than 5.
**Patient was not hospitalized for 24 hours or more.

Program: RMP.H38SGGIO.SASPGM(CVCTACH1) Data: RMP.SAS.H38M.L.MCGGIOSA.FINAL.MAIN Output: RMP.H38O.GGIO.FINAL(CVTACH1)

Biochemical Markers of Cardiovascular Risk (11.4.5.)

The change in biochemical markers of cardiovascular risk were assessed only for those patients who had a baseline and endpoint measurement.

- **Descriptive statistics** by-visit for the biochemical markers of CV risk are shown in Table GGIO.14.40 to Table GGIO.14.46.
- **Changes in biochemical markers of CV risk from baseline to Year 1** are shown in Table GGIO.11.50. **Percent changes** in biochemical markers of CV risk from baseline to Year 1 are presented in Table GGIO.14.37.

- Raloxifene significantly reduced total cholesterol, LDL-C, non-HDL-C, total cholesterol/HDL-C, and fibrinogen levels compared with placebo during the first year of follow-up. There was no difference between treatment groups in triglyceride levels. Raloxifene significantly increased HDL-C levels compared with placebo. **All these differences were small in magnitude, none of these changes were deemed to be clinically relevant.**

- Table GGIO.14.38 presents changes in biochemical markers of CV risk **from baseline to endpoint** and Table GGIO.14.39 presents percent changes in biochemical markers of CV risk from baseline to endpoint. The results of these analyses were consistent with those of the change from baseline to Year 1 analyses.

Table GGIO.11.50. Biochemical Markers of Cardiovascular Risk (Change from Baseline to Year 1, All Randomized Patients)

Lab	Unit	Therapy	N**	Baseline Mean	Baseline STD	Year 1 Mean	Year 1 STD	Change to Year 1 Mean	Change to Year 1 STD	p-Value* Therapy
CHOL	mmol/L	1) Placebo	4511	5.66	1.15	5.65	1.19	-0.01	0.95	<.001
		2) Ralox	4510	5.62	1.12	5.41	1.08	-0.22	0.93	
LDL-C	mmol/L	1) Placebo	4488	3.15	0.96	3.12	1.00	-0.02	0.91	<.001
		2) Ralox	4501	3.13	0.94	2.88	0.91	-0.26	0.87	
HDL-C	mmol/L	1) Placebo	4482	1.36	0.37	1.36	0.38	-0.00	0.23	<.001
		2) Ralox	4475	1.35	0.36	1.37	0.38	0.01	0.24	
NONHDL	mmol/L	1) Placebo	4477	4.29	1.14	4.28	1.19	-0.00	0.92	<.001
		2) Ralox	4469	4.27	1.12	4.03	1.08	-0.23	0.92	
C/HDL	ratio	1) Placebo	4477	4.41	1.42	4.44	1.49	0.03	1.03	<.001
		2) Ralox	4469	4.42	1.44	4.23	1.57	-0.19	1.20	
TRIG	mmol/L	1) Placebo	4511	1.78	1.12	1.84	1.25	0.06	1.01	.497
		2) Ralox	4510	1.79	1.28	1.88	1.41	0.09	1.17	
FIBOGN	g/L	1) Placebo	226	3.55	0.76	3.65	0.93	0.10	0.87	<.001
		2) Ralox	219	3.48	0.85	3.23	0.87	-0.25	0.88	

Abbreviations: STD=standard deviation; CHOL=total cholesterol; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; NONHDL=non-HDL cholesterol; C/HDL=ratio of CHOL to HDL-C; TRIG=triglycerides; FIBOGN=fibrinogen.
*p-Value is obtained from a ranked ANOVA model: ranked response=therapy.
**N is the number of patients having both a baseline and an endpoint measurement.

Note: Baseline measurement is determined using the last observation carried forward (LOCF) principle in the baseline period.
Fibrinogen was collected in only a subset of randomized patients.

Program: RMP.H3SSGGIO.SASPGM(CVCMLAB2)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.LABS Output: RMP.H3SO.GGIO.FINAL(CVT1YCHG)

Pharmacokinetic Analyses and Results (11.4.6.)

Pharmacokinetic Subset Patient Characteristics (11.4.6.1.)

The raloxifene concentration evaluation of GGIO included data from 253 postmenopausal women at risk for major coronary events who were a subset of patients enrolled in 11 investigator sites.
Appendix 16.1.17 contains a summary of data disposition. Patient age ranged from 55 to 86 years at study entry and baseline body weight ranged from 41.0 to 138.5 kg. Table GGIO.11.51 shows the range and mean values of age, weight, and Cockcroft-Gault creatinine clearance normalized by lean body mass. Table GGIO.11.52 shows a summary of ethnic origin.

Table GGIO.11.51. Summary of Baseline Age, Weight, and Cockcroft-Gault Creatinine Clearance Normalized by Lean Body Mass

	Age (years)	Weight (kg)	Cockcroft-Gault Creatine Clearance Normalized by Lean Body Mass (mL/min)
Range	55.0 – 86.1	41.0 – 138.5	15.6 – 76.9
Mean (CoV as %)	71.2 (9%)	73.9 (23%)	37.8 (29.0%)
n[a]	253	252[b]	253

Abbreviation: CoV = coefficient of variation.
[a] Total number of patients included in the pharmacokinetic analysis.
[b] Entry weight missing for 1 patient.

Table GGIO.11.52. Summary of Ethnic Origin for Patients Randomly Assigned to Raloxifene and Included in Pharmacokinetic Evaluations

Ethnic Group	Percentage of Total Patients
Caucasian	88.9
Asian	1.2
Hispanic	0.8
African Descent	8.7
Other	0.4
n[a]	253

[a] Total number of patients included in the pharmacokinetic analysis.

Observed Steady-State Raloxifene Concentrations (11.4.6.2.)

Two blood samples were collected from patients following 12 and 24 months of 60 mg raloxifene HCl once daily at Visits 5 and 7, respectively. Samples were collected at least 1 hour apart during each visit. The mean steady-state plasma concentration data in Figure GGIO.11.23 and Table GGIO.11.53 were obtained from patients for whom quantifiable plasma raloxifene concentrations, time of last prior active dose, and time of sample draw were available. The overall mean (CoV%) steady-state raloxifene plasma concentration in this patient population was 1.38 ng/mL (69.3%), which is similar to the mean (CoV%) concentration of 1.09 ng/mL (56.4%) in postmenopausal women with osteoporosis (Study H3S-MC-GGGK [3-year Data] Raloxifene Hydrochloride and Placebo in the Treatment of Postmenopausal Women with Osteoporosis: Population Analyses).

