Theoretical:	$S(t)$, & complement Cum. Inc./Risk : $CI(t) = Risk(t) = 1 - S(t)$	N O T E S [see also: Armitage & Berry, and Collett Ch 2]
(1) Empirical:	$\{\widehat{ID_1}, \widehat{ID_2}, \ldots, \widehat{ID_K}\}$ in K sub-intervals spanning time interval $[0, t]$. The (not necessarily equal) widths of the K sub-intervals are $\Delta T_1, \ldots, \Delta T_K$.	Also called "rates"/"intensities". Statisticians call them $\{\hat{\lambda}_1, \hat{\lambda}_2, \ldots, \hat{\lambda}_K\}$. [`Stata` has a helpful function `stptime` that does such calculations.] This general formula links the $S(t)$ with the $ID(t)$ or $\lambda(t)$ function.
Target:	Approximation to smooth function $S(t) = \exp\{ -\int_0^t ID(u)du \}$	Integral = expected no. (μ) of events in $(0, t)$ **if always 1 person at risk**. (Poisson) $Pr[0 \text{ events in } (0,t)] = \exp[-\mu] = \Pr[(\text{initial}) \text{ person 'survives' to } t]$.
Point Est.:	$\widehat{S(t)} = \exp\{ -\sum_k \widehat{ID_k} \times \Delta T_k \} = \exp\{ -integral \}$; $\widehat{CI(t)} = 1 - \widehat{S(t)}$	For simplicity, subscript omitted for now on.
Variance	of the *integral*: $V = \sum Var[\widehat{ID_k}] \times (\Delta T_k)^2$	
IE for $S(t)$	$\exp\{ -[integral \pm z_{\alpha/2} \times V^{1/2}] \}$; IE for $CI(t) = 1$ - IE for $S(t)$	IE: interval-estimate; used to avoid using 'CI' with 2 different meanings
=======	==========	
(**2**) Empirical:	J *narrow* event-containing intervals spanning portion of $[0, t]$. n_j at risk just before the event(s) [death(s)] in interval j. s_j survive event-containing interval j. Remaining d_j do not.	Interval j defined by distinct event-time t_j. Intervals in $[0, t]$ that don't contain events can be ignored. 'Riskset' = the 'candidates'. The letter d is used because 'transition' in many studies is *d*eath; *desirable transitions OK too!*
(2a):	*conditional* probabilities: $\widehat{S_1} = \frac{s_1}{n_1}$, $\widehat{S_2} = \frac{s_2}{n_2}$, ..., $\widehat{S_J} = \frac{s_J}{n_J}$	
	$\widehat{S_j} \sim Binomial(n_j, S_j)$	Binomial model is only used in variance calculations
Point Est.:	$\widehat{S_{KM}(t)} = \widehat{S_1} \times \widehat{S_2} \cdots \times \widehat{S_J}$ **Kaplan-Meier Product Limit Estimator**	Fraction of a fraction... Intervals with $d = 0$ would contribute multipliers of 1.
Variance	$\log \widehat{S_{KM}(t)} = \sum \log \widehat{S_k} \rightarrow Var[\log \widehat{S_{KM}(t)}] = \sum \frac{d_j}{s_j \times n_j} = V$ (say)	Var[log of a product of $\widehat{S_{KM}(t)}$'s] = sum of variances of individual logs.
IE for $S(t)$	• $\exp\{ \log \widehat{S_{KM}(t)} \pm z_{\alpha/2} \times V^{1/2} = \log \widehat{S_{KM}(t)} \pm z_{\alpha/2} \times SE \text{ of } \log \}$. •$\widehat{S_{KM}(t)} \pm z_{\alpha/2} \times \widehat{S_{KM}(t)} \times V^{1/2}$ • others, based on other transformations; $t()$ = c-log-log recommended	ie in $\log S$ scale $\rightarrow$ IE in S scale. SE of $\log S$: **"Greenwood's formula"** This version avoids logs, but can more easily yield limits beyond the (0,1) scale The only transform guaranteed to say in the (0,1) scale is the logit transform.
(**2b**):	"counting process"; $\widehat{d_j} \sim Poisson()$ – only for variance calculations below	
Point Est.:	$\widehat{S_{NA}(t)} = \exp\{ -integral \} = \exp\{ -\sum \frac{d_j}{n_j} \}$ **Nelson-Aalen Estimator**	This uses the same formula that links the $S(t)$ and $ID(t)$ or $\lambda(t)$ functions. Think of a fitted ID function $ID(t)$ with $\widehat{ID(t)} = 0$ everywhere on $(0, t)$ except within the small event-containing intervals of width δt, where $\widehat{ID(t)} = d_j/(n_j \times \delta t)$. Thus, $integral = \sum_j \{\widehat{ID(t)} \times \delta t\} = \sum_j d_j/n_j$.
Variance	$Var[integral] = \sum \frac{d_j}{n_j^2} = V$ (say)	
CI for $S(t)$	$\exp\{ -[integral \pm z_{\alpha/2} \times V^{1/2}] \}$	(symmetric) ie in $\log S$ scale $\rightarrow$ (asymmetric) IE in S scale. Interval estimate for cum. incidence: $CI(t) = 1$ - interval estimate for $S(t)$ cf Pocock. Survival plots in clinical trials: good practice & pitfalls. Lancet. 2002.