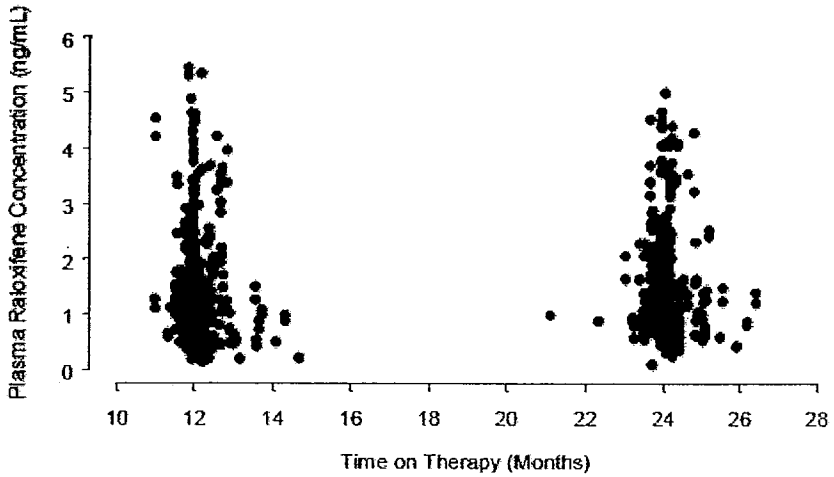


Figure GGIO.11.23. Plasma raloxifene concentration versus time on therapy for individual patients.

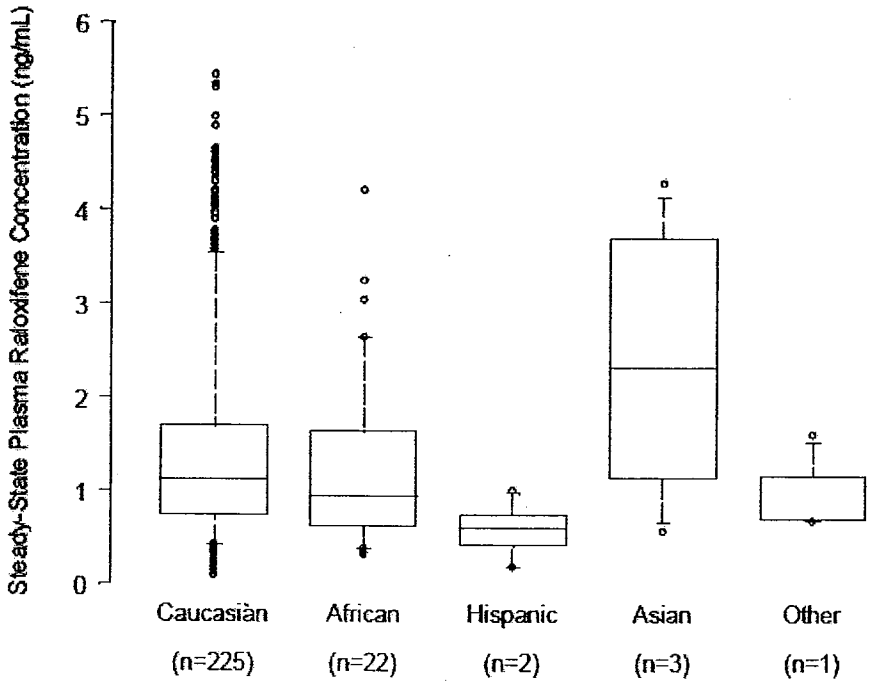
Table GGIO.11.53. Mean Observed Steady-State Raloxifene Concentrations

	12 Months	24 Months	Overall
Mean (ng/mL)	1.34	1.43	1.38
CoV (%)	71.6	66.7	69.3
n [a]	483	400	883

Abbreviation: CoV = coefficient of variation.

[a] Number of quantifiable plasma concentrations obtained from patients for whom time of dose and time of sample draw were available.

No discernible differences in plasma raloxifene concentrations were observed based on the ethnic origin of Caucasians and patients of African descent represented in the pharmacokinetic patient population (Figure GGIO.11.24). Data from patients of Hispanic (2 patients, 8 observations), Asian (3 patients, 10 observations), and other (1 patient, 3 observations) descent were too limited to draw any conclusions.



Box and whisker plots summarize the data descriptively. The solid horizontal line in each box represents the median. The box represents the inter-quartile distance; the whiskers extend to the 5th and 95th percentiles. The number of patients in each group is represented by n.

Figure GGIO.11.24. Observed plasma raloxifene concentrations by ethnic origin.

Graphical visualization and descriptive statistical analysis of the GGIO pharmacokinetic data resulted in consistent findings with prior Phase 3 raloxifene studies (GGGF, GGGG, GGGH, and GGGK). As a result, a population pharmacokinetic analysis using the nonlinear mixed-effects modeling program NONMEM was not performed as discussed in the protocol.

Efficacy Conclusions (11.5.)

This study (GGIO) was designed to assess the effects of raloxifene on the incidence of major coronary events and invasive breast cancer in postmenopausal women with established CHD or at increased risk for CHD.

Demographics and Compliance

- The treatment groups were balanced for baseline demographics, breast cancer and VTE risk assessment characteristics, biochemical markers of cardiovascular risk, and baseline concomitant medication use.
- The baseline CV risk assessment characteristics were also balanced between treatment groups except for **CV risk score** which was significantly **higher in the raloxifene group**. This difference was due to significantly more patients in the raloxifene group than in the placebo group reporting a history of CABG. The magnitudes of these differences were small and these imbalances were not considered clinically relevant.
- **Median follow-up** in the study was 5.6 years.
- **Mean overall treatment compliance** was 75.4% and was comparable between treatment groups.

Breast Cancer Primary Endpoint

Compared with placebo, raloxifene significantly reduced **the incidence of invasive breast cancer** by 44% (p=0.0032). As the protocol-specified significance level was 0.008, the primary invasive breast cancer objective was achieved. The reduction in incidence of invasive breast cancer was primarily due to a significant 55% reduction in **ER-positive invasive breast cancer**. This is an absolute risk reduction of 1.2 cases of invasive breast cancer (1.2 cases of ER-positive invasive breast cancer) per 1000 woman-years in the raloxifene group compared with the placebo group.