* CI curves easier to read; make more use of white space, than (decreasing from 1) "survival" curves.

Comparison of 2 Survival or Cumulative Incidence curves: index($_1$) vs. ref. ($_0$) categories — N O T E S

=======

In words Survival or Risk (i.e., Cum. Inc., CI) **Difference at a specific timepoint** t

In symbols $S_1(t) - S_0(t)$; $CI(t)_1 - CI(t)_0$; or $Risk_{1[0\rightarrow t]} - Risk_{0[0\rightarrow t]}$; $NNT = 1 \div Risk\Delta$ — Interval est. for $NNT = 1 \div$ Interval est. for $Risk\Delta$

Empirical: $\widehat{S_1(t)} - \widehat{S_0(t)}$, along with SE_1 and SE_0 (Greenwood SE's) — $SE = Var^{1/2}$.

Test Statistic: $ratio = \{\widehat{S_1(t)} - \widehat{S_0(t)}\}/\{SE_1^2 + SE_0^2\}^{1/2} \sim N(0,1)$ *under* $H_0 \rightarrow Z$-statistic

Conf. Int: $\widehat{S_1(t)} - \widehat{S_0(t)} \mp z_\alpha \times \{SE_1^2 + SE_0^2\}^{1/2}$ — Interval est. for Risk**Ratio** $\rightarrow e^{\text{Int. est. for } \log[RiskRatio]}$

=======

Test of equality (H_0) of 2 entire Survival or Cumulative Incidence curves

Empirical: J *narrow* event-containing intervals in $[0, t_{max}]$.

n_j at risk just before event(s) in interval j (n_j persons comprise '**riskset**' j)
s_j avoid event in ('survive') interval j (stay in initial state). Remaining d_j don't.

2×2 table for j^{th} riskset, along with $E[d_{1j}|H_0]$ and $Var[d_{1j}|H_0]$

d_{1j} s_{1j} $\mid n_{1j}$ $\quad E[d_{1j}|H_0] = (n_{1j}/n_j) \times d_j$
d_{2j} s_{2j} $\mid n_{2j}$ $\quad Var[d_{1j}|H_0] = n_{1j}n_{2j}d_j s_j/\{n_j^2(n_j-1)\}$
$- - - - - -$
d_j s_j $\mid n_j$

Cf. worked e.g., Statistics at Square One - c634.

Test Statistic: $X^2 = \frac{\{\sum_j d_{1j} - \sum_j E[d_{1j}|H_0]\}^2}{\sum_j Var[d_{1j}|H_0]} \sim \chi_1^2$ — Mantel Haenszel 1df Chi-Sq. Test Statistic

Article has summary OR estimator **and** test statistic

Terminology: This is called the "**Log-rank" test**

Has same structure as Mantel & Haenszel's test: $H_0 : OR_1 = \cdots = OR_J = 1$. — Worked e.g. in M-H 1959 classic - c634-stratified.

In M and H's application, each 2×2 table refers to distinct persons.

Here, each table is for a 'riskset'; each riskset is a subset of the one before.

Note: For valid use of χ_1^2, good if $\sum_j E[d_{1j}|H_0] > 5$; do not need **each** $E[d_{1j}] > 5$.

EPIB 634 Survival Analysis & Related Topics **Survival Analysis / Follow-up Studies**

Example: Kaplan-Meier survival curves, log-rank test, and illustration of ***Risksets***

from Statistics at Square One: Survival analysis [http://bmj.bmjjournals.com/collections/statsbk/12.shtml]

"Mclllmurray and Turkie (2) describe a clinical trial of 69 patients for the treatment of Dukes' C colorectal cancer. The data for the two treatments, linoleic acid (tx = 1, n = 25) or control (tx = 0, n = 24) are given in Table 12.1 (3) .. "

	Follow-up Month	1	2	3	6	8	10	12	20	24	30	32	42	44	**Sum**
[a]	tx 1: deaths:	0	0	0	2	0	2	4	0	1	0	1	0	0	10
[b]	tx 1: survived:	25	24	24	21	21	18	13	9	7	5	4	1	1	
		--	--	--	--	--	--	--	--	--	--	--	--	--	
	tx 1: At Risk:	25	24	24	23	21	20	17	9	8	5	5	1	1	
[c]	tx 0: deaths:	0	0	0	4	2	0	2	1	1	1	0	1	0	12
[d]	tx 0: survived:	24	24	24	19	17	17	15	9	7	3	2	0	0	
		--	--	--	--	--	--	--	--	--	--	--	--	--	
	tx 0: At Risk:	24	24	24	23	19	17	17	10	8	4	2	1	0	
		==	==	==	==	==	==	==	==	==	==	==	==	==	
	tx 0&1: deaths:	0	0	0	6	2	2	6	1	2	1	1	1	0	
	tx 0&1: At Risk:	49	48	48	46	40	37	34	19	16	9	7	2	1	
	Riskset # :	.	.	.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	.	
E[a] ...	under H0:	.	.	.	3.0	1.1	1.1	3.0	0.5	1.0	0.6	0.7	0.5	.	11.4
V[a] ...	under H0:	.	.	.	1.3	0.5	0.5	1.3	0.2	0.5	0.2	0.2	0.3	.	5.0