Sensitivity analyses, conducted in the PP population, in women at least 60 years of age, stratified by region, or adjusted for baseline risk factors, confirmed that the effect of raloxifene on invasive breast cancer was robust.
Subgroup analyses showed that the effect of raloxifene on reducing the incidence of invasive breast cancer was consistent among women above or below age 65 or with a 5-year predicted risk of invasive breast cancer risk less than 1.66% or ≥1.66%.

In the placebo group, the incidence rate of invasive breast cancer was 2.66 per 1000 woman-years. This rate is lower than that observed in the placebo group (ie, 4.7 to 5.2 per 1000 woman-years) of clinical trials assessing the effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis. However, the statistically significant reduction in relative risk observed in GGIO has been consistently observed in these other raloxifene clinical trials.

Raloxifene had no significant effect on the incidence of **ER-negative invasive** breast cancer or **non-invasive** breast cancer; however, the proportion of women with these respective events was numerically greater in the patients assigned to raloxifene compared with those assigned to placebo.

There was a significant 33% reduction in the incidence of **all breast cancers**, regardless of invasiveness, in the raloxifene group compared with the placebo group; this reduction was primarily due to the significant reduction in invasive breast cancer.

Coronary Primary Endpoint

Compared with placebo, raloxifene had no effect on the **incidence of the combined coronary primary endpoint** events of coronary death, nonfatal MI, or hospitalized ACS other than MI (p=0.4038). The protocol-specified significance level was 0.0423, so the primary coronary objective of the trial was not met. Raloxifene had no effect on the incidence of any of the coronary primary endpoint events individually. The effect of raloxifene on the primary coronary endpoint events did not differ significantly among women with established CHD (ie, secondary prevention) or women at increased risk for CHD (ie, primary prevention). There was no evidence that raloxifene use was associated with an early increase in CHD events.

Biochemical markers of CV risk

Raloxifene significantly decreased total cholesterol, LDL-C, and fibrinogen levels, significantly increased HDL-C levels, and had no significant effect on triglyceride levels compared with placebo. The significant increase in HDL-C in the raloxifene group has not been observed in previous clinical trials of raloxifene. The magnitudes of these differences were not large enough to translate into a clinical coronary benefit as evidenced by the null effect of raloxifene on the coronary primary endpoint events.

Secondary CV Endpoints

Combined CV endpoints

There was no significant difference between treatment groups for the combined events of CV death, nonfatal MI, hospitalized ACS other than MI, stroke, or myocardial revascularization.

Stroke

The incidences of all strokes, hemorrhagic strokes, or ischemic strokes were not significantly different between treatment groups. Subgroup analyses showed that the effect of raloxifene on the incidence of all strokes did not differ by baseline demographics, co-morbidities or co-medications, with the exception of smoking. The smoking by treatment group interaction was not considered clinically relevant because an increased risk of stroke was observed in women assigned to placebo who did not smoke compared with women assigned to placebo who did smoke; this finding contradicts epidemiologic data.

VTE

Raloxifene use significantly increased the incidence of all VTEs and the incidence of PE or DVT combined by 44% each, compared to placebo. This equates to an absolute risk increase of 1.2 VTEs per 1000 woman-years. Overall, these findings were expected as VTE has been shown in prior clinical trials to be an SAE associated with the use of raloxifene.

In the analysis of VTEs from randomization to the end of each year of study follow-up, the incidence of VTE did not differ significantly between treatment groups at the end of Year 1. However, at the end of Year 2, the incidence of VTE was significantly greater in the raloxifene group compared with the placebo group and this finding persisted until the end of the trial. In prior raloxifene clinical trials, the greatest risk of VTE was observed within the first 4 months following initiation of raloxifene therapy.

All Cause Mortality

Raloxifene had no effect on the incidence of **overall mortality**, including **overall CV mortality**.

- A significant 20% reduction in **death due to non-CV causes** was observed in women assigned raloxifene; the clinical relevance of this is unknown.
- A significant 49% increase in the incidence of **death due to stroke** was observed in women assigned to raloxifene, which translates into **an absolute risk increase of 0.7 deaths due stroke per 1000 woman-years**. The statistical significance of the increased incidence of death due to stroke was relatively weak (p=0.0499).
- After Year 3, there was an increased incidence of death due to stroke in the raloxifene group compared with placebo; this increased incidence persisted thereafter, becoming statistically significant in Year 7.

This is a new finding not previously seen in prior clinical trials with raloxifene. It is perplexing as **no significant increase in the incidence of all strokes** was observed in women assigned raloxifene. Since the statistical significance of the increased incidence of death due to stroke was relatively weak (p=0.0499), this observation may be due to chance or may be real.

Exploratory post-hoc analyses were performed for all strokes and deaths due to stroke.

- No single risk factor could be identified from statistical modeling that would predict which women treated with raloxifene might experience a stroke and subsequently die from it.
- Given that the postmenopausal women enrolled in GGIO either had established CHD or risk factors for CHD, that most of these CHD risk factors are also stroke risk factors, that these risk factors were well treated based on the substantial concomitant CV medication usage, and that there was no difference between treatment groups in the incidence of all strokes, it is not surprising that the statistical modeling failed to identify a single risk factor predictive of stroke or death due to stroke. The low number of deaths due to stroke in this large cohort of postmenopausal women also limited the ability to identify any predictive risk factors.

A woman who has had a stroke is at an increased risk of having another stroke, in comparison to a woman who has never had a stroke (Fuster et al. 2001). Atrial fibrillation and TIA are also known stroke risk factors (Friberg et al. 2004; Marini et al. 2005; Goldstein et al. 2006; Sacco et al. 2006). The exploratory analyses did provide limited evidence suggesting that these risk factors might have contributed to the increased incidence of death due to stroke in this population of women assigned raloxifene.
Therefore, postmenopausal women at risk for major coronary events who also have a history of stroke, atrial fibrillation, or TIA may be at increased risk of having a stroke and possibly dying from it; thus, the benefits and risks of raloxifene therapy should be carefully considered in these postmenopausal women.