1. Order all the survival times from smallest to largest; identify the distinct death-times; concentrate on those at risk just before each distinct death-time - this is the "**Risk-Set**' (i.e. the 'candidates") for the failure time. Subjects remain. in successive Risk Sets until removed by censoring, or event of interest

2. **Kaplan-Meier curve for each separate group:** Multiply the successive fractions that make it out of (past) each risk set to yield successively lower "estimated fractions still alive". [Skip risk set if no event in that group] eg tx 1: S[6] = (21/23); S[10] = S[6] × (18/20), etc.
Nelson-Aalen curve: "Integrated hazard" estimated as Σ(deaths/At Risk) summed to t of interest.: S[t] = exp[- Integrated hazard]: S[6] = exp(-2/23); S[10] = exp[-{2/23 +2/20}], etc.

3. **Log-Rank Test:** Form 2 x 2 table for the outcome in each risk set, and carry out Mantel-Haenszel test, summing the excesses or deficits (the values of {a – E[a | H_0] }) in the target (usually "a") cell over the tables. Compare the overall deficit/excess with its sampling variation

2 versions of log-rank test: (i) M-H 'focus only on "a"-cell' version,, with appropriate variance
(ii) traditional chi-square version $(O_1 - E_1)^2/E_1 + (O_2 - E_2)^2/E_2$ (avoid calculating variance)

Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial

Elvin Kedhi, Kaiyum Sheik Joesoef, Eugene McFadden, Jochem Wassing, Carlos van Mieghem, Dick Goedhart, Pieter Cornelis Smits

Summary

Background Everolimus-eluting and paclitaxel-eluting stents, compared with bare metal stents, reduced the risk of restenosis in clinical trials with strict inclusion and exclusion criteria. We compared the safety and efficacy of the second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice.

Methods We randomly assigned 1800 consecutive patients (aged 18–85 years) undergoing percutaneous coronary intervention at one centre to treatment with everolimus-eluting or paclitaxel-eluting stents. The primary endpoint was a composite of safety and efficacy (all-cause mortality, myocardial infarction, and target vessel revascularisation) within 12 months. Patients were not told which stent they had been allocated. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT01016041.

Findings Follow-up was completed in 1797 patients. The primary endpoint occurred in 56 (6%) of 897 patients in the everolimus-eluting stent group versus 82 (9%) of 903 in the paclitaxel-eluting stent group (relative risk 0·69 [95% CI 0·50–0·95], p value for superiority=0·02). The difference was attributable to a lower rate of stent thrombosis (6 [<1%] *vs* 23 [3%], 0·26 [0·11–0·64], p=0·002), myocardial infarction (25 [3%] *vs* 48 [5%], 0·52 [0·33–0·84], p=0·007), and target vessel revascularisation (21 [2%] *vs* 54 [6%], 0·39 [0·24–0·64], p=0·0001). Cardiac death, non-fatal myocardial infarction, or target lesion revascularisation occurred in 44 [5%] patients in the everolimus-eluting stent group versus 74 [8%] patients in the paclitaxel-eluting stent group, p value for superiority was 0·005.

Interpretation The everolimus-eluting stent is better than the second generation paclitaxel-eluting stent in unselected patients in terms of safety and efficacy. On the basis of our results, we suggest that paclitaxel-eluting stents should no longer be used in everyday clinical practice.

Funding Unrestricted grants from Abbott Vascular and Boston Scientific.

Lancet 2010; 375: 201–09

Published Online January 8, 2010 DOI:10.1016/S0140-6736(09)62127-9

See Comment page 174

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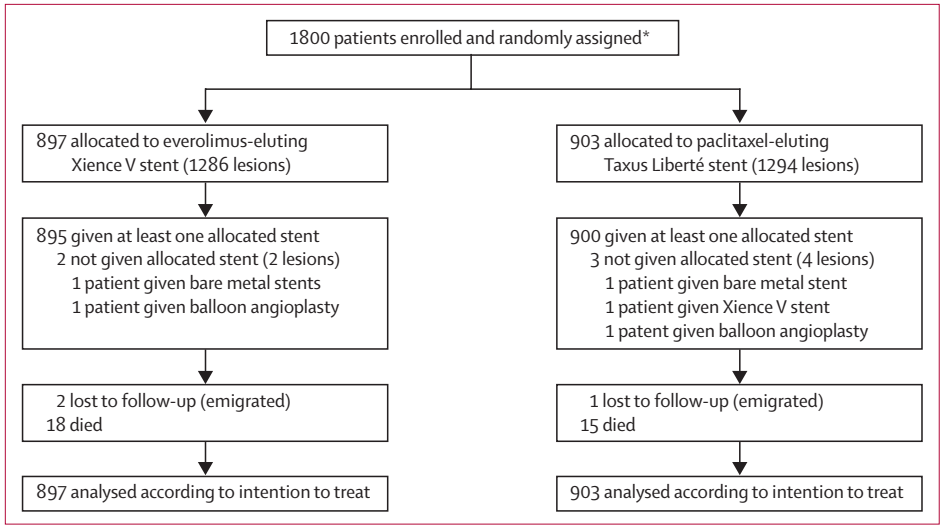

Figure 1: **Trial profile**

*We have no reliable data for patients assessed for eligibility.