In clinical trials assessing the effects of raloxifene in postmenopausal women with osteoporosis, raloxifene did not significantly increase the incidences of stroke or overall mortality, including deaths due to coronary or cerebrovascular etiologies (Barrett-Connor et al. 2002; Ensrud et al. 2006). On retrospective assessment, the prevalence of CHD or CHD risk factors was lower in these postmenopausal women with osteoporosis and, therefore, they were likely to be at lower risk for stroke or death due to stroke, in comparison to the women enrolled in GGIO (Barrett-Connor et al. 2002; Ensrud et al. 2006). **This increased incidence of death due to stroke has only been observed in one study of raloxifene in postmenopausal women at risk for major coronary events.**

Revascularizations and Amputations

Raloxifene did not significantly affect the incidences of all revascularizations, including myocardial or non-coronary arterial revascularizations, or non-traumatic lower extremity amputations.

Fractures

Patients in this study were not selected on the basis of an increased risk of osteoporosis nor were scheduled vertebral radiographs obtained.

Raloxifene significantly reduced **clinical vertebral fracture incidence** by 35% compared to placebo. This equates to an absolute risk decrease of 1.3 clinical vertebral fractures per 1000 woman-years in this population. These findings are consistent with the known skeletal efficacy profile of raloxifene.

Raloxifene did not significantly affect the **incidences of non-vertebral fractures or hip/femur or wrist fractures**, compared to placebo.

Hospitalizations

- Fewer patients in the raloxifene group than in the placebo group had one or more hospitalizations for **any cause**.

- Significantly more patients in the raloxifene group compared to the placebo group were hospitalized **due to VTE**; however the proportion of patients with a VTE was also greater in the raloxifene group. Therefore, this finding is not unexpected.
- Significantly more patients in the placebo group were hospitalized due to **"other" reasons** compared to the raloxifene group. The significance of this observation is unclear.

Pharmacokinetics

The overall mean steady-state raloxifene plasma concentration in this patient population was similar to that previously determined in postmenopausal women with osteoporosis. No discernible differences in plasma raloxifene concentrations were observed based on the ethnic origin of Caucasians and patients of African descent represented in this population.

Safety Evaluation (12.)

Safety analyses were performed on the ITT principle, except where otherwise noted. The ITT population is referred to as "all randomized patients" throughout this report. To evaluate results of this trial, prespecified and post-hoc analyses were conducted. Results presented in this report are based on the prespecified analyses, and statistical significance was defined as a $p<0.05$, unless otherwise noted. The term "significant" used in this section refers to those differences that are both statistically significant and clinically relevant unless otherwise noted. Results presented in text are at the Preferred Term level. If there was a significant difference between raloxifene and placebo at the High-level Term without a corresponding significant difference at a Preferred Term level, results are reported only if the incidence is higher in the raloxifene group compared with the placebo group.

Extent of Exposure (12.1.)

Randomized patients = 10,101; Placebo = 5057; Raloxifene = 5044.

- Exposure (similar between the two treatment groups): **Median = 5.05 years**
  - More than 53% of patients in both treatment groups were exposed to study drug for ≥5 years.

Table GGIO.12.1. Exposure to Study Drug (All Randomized Patients)

	Placebo (N=5057)	Ralox (N=5044)	Total (N=10101)	p-Value*
Years of study exposure				
Mean	4.31	4.32	4.31	.708
Median	5.05	5.06	5.05	
Standard deviation	2.06	2.06	2.06	
Minimum	0.00	0.00	0.00	
Maximum	7.01	7.01	7.01	

*p-Value is obtained from an F-test using Type III Sum of Squares from an ANOVA model: response=therapy.

Program: RMP.H3SSGGIO.SASPGM(MSCTEXP1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(MSTEXP1)

Table GGIO.12.2. Exposure to Study Drug by Year (All Randomized Patients)

Study drug exposure	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	*p-Value
>= 1 year	4444(87.88)	4416(87.55)	8860(87.71)	.615
>= 2 years	4033(79.75)	4030(79.90)	8063(79.82)	.855
>= 3 years	3678(72.73)	3713(73.61)	7391(73.17)	.318
>= 4 years	3360(66.44)	3390(67.21)	6750(66.83)	.414
>= 5 years	2722(53.83)	2723(53.98)	5445(53.91)	.973

*p-Value is obtained from a Pearson's Chi-square test.

Program: RMP.H3SSGGIO.SASPGM(MSCTEXP1)
Data: RMP.SAS.H3SM.L.MCGGIOSA.FINAL.MAIN Output: RMP.H3SO.GGIO.FINAL(MSTEXP2)

Adverse Events (12.2.)

An AE was defined as any untoward medical occurrence in a patient who was randomized in this clinical study, without regard to the possibility of a causal relationship to study drug, and without regard to treatment group assignment, even if no study drug had been taken. Analyses of AEs were based on investigator-reported AEs, coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 8.0.

Brief Summary of Adverse Events (12.2.1.)

Table GGIO.12.3. Overview of Adverse Events (All Randomized Patients)

Adverse Event[a]	Placebo N=5057 n (%)	Raloxifene N=5044 n (%)
Treatment-emergent adverse events (pts with ≥1 event)	4688 (92.7%)	4684 (92.9%)
Adverse reactions[b]	359 (7.1%)	483 (9.6%)
Serious adverse events[c]	392 (7.8%)	436 (8.6%)
Deaths[d]	595 (11.8%)	554 (11.0%)
Study drug discontinuations due to an adverse event	1195 (23.6%)	1270 (25.2%)

Abbreviations: AE = adverse event; N = number of patients assessed; n = number of patients with events in each category; pts = patients; SAE = serious adverse event.

a Patients may be counted in more than one category.

b Adverse reactions are AEs which were deemed by the investigator to be reasonably, possibly related to either study drug administration or protocol procedures.

c Refer to Section 9.7.1.13.2.2 for the protocol definition of an SAE.

d In this study, deaths were reported as study endpoints and were not considered as SAEs unless they fulfilled the protocol definition of an SAE (Section 9.7.1.13.2.2). Refer to Section 11.4.4.4 for results for deaths.

Sources: SFTTEAE2, SFTSAE, SFTADR, SFTAEDSC, CVTHRMOR.

Display and Analysis of Adverse Events (12.2.2.)

Treatment-Emergent Adverse Events (12.2.2.1.)

A TEAE was defined as an event that first occurred or worsened (increased in severity) after baseline (Visit 2). Table GGIO.14.47 contains the analyses of all TEAEs by system organ class (SOC), High-level Term and Preferred Term.

- The proportion of patients who reported ≥1 TEAE was not significantly different between treatment groups (p=0.705).
- A number of AEs at the SOC, High-level Term, and Preferred Term level were reported significantly more frequently in women assigned raloxifene compared with placebo. Many of these events were either not considered to be clinically relevant or were considered to be due to chance given the number of statistical comparisons performed. The remaining events are discussed in the sections that follow.