Statistical analysis

On the basis of results from the T-SEARCH registry,[4] and SIRTAX[11] and SPIRIT II trials,[12] we assumed an incidence of the primary endpoint of 9% in the everolimus-eluting stent group and 14% in the paclitaxel-eluting stent group. Enrolment of 1800 patients would provide the study with a statistical power of 85% to detect this difference with a two-sided significance level of 0·05, allowing for 3–4% of patients lost to follow-up. All analyses were done according to the intention-to-treat principle. Patients were censored from the Kaplan-Meier plots when they reached any component of the composite endpoint. Categorical variables were assessed with use of χ^2 or Fisher's exact tests, whereas continuous variables were assessed with the Wilcoxon rank-sum test.

The time to the primary endpoint was assessed according to the method of Kaplan-Meier, and the log-rank test was applied to compare the incidence of the endpoint between groups. Relative risks with 95% CIs, were calculated with the log-binomial method.[13] The Kaplan-Meier curves were drawn with the guidelines provided by Pocock and colleagues.[14] All p values were two-sided, and a p value of less than 0·05 was regarded as significant. Analyses were done with SAS (version 8.02).

The trial is registered with ClinicalTrials.gov, number NCT01016041.

Role of the funding source

The sponsors had no involvement in the design, conduct, or analysis of the study. The corresponding author had full access to all the data in the study, and had full responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1800 patients were enrolled between February, 2007, and September, 2008. Five (<1%) were not given the designated stent. Staged procedures were done in 191 (21%) patients in the everolimus-eluting stent group and in 172 (19%) patients in the paclitaxel-eluting stent group (p=0·23). Three were lost to follow-up. The groups had similar baseline clinical (table 1), angiographic (table 2), and procedural characteristics (table 3).

Most patients presented with an acute coronary syndrome (table 1); the subtype of acute coronary syndrome was equally distributed in the two groups; 74% of lesions were complex (type B2 or C; table 2). The

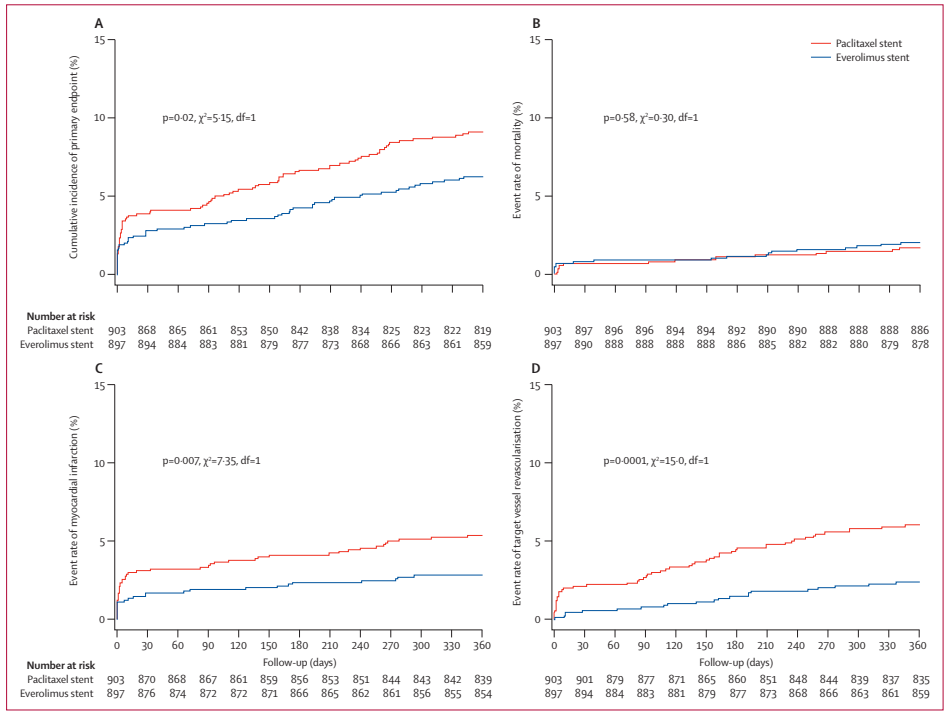

Figure 2: **Kaplan-Meier cumulative events curves at 12 months for primary endpoint (A), mortality (B), myocardial infarction (C), and target vessel revascularisation (D)**

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

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ABSTRACT

BACKGROUND

Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment.

METHODS

We randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

RESULTS

The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; P<0.00001), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; P=0.0002), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; P=0.002), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; P<0.00001), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; P<0.00001), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes.

CONCLUSIONS

In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. (ClinicalTrials.gov number, NCT00239681.)

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*Members of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study group are listed in the Appendix and in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

This article (10.1056/NEJMoa0807646) was published at www.nejm.org on November 9, 2008.

N Engl J Med 2008;359:2195-207.