The Preferred Term "vaginal mycosis" and the High-level Term "Candida infections" were reported significantly more frequently in the raloxifene group than the placebo group. Within the High-level Term Candida infections, most events mapped to the Preferred Terms candidiasis, oral candidiasis, or vaginal candidiasis. There were no significant between-treatment group differences for any of these Preferred Terms; however, each was reported in a greater proportion of women assigned raloxifene than placebo. None of these events were considered serious; one event of vaginal candidiasis led to discontinuation of study drug in a patient assigned raloxifene (Table GGIO.14.53).
In clinical trials of raloxifene in postmenopausal women with osteoporosis, the preferred term vaginosis fungal NOS (not otherwise specified) was reported significantly more frequently in women assigned raloxifene.

Vaginal candidiasis is rare in postmenopausal women, presumably due to the low levels of endogenous estrogen. An increase in vaginal thrush was noted in both pre-and postmenopausal patients assigned to tamoxifen (IBIS Investigators 2002). There are a few case reports in the literature of tamoxifen associated with vaginal yeast infection (Sobel et al. 1996). In conclusion, although the event rates of these infections in GGIO were very low, a treatment effect of raloxifene is possible.

Table GGIO.12.4 presents TEAEs reported in at least 2% of raloxifene-assigned patients by SOC, High-level Term, and Preferred Term.

The following TEAEs, reported in at least 2% of raloxifene-assigned patients at the Preferred Term level, were reported significantly more frequently by raloxifene-assigned patients than by placebo-assigned patients (in decreasing order of frequency): oedema peripheral, muscle spasms, hot flush, dyspepsia, cholelithiasis, arthritis, and intermittent claudication.

Peripheral edema, muscle spasms, and hot flushes are known to be associated with use of raloxifene and therefore the increased reporting in patients assigned raloxifene was not unexpected.

Cholelithiasis is discussed in Section 12.3.3.1 below.

Dyspepsia and arthritis are single Preferred Terms and no between-treatment group differences were observed at the High-level Term to which these respective Preferred Terms map. None of the dyspepsia AEs was reported as serious. Four patients discontinued study drug (2 in raloxifene) due to dyspepsia (Table GGIO.14.53). One report of arthritis in a patient assigned raloxifene was considered serious (Table GGIO.12.5). Two patients discontinued study drug due to arthritis and both were in the placebo group (Table GGIO.14.53). The clinical relevance of the increased reporting of dyspepsia and arthritis is unknown.

Intermittent claudication is a symptom of lower extremity peripheral arterial disease which is usually caused by atherosclerosis. Approximately 11% of patients at baseline reported a history of lower extremity arterial disease. In a post-hoc assessment, about one-third of these patients reported the TEAE of intermittent claudication. Intermittent claudication was considered serious

in only 1 patient who was assigned placebo and led to discontinuation of study drug in 2 patients assigned to placebo. Given this, and that raloxifene had no effect on coronary or cerebrovascular events, or lower extremity revascularizations or amputations, there is no obvious biologically plausible explanation for the increased reporting of intermittent claudication in patients assigned raloxifene.

Conversely, the following TEAEs at the Preferred Term level were reported significantly more frequently by placebo-assigned patients than raloxifene-assigned patients (in decreasing order of frequency): osteoporosis, constipation, ACS, and anxiety.

Table GGIO.12.4. Treatment-Emergent Adverse Events Occurring in at Least 2% of Raloxifene-Assigned Patients (By System Organ Class, High-level Term, and Preferred Term; All Randomized Patients)

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Overall				
Patients with >=1 TEAE	4688(92.70)	4684(92.86)	9372(92.78)	.705
Patients with no TEAEs	369(7.30)	360(7.14)	729(7.22)	
Blood and lymphatic system disorders				
Patients with >=1 TEAE	418(8.27)	428(8.49)	846(8.38)	.656
Patients with no TEAEs	4639(91.73)	4616(91.51)	9255(91.62)	
Anaemias NEC	311(6.15)	332(6.58)	643(6.37)	.353
Anaemia	291(5.75)	314(6.23)	605(5.99)	.301
Cardiac disorders				
Patients with >=1 TEAE	2044(40.42)	2005(39.75)	4049(40.09)	.488
Patients with no TEAEs	3013(59.58)	3039(60.25)	6052(59.91)	
Cardiac conduction disorders	171(3.38)	162(3.21)	333(3.30)	.634
Cardiac signs and symptoms NEC	213(4.21)	207(4.10)	420(4.16)	.756
Palpitations	206(4.07)	205(4.06)	411(4.07)	.961
Coronary artery disorders NEC	219(4.33)	199(3.95)	418(4.14)	.347
Coronary artery disease	187(3.70)	165(3.27)	352(3.48)	.259
Heart failures NEC	402(7.95)	409(8.11)	811(8.03)	.755
Cardiac failure	231(4.57)	231(4.58)	462(4.57)	.992
Cardiac failure congestive	131(2.59)	146(2.89)	277(2.74)	.311
Ischaemic coronary artery disorders	1026(20.29)	1023(20.28)	2049(20.29)	.986
Acute coronary syndrome	248(4.90)	204(4.04)	452(4.47)	.037
Angina pectoris	519(10.26)	540(10.71)	1059(10.48)	.477
Angina unstable	136(2.69)	124(2.46)	260(2.57)	.453
Myocardial infarction	254(5.02)	249(4.94)	503(4.98)	.834
Myocardial ischaemia	111(2.19)	113(2.24)	224(2.22)	.861
Mitral valvular disorders	121(2.39)	129(2.56)	250(2.48)	.592
Mitral valve incompetence	90(1.78)	104(2.06)	194(1.92)	.296
Myocardial disorders NEC	164(3.24)	143(2.84)	307(3.04)	.226
Rate and rhythm disorders NEC	201(3.97)	192(3.81)	393(3.89)	.660
Supraventricular arrhythmias	469(9.27)	443(8.78)	912(9.03)	.385
Atrial fibrillation	323(6.39)	309(6.13)	632(6.26)	.587
Ventricular arrhythmias and cardiac arrest	119(2.35)	126(2.50)	245(2.43)	.640
Ear and labyrinth disorders				
Patients with >=1 TEAE	416(8.23)	417(8.27)	833(8.25)	.926
Patients with no TEAEs	4641(91.77)	4627(91.73)	9268(91.75)	
Inner ear signs and symptoms	295(5.83)	317(6.28)	612(6.06)	.319
Vertigo	220(4.35)	256(5.08)	476(4.71)	.073
Endocrine disorders				
Patients with >=1 TEAE	308(6.09)	301(5.97)	609(6.03)	.792
Patients with no TEAEs.	4749(93.91)	4743(94.03)	9492(93.97)	
Thyroid hypofunction disorders	166(3.28)	188(3.73)	354(3.50)	.222
Hypothyroidism	165(3.26)	184(3.65)	349(3.46)	.207
Eye disorders				
Patients with >=1 TEAE	803(15.88)	816(16.18)	1619(16.03)	.633
Patients with no TEAEs	4254(84.12)	4228(83.82)	8482(83.97)	
Cataracts (excl congenital)	374(7.40)	369(7.32)	743(7.36)	.906
Cataract	371(7.34)	362(7.18)	733(7.26)	.780
Retinopathies NEC	113(2.23)	115(2.28)	228(2.26)	.868
Visual disorders NEC	103(2.04)	102(2.02)	205(2.03)	.976
Gastrointestinal disorders				
Patients with >=1 TEAE	1917(37.91)	1852(36.72)	3769(37.31)	.214
Patients with no TEAEs	3140(62.09)	3192(63.28)	6332(62.69)	
Diarrhoea (excl infective)	329(6.51)	341(6.76)	670(6.63)	.568
Diarrhoea	326(6.45)	341(6.76)	667(6.60)	.496
Dyspeptic signs and symptoms	205(4.05)	243(4.82)	448(4.44)	.057
Dyspepsia	183(3.62)	226(4.48)	409(4.05)	.026
Flatulence, bloating and distension	120(2.37)	117(2.32)	237(2.35)	.871
Gastritis (excl infective)	253(5.00)	237(4.70)	490(4.85)	.482
Gastritis	241(4.77)	226(4.48)	467(4.62)	.503
Gastrointestinal and abdominal pains (excl oral and throat)	494(9.77)	468(9.28)	962(9.52)	.398
Abdominal pain	258(5.10)	237(4.70)	495(4.90)	.341
Abdominal pain upper	253(5.00)	236(4.68)	489(4.84)	.448
Gastrointestinal atonic and hypomotility disorders NEC	495(9.79)	401(7.95)	896(8.87)	<.001
Constipation	376(7.44)	295(5.85)	671(6.64)	.001
Gastrooesophageal reflux disease	137(2.71)	127(2.52)	264(2.61)	.559
Nausea and vomiting symptoms	382(7.55)	406(8.05)	788(7.80)	.321
Nausea	284(5.62)	295(5.85)	579(5.73)	.593
Vomiting	184(3.64)	212(4.20)	396(3.92)	.125

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
General disorders and administration site conditions				
Patients with >=1 TEAE	1698 (33.58)	1748 (34.66)	3446 (34.12)	.203
Patients with no TEAEs	3359 (66.42)	3296 (65.34)	6655 (65.88)	
Asthenic conditions	580 (11.47)	598 (11.86)	1178 (11.66)	.530
Asthenia	238 (4.71)	265 (5.25)	503 (4.98)	.181
Fatigue	341 (6.74)	341 (6.76)	682 (6.75)	.989
Febrile disorders	159 (3.14)	159 (3.15)	318 (3.15)	.988
Pyrexia	158 (3.12)	159 (3.15)	317 (3.14)	.910
General signs and symptoms NEC	235 (4.65)	213 (4.22)	448 (4.44)	.273
Chest discomfort	128 (2.53)	114 (2.26)	242 (2.40)	.324
Oedema NEC	671 (12.27)	790 (15.66)	1461 (14.46)	<.001
Oedema peripheral	591 (11.69)	713 (14.14)	1304 (12.92)	<.001
Pain and discomfort NEC	578 (11.43)	582 (11.54)	1160 (11.48)	.848
Chest pain	511 (10.10)	508 (10.07)	1019 (10.09)	.956
Hepatobiliary disorders				
Patients with >=1 TEAE	290 (5.73)	372 (7.38)	662 (6.55)	<.001
Patients with no TEAEs	4767 (94.27)	4672 (92.62)	9439 (93.45)	
Cholecystitis and cholelithiasis	177 (3.50)	215 (4.26)	392 (3.88)	.047
Cholelithiasis	131 (2.59)	168 (3.33)	299 (2.96)	.028
Immune system disorders				
Patients with >=1 TEAE	124 (2.45)	122 (2.42)	246 (2.44)	.922
Patients with no TEAEs	4933 (97.55)	4922 (97.58)	9855 (97.56)	
Infections and infestations				
Patients with >=1 TEAE	2474 (48.92)	2508 (49.72)	4982 (49.32)	.356
Patients with no TEAEs	2583 (51.08)	2536 (50.28)	5119 (50.68)	
Abdominal and gastrointestinal infections	161 (3.18)	161 (3.19)	322 (3.19)	.948
Bacterial infections NEC	95 (1.88)	105 (2.08)	200 (1.98)	.438
Fungal infections NEC	127 (2.51)	115 (2.28)	242 (2.40)	.476
Herpes viral infections	166 (3.28)	123 (2.44)	289 (2.86)	.011
Herpes zoster	132 (2.61)	104 (2.06)	236 (2.34)	.067
Infections NEC	281 (5.56)	263 (5.21)	544 (5.39)	.454
Respiratory tract infection	103 (2.04)	110 (2.18)	213 (2.11)	.616
Influenza viral infections	453 (8.96)	440 (8.72)	893 (8.84)	.657
Influenza	453 (8.96)	440 (8.72)	893 (8.84)	.657
Lower respiratory tract and lung infections	842 (16.65)	890 (17.64)	1732 (17.15)	.161
Bronchitis	350 (6.92)	387 (7.67)	737 (7.30)	.140
Bronchitis acute	99 (1.96)	124 (2.46)	223 (2.21)	.075
Pneumonia	339 (6.70)	328 (6.50)	667 (6.60)	.715
Upper respiratory tract infections	805 (15.92)	801 (15.88)	1606 (15.90)	.989
Nasopharyngitis	345 (6.82)	327 (6.48)	672 (6.65)	.482
Sinusitis	127 (2.51)	124 (2.46)	251 (2.48)	.879
Upper respiratory tract infection	248 (4.90)	244 (4.84)	492 (4.87)	.928
Urinary tract infections	792 (15.66)	828 (16.42)	1620 (16.04)	.275
Cystitis	165 (2.87)	165 (3.27)	330 (3.07)	.222
Urinary tract infection	625 (12.36)	658 (13.05)	1283 (12.70)	.272
Injury, poisoning and procedural complications				
Patients with >=1 TEAE	1102 (21.79)	1059 (21.00)	2161 (21.39)	.340
Patients with no TEAEs	3955 (78.21)	3985 (79.00)	7940 (78.61)	
Limb injuries NEC (incl traumatic amputation)	120 (2.37)	142 (2.82)	262 (2.59)	.152
Lower limb fractures and dislocations	219 (4.33)	202 (4.00)	421 (4.17)	.420
Non-site specific injuries NEC	296 (5.85)	303 (6.01)	599 (5.93)	.705
Fall	169 (3.34)	184 (3.65)	353 (3.49)	.366
Skin injuries NEC	103 (2.04)	111 (2.20)	214 (2.12)	.536
Upper limb fractures and dislocations	253 (5.00)	214 (4.24)	467 (4.62)	.073
Investigations				
Patients with >=1 TEAE	1270 (25.11)	1272 (25.22)	2542 (25.17)	.860
Patients with no TEAEs	3787 (74.89)	3772 (74.78)	7559 (74.83)	
Cardiac auscultatory investigations	129 (2.55)	119 (2.36)	248 (2.46)	.500
Cardiac murmur	108 (2.14)	110 (2.18)	218 (2.16)	.866
Cardiac imaging procedures	319 (6.31)	318 (6.30)	637 (6.31)	.993
Arteriogram coronary	223 (4.41)	228 (4.52)	451 (4.46)	.798
ECG investigations	280 (5.54)	285 (5.65)	565 (5.59)	.782
Physical examination procedures	211 (4.17)	207 (4.10)	418 (4.14)	.884
Weight increased	98 (1.94)	102 (2.02)	200 (1.98)	.755
Metabolism and nutrition disorders				
Patients with >=1 TEAE	1313 (25.96)	1283 (25.44)	2596 (25.70)	.560
Patients with no TEAEs	3744 (74.04)	3761 (74.56)	7505 (74.30)	
Appetite disorders	87 (1.72)	108 (2.14)	195 (1.93)	.098
Diabetes mellitus (incl subtypes)	487 (9.63)	474 (9.40)	961 (9.51)	.692
Diabetes mellitus	382 (7.55)	388 (7.69)	770 (7.62)	.791
Elevated cholesterol	172 (3.40)	145 (2.87)	317 (3.14)	.135
Hypercholesterolaemia	172 (3.40)	145 (2.87)	317 (3.14)	.135
Hyperlipidaemias NEC	239 (4.73)	230 (4.56)	469 (4.64)	.699
Hyperlipidaemia	239 (4.73)	230 (4.56)	469 (4.64)	.699
Potassium imbalance	88 (1.74)	101 (2.00)	189 (1.87)	.311
Purine metabolism disorders NEC	156 (3.08)	175 (3.47)	331 (3.28)	.266
Gout	85 (1.68)	106 (2.10)	191 (1.89)	.110