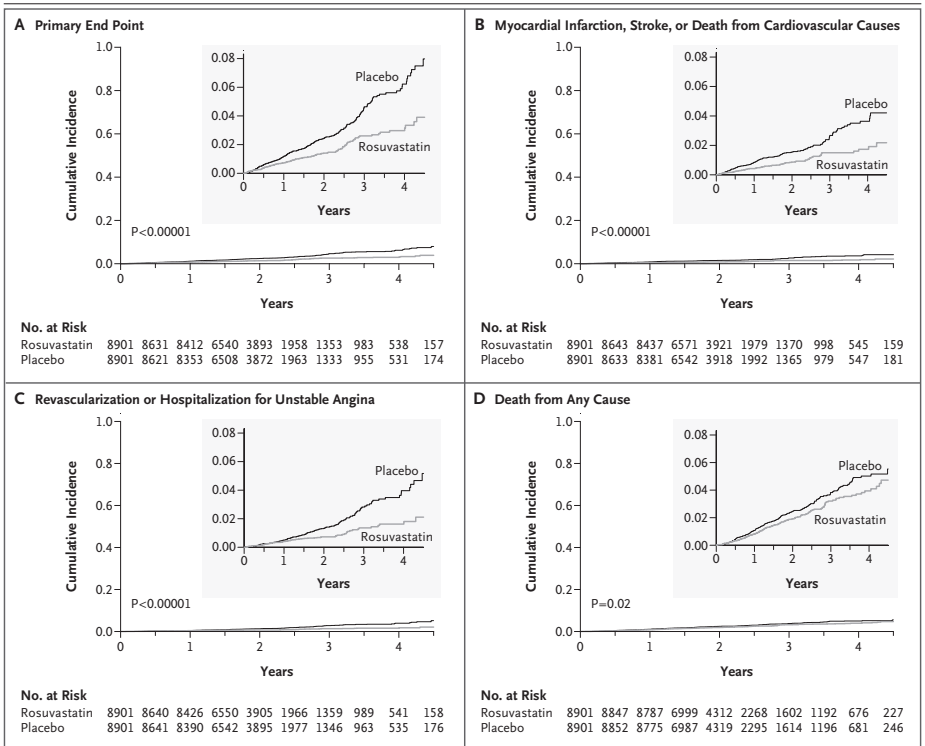


Figure 1. Cumulative Incidence of Cardiovascular Events According to Study Group.

Panel A shows the cumulative incidence of the primary end point (nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or confirmed death from cardiovascular causes). The hazard ratio for rosuvastatin, as compared with placebo, was 0.56 (95% confidence interval [CI], 0.46 to 0.69; P<0.00001). Panel B shows the cumulative incidence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, for which the hazard ratio in the rosuvastatin group was 0.53 (95% CI, 0.40 to 0.69; P<0.00001). Panel C shows the cumulative incidence of arterial revascularization or hospitalization for unstable angina, for which the hazard ratio in the rosuvastatin group was 0.53 (95% CI, 0.40 to 0.70; P<0.00001). Panel D shows the cumulative incidence of death from any cause, for which the hazard ratio in the rosuvastatin group was 0.80 (95% CI, 0.67 to 0.97; P=0.02). In each panel, the inset shows the same data on an enlarged y axis and on a condensed x axis.

A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism

Robert J. Glynn, Sc.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Paul M Ridker, M.D.

ABSTRACT

BACKGROUND

Controversy persists regarding the extent of shared pathways between arterial and venous thrombosis and whether treatments of known efficacy for one disease process have consistent benefits for the other. Observational studies have yielded variable estimates of the effect of statin therapy on the risk of venous thromboembolism, and evidence from randomized trials is lacking.

METHODS

We randomly assigned 17,802 apparently healthy men and women with both low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to receive rosuvastatin, 20 mg per day, or placebo. We followed participants for the first occurrence of pulmonary embolism or deep-vein thrombosis and performed analyses of the data on an intention-to-treat basis.

RESULTS

During a median follow-up period of 1.9 years (maximum, 5.0), symptomatic venous thromboembolism occurred in 94 participants: 34 in the rosuvastatin group and 60 in the placebo group. The rates of venous thromboembolism were 0.18 and 0.32 event per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio with rosuvastatin, 0.57; 95% confidence interval [CI], 0.37 to 0.86; P=0.007); the corresponding rates for unprovoked venous thromboembolism (i.e., occurring in the absence of a known malignant condition, trauma, hospitalization, or surgery) were 0.10 and 0.17 (hazard ratio, 0.61; 95% CI, 0.35 to 1.09; P=0.09) and for provoked venous thromboembolism (i.e., occurring in patients with cancer or during or shortly after trauma, hospitalization, or surgery), 0.08 and 0.16 (hazard ratio, 0.52; 95% CI, 0.28 to 0.96; P=0.03). The rates of pulmonary embolism were 0.09 in the rosuvastatin group and 0.12 in the placebo group (hazard ratio, 0.77; 95% CI, 0.41 to 1.45; P=0.42), whereas the rates of deep-vein thrombosis only were 0.09 and 0.20, respectively (hazard ratio, 0.45; 95% CI, 0.25 to 0.79; P=0.004). Consistent effects were observed in all the subgroups examined. No significant differences were seen between treatment groups in the rates of bleeding episodes.