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Musculoskeletal and connective tissue disorders				
Patients with >=1 TEAE	2551(50.44)	2619(51.92)	5170(51.18)	.091
Patients with no TEAEs	2506(49.56)	2425(48.08)	4931(48.82)	
Arthropathies NEC	199(3.94)	218(4.32)	417(4.13)	.303
Arthritis	117(2.31)	148(2.93)	265(2.62)	.042
Bone disorders NEC	203(4.01)	196(3.89)	399(3.95)	.700
Osteopenia	140(2.77)	150(2.97)	290(2.87)	.503
Joint related signs and symptoms	616(12.18)	576(11.42)	1192(11.78)	.257
Arthralgia	559(11.05)	512(10.15)	1071(10.60)	.126
Metabolic bone disorders	404(7.99)	347(6.88)	751(7.43)	.032
Osteoporosis	403(7.97)	346(6.86)	749(7.42)	.032
Muscle pains	171(3.38)	174(3.45)	345(3.42)	.830
Myalgia	145(2.87)	148(2.93)	293(2.90)	.825
Muscle related signs and symptoms NEC	457(9.04)	639(12.67)	1096(10.85)	<.001
Muscle spasms	422(8.34)	611(12.11)	1033(10.23)	<.001
Musculoskeletal and connective tissue signs and symptoms NEC	1248(24.68)	1322(26.21)	2570(25.44)	.055
Back pain	602(11.90)	652(12.93)	1254(12.41)	.105
Neck pain	86(1.70)	108(2.14)	194(1.92)	.096
Pain in extremity	554(10.96)	583(11.56)	1137(11.26)	.314
Shoulder pain	135(2.67)	153(3.03)	288(2.85)	.266
Osteoarthropathies	655(12.95)	653(12.95)	1308(12.95)	.969
Osteoarthritis	565(11.17)	579(11.48)	1144(11.33)	.596
Spinal osteoarthritis	123(2.43)	105(2.08)	228(2.26)	.250
Spine and neck deformities	85(1.68)	102(2.02)	187(1.85)	.189
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Patients with >=1 TEAE	593(11.73)	551(10.92)	1144(11.33)	.205
Patients with no TEAEs	4464(88.27)	4493(89.08)	8957(88.67)	
Nervous system disorders				
Patients with >=1 TEAE	1815(35.89)	1860(36.88)	3675(36.38)	.265
Patients with no TEAEs	3242(64.11)	3184(63.12)	6426(63.62)	
Central nervous system haemorrhages and cerebrovascular accidents	283(5.60)	295(5.85)	578(5.72)	.578
Cerebrovascular accident	216(4.27)	238(4.72)	454(4.49)	.276
Central nervous system vascular disorders NEC	175(3.46)	175(3.47)	350(3.47)	.983
Chronic polyneuropathies	108(2.14)	126(2.50)	234(2.32)	.226
Diabetic neuropathy	106(2.10)	126(2.50)	232(2.30)	.177
Disturbances in consciousness NEC	219(4.33)	208(4.12)	427(4.23)	.609
Syncope	155(3.07)	148(2.93)	303(3.00)	.695
Headaches NEC	406(8.03)	399(7.91)	805(7.97)	.823
Headache	398(7.87)	392(7.77)	790(7.82)	.849
Lumbar spinal cord and nerve root disorders	119(2.35)	128(2.54)	247(2.45)	.529
Sciatica	115(2.27)	121(2.40)	236(2.34)	.657
Memory loss (excl dementia)	89(1.76)	107(2.12)	196(1.94)	.187
Neurological signs and symptoms NEC	559(11.05)	582(11.54)	1141(11.30)	.407
Dizziness	545(10.78)	555(11.00)	1100(10.89)	.690
Paraesthesias and dysaesthesias	240(4.75)	271(5.37)	511(5.06)	.126
Hypoaesthesia	130(2.57)	139(2.76)	269(2.66)	.510
Paraesthesia	100(1.98)	112(2.22)	212(2.10)	.396
Psychiatric disorders				
Patients with >=1 TEAE	1061(20.98)	1046(20.74)	2107(20.86)	.769
Patients with no TEAEs	3996(79.02)	3998(79.26)	7994(79.14)	
Anxiety symptoms	327(6.47)	277(5.49)	604(5.98)	.031
Anxiety	230(4.55)	190(3.77)	420(4.16)	.043
Depressive disorders	380(7.51)	388(7.69)	768(7.60)	.726
Depression	364(7.20)	374(7.41)	738(7.31)	.665
Disturbances in initiating and maintaining sleep	385(7.61)	387(7.67)	772(7.64)	.855
Insomnia	384(7.59)	386(7.65)	770(7.62)	.856
Renal and urinary disorders				
Patients with >=1 TEAE	717(14.18)	723(14.33)	1440(14.26)	.789
Patients with no TEAEs	4340(85.82)	4321(85.67)	8661(85.74)	
Bladder and urethral symptoms	235(4.65)	247(4.90)	482(4.77)	.513
Urinary incontinence	103(2.04)	113(2.24)	216(2.14)	.463
Renal failure and impairment	270(5.34)	254(5.04)	524(5.19)	.490
Renal failure	140(2.77)	141(2.80)	281(2.78)	.946
Reproductive system and breast disorders				
Patients with >=1 TEAE	548(10.84)	528(10.47)	1076(10.65)	.545
Patients with no TEAEs	4509(89.16)	4516(89.53)	9025(89.35)	
Breast disorders NEC	206(4.07)	178(3.53)	384(3.80)	.149