CONCLUSIONS

In this trial of apparently healthy persons, rosuvastatin significantly reduced the occurrence of symptomatic venous thromboembolism. (ClinicalTrials.gov number, NCT00239681.)

Table 2. Occurrence of Venous Thromboembolism According to Study Group.

End Point	Rosuvastatin (N=8901)		Placebo (N=8901)		Hazard Ratio (95% CI)	P Value
	no. of patients	*no. of events/ 100 person-yr*	*no. of patients*	*no. of events/ 100 person-yr*		
Primary efficacy analysis*						
Venous thromboembolism						
Total	34	0.18	60	0.32	0.57 (0.37–0.86)	0.007
Unprovoked	19	0.10	31	0.17	0.61 (0.35–1.09)	0.09
Provoked	15	0.08	29	0.16	0.52 (0.28–0.96)	0.03
Pulmonary embolism	17	0.09	22	0.12	0.77 (0.41–1.45)	0.42
Deep-vein thrombosis only	17	0.09	38	0.20	0.45 (0.25–0.79)	0.004
Safety analysis†						
Venous thromboembolism						
Total	35	0.18	64	0.33	0.55 (0.36–0.82)	0.003
Unprovoked	20	0.10	34	0.18	0.59 (0.34–1.02)	0.06
Provoked	15	0.08	30	0.16	0.50 (0.27–0.93)	0.02
Pulmonary embolism	17	0.09	24	0.12	0.71 (0.38–1.32)	0.27
Deep-vein thrombosis only	18	0.09	40	0.21	0.45 (0.26–0.78)	0.003

* The primary efficacy analysis was performed on the basis of 94 cases identified by March 30, 2008.
† The safety analysis was performed on the basis of 99 cases that were identified before the study was unblinded.

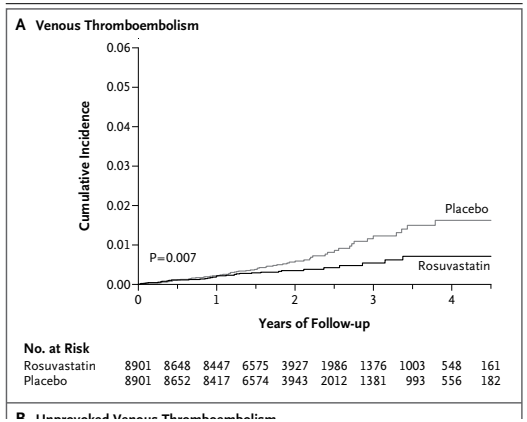
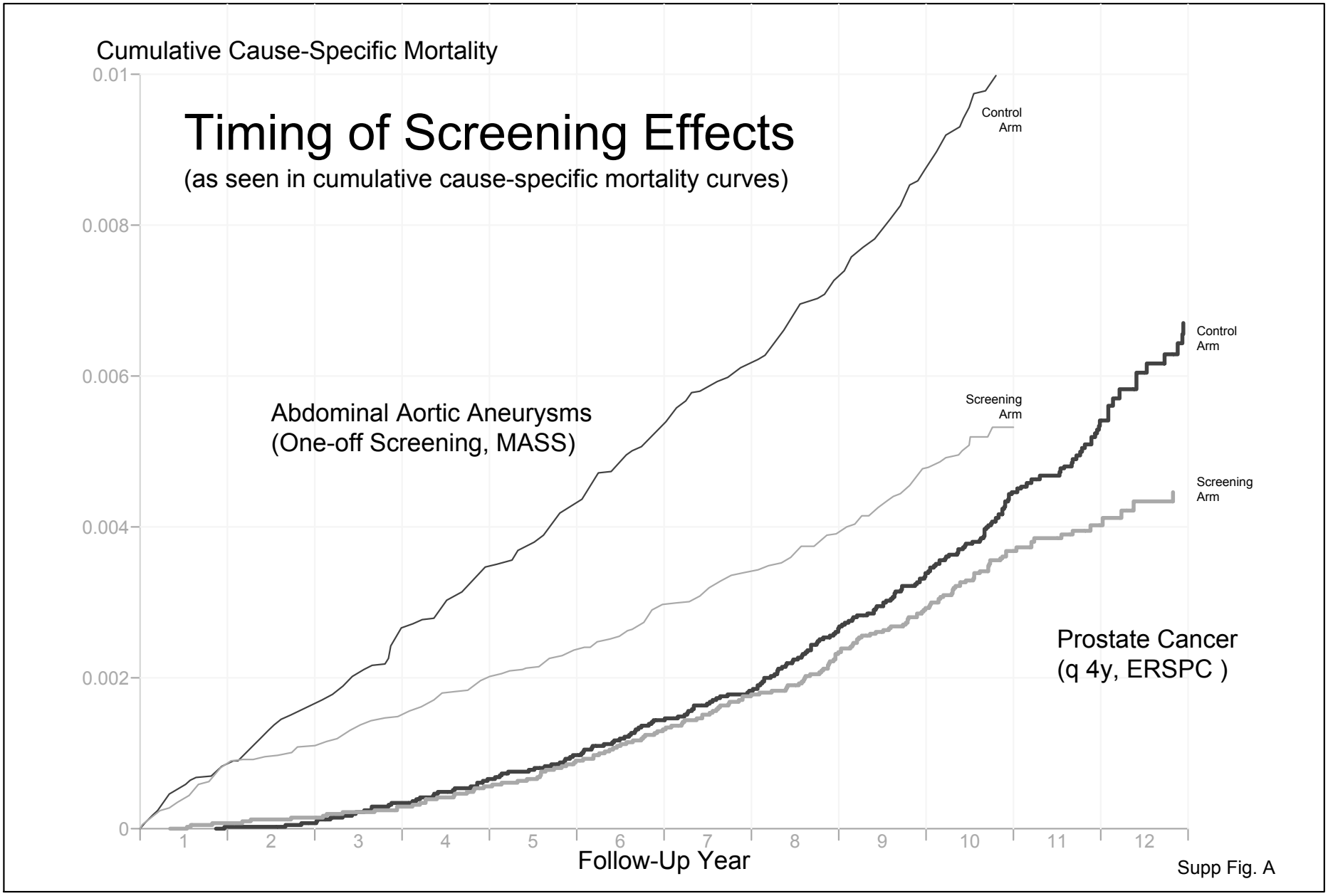


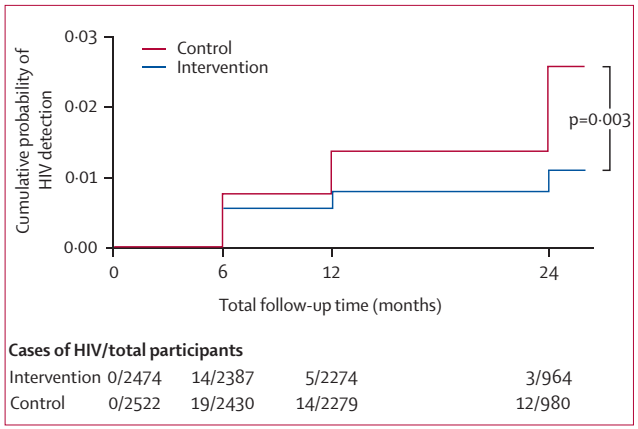
Figure 1. Cumulative Incidence of Venous Thromboembolism in the Rosuvastatin and Placebo Groups.
Panel A shows the incidence of any venous thromboembolism, Panel B the incidence of unprovoked venous thromboembolism (i.e., occurring in the absence of a known malignant condition, trauma, hospitalization, or surgery), and Panel C the incidence of provoked venous thromboembolism (i.e., occurring in patients with cancer or during or shortly after trauma, hospitalization, or surgery). The P values were calculated on the basis of a likelihood-ratio test of the effect of rosuvastatin, with the use of a proportional-hazards model.

venous thromboembolism (P>0.10 for each interaction) (Fig. 2). Subgroups with the highest rates of venous thromboembolism in the placebo group included participants who were 70 years of age or older, those who had a body-mass index of 30 or higher, and those who had a waist circum-


Cumulative Cause-Specific Mortality
Timing of Screening Effects
(as seen in cumulative cause-specific mortality curves)
0.01
0.008
0.006
0.004
0.002
0
Control Arm
Screening Arm
Abdominal Aortic Aneurysms
(One-off Screening, MASS)
Control Arm
Screening Arm
Prostate Cancer
(q 4y, ERSPC)
1
2
3
4
5
6
7
8
9
10
11
12
Follow-Up Year
Supp Fig. A

	Intervention group	Control group	Incidence rate ratio (95% CI)	p value
0–6 months follow-up interval				
Number of participants	2263	2319		
Incident events	14	19		
Person-years	1172·1	1206·7		
Incidence per 100 person-years	1·19	1·58	0·76 (0·35–1·60)	0·439
6–12 months follow-up interval				
Number of participants	2235	2229		
Incident events	5	14		
Person-years	1190·7	1176·3		
Incidence per 100 person-years	0·42	1·19	0·35 (0·10–1·04)	0·0389
12–24 months follow-up interval				
Number of participants	964	980		
Incident events	3	12		
Person-years	989·7	1008·7		
Incidence per 100 person-years	0·30	1·19	0·25 (0·05–0·94)	0·0233
Total 0–24 months follow-up				
Cumulative number of participants	2387	2430		
Cumulative incident events	22	45		
Cumulative person-years	3352·4	3391·8		
Cumulative incidence per 100 person-years	0·66	1·33	0·49 (0·28–0·84)	0·0057

Table 3: **HIV incidence by study group and follow-up interval, and cumulative HIV incidence over 2 years**