Respiratory, thoracic and mediastinal disorders				
Patients with >=1 TEAE	1434(28.36)	1401(27.78)	2835(28.07)	.505
Patients with no TEAEs	3623(71.64)	3643(72.22)	7266(71.93)	
Breathing abnormalities	675(13.35)	661(13.10)	1336(13.23)	.686
Dyspnoea	539(10.66)	529(10.49)	1068(10.57)	.752
Dyspnoea exertional	136(2.69)	147(2.91)	283(2.80)	.461
Bronchospasm and obstruction	268(5.30)	262(5.19)	530(5.25)	.840
Asthma	102(2.02)	108(2.14)	210(2.08)	.633
Coughing and associated symptoms	576(11.35)	588(11.66)	1162(11.50)	.533
Cough	531(10.50)	552(10.94)	1083(10.72)	.383
Upper respiratory tract signs and symptoms	162(3.20)	175(3.47)	337(3.34)	.391

SOC: System Organ Class HLT: High-Level Term PT: Preferred Term	Placebo (N=5057) n (%)	Ralox (N=5044) n (%)	Total (N=10101) n (%)	p-Value*
Skin and subcutaneous tissue disorders				
Patients with >=1 TEAE	894(17.68)	895(17.74)	1789(17.71)	.898
Patients with no TEAEs	4163(82.32)	4149(82.26)	8312(82.29)	
Apocrine and eccrine gland disorders	148(2.93)	180(3.57)	328(3.25)	.064
Hyperhidrosis	104(2.06)	132(2.62)	236(2.34)	.061
Dermatitis and eczema	171(3.38)	185(3.67)	356(3.52)	.400
Pruritus NEC	130(2.73)	126(2.50)	264(2.61)	.460
Pruritus	116(2.33)	116(2.30)	224(2.32)	.911
Surgical and medical procedures				
Patients with >=1 TEAE	1897(37.51)	1860(36.88)	3757(37.19)	.521
Patients with no TEAEs	3160(62.49)	3184(63.12)	6344(62.81)	
Arterial therapeutic procedures (excl aortic)	563(11.13)	551(10.92)	1116(11.02)	.747
Coronary angioplasty	218(4.31)	225(4.46)	443(4.39)	.710
Coronary artery surgery	151(2.99)	143(2.84)	294(2.91)	.667
Biliary tract and gallbladder therapeutic procedures	108(2.14)	129(2.56)	237(2.35)	.162
Cholecystectomy	100(1.98)	118(2.34)	218(2.16)	.211
Joint therapeutic procedures	258(5.10)	265(5.25)	523(5.18)	.702
Lens therapeutic procedures	344(6.80)	353(7.00)	697(6.90)	.680
Cataract operation	305(6.03)	316(6.26)	621(6.15)	.623
Therapeutic procedures NEC	215(4.25)	173(3.43)	388(3.84)	.030
Vascular therapeutic procedures NEC	79(1.56)	105(2.08)	184(1.82)	.049
Vascular disorders				
Patients with >=1 TEAE	1559(30.83)	1693(33.56)	3252(32.19)	.002
Patients with no TEAEs	3498(69.17)	3351(66.44)	6849(67.81)	
Non-site specific necrosis and vascular insufficiency NEC	118(2.33)	138(2.74)	256(2.53)	.184
Peripheral embolism and thrombosis	95(1.88)	136(2.70)	231(2.29)	.006
Peripheral vascular disorders NEC	353(6.98)	526(10.43)	879(8.70)	<.001
Hot flush	238(4.71)	391(7.75)	629(6.23)	<.001
Peripheral vasoconstriction, necrosis and vascular insufficiency	205(4.05)	251(4.98)	456(4.51)	.024
Intermittent claudication	97(1.92)	128(2.54)	225(2.23)	.031
Varicose veins non-site specific	154(3.05)	145(2.87)	299(2.96)	.597
Varicose vein	147(2.91)	140(2.78)	287(2.84)	.674
Vascular hypertensive disorders NEC	676(13.37)	638(12.65)	1314(13.01)	.284
Hypertension	672(13.29)	633(12.55)	1305(12.92)	.269