Cases of HIV/total participants

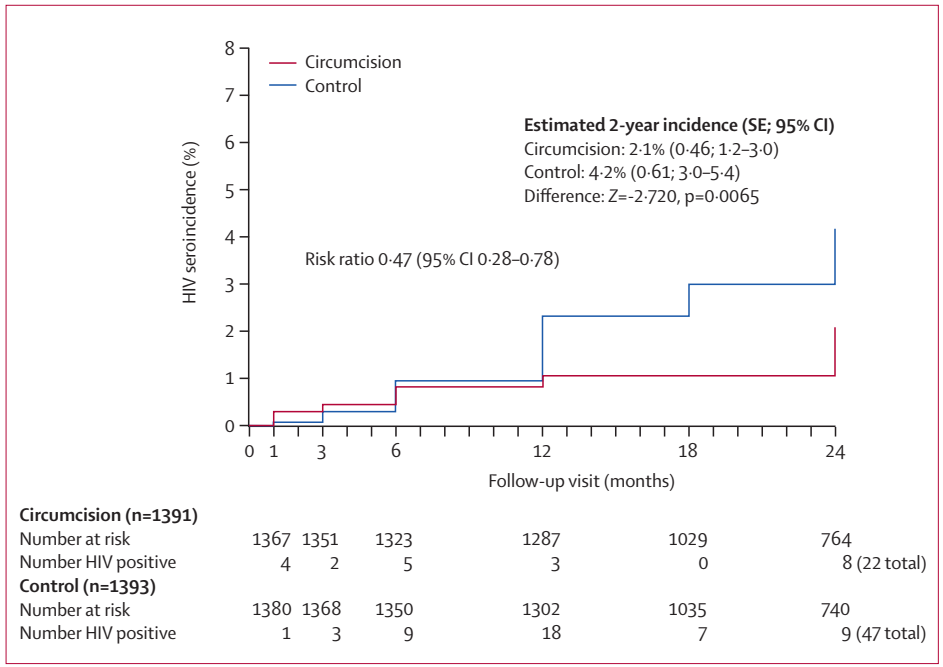
Intervention	0/2474	14/2387	5/2274	3/964
Control	0/2522	19/2430	14/2279	12/980

Figure 2: **Kaplan-Meier cumulative probabilities of HIV detection by study group**

Actual visits grouped by the three scheduled visits at 6 months, 12 months, and 24 months after enrolment. The cumulative probabilities of HIV infection were 1·1% in the intervention group and 2·6% in the control group over 24 months.

LEFT: From "Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial," Lancet 2007; 369: 657-666.

BELOW: From Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet 2007; 369: 643-56.



Circumcision (n=1391)						
Number at risk	1367	1351	1323	1287	1029	764
Number HIV positive	4	2	5	3	0	8 (22 total)
Control (n=1393)						
Number at risk	1380	1368	1350	1302	1035	740
Number HIV positive	1	3	9	18	7	9 (47 total)

Figure 2: **Cumulative HIV seroincidence across follow-up visits by treatment**

Time to HIV-positive status is taken as the first visit when a positive HIV test result is noted. Time is credited as the follow-up visit month. Participants without HIV-positive status are censored at the last regular follow-up visit completed where HIV testing was done, credited specifically as months 1, 3, 6, 12, 18, and 24.

Weekend versus Weekday Admission and Mortality from Myocardial Infarction

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ABSTRACT

BACKGROUND

Management of acute myocardial infarction requires urgent diagnostic and therapeutic procedures, which may not be uniformly available throughout the week.

METHODS

We examined differences in mortality between patients admitted on weekends and those admitted on weekdays for a first acute myocardial infarction, using the Myocardial Infarction Data Acquisition System. All such admissions in New Jersey from 1987 to 2002 (231,164) were included and grouped in 4-year intervals.

RESULTS

There were no significant differences in demographic characteristics, coexisting conditions, or infarction site between patients admitted on weekends and those admitted on weekdays. However, patients admitted on weekends were less likely to undergo invasive cardiac procedures, especially on the first and second days of hospitalization (P<0.001). In the interval from 1999 to 2002 (59,786 admissions), mortality at 30 days was significantly higher for patients admitted on weekends (12.9% vs. 12.0%, P=0.006). The difference became significant the day after admission (3.3% vs. 2.7%, P<0.001) and persisted at 1 year (1% absolute difference in mortality). The difference in mortality at 30 days remained significant after adjustment for demographic characteristics, coexisting conditions, and site of infarction (hazard ratio, 1.048; 95% confidence interval [CI], 1.022 to 1.076; P<0.001), but it became nonsignificant after additional adjustment for invasive cardiac procedures (hazard ratio, 1.023; 95% CI, 0.997 to 1.049; P=0.09).

CONCLUSIONS

For patients with myocardial infarction, admission on weekends is associated with higher mortality and lower use of invasive cardiac procedures. Our findings suggest that the higher mortality on weekends is mediated in part by the lower rate of invasive procedures, and we speculate that better access to care on weekends could improve the outcome for patients with acute myocardial infarction.

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N Engl J Med 2007;356:1099-109.

Table 3. Mortality among Patients Admitted on Weekends and Patients Admitted on Weekdays.*

No. of Days from Admission	1987–1990			1991–1994			1995–1998			1999–2002		
	Weekdays	Weekends	P Value	Weekdays	Weekends	P Value	Weekdays	Weekends	P Value	Weekdays	Weekends	P Value
	percent (mortality)			*percent (mortality)*			*percent (mortality)*			*percent (mortality)*		
Day of admission	2.2	2.5	0.04	1.8	1.8	0.94	1.6	1.6	0.34	1.1	1.3	0.09
Day 2	4.5	5.2	0.001	3.8	4.0	0.35	3.6	3.5	0.71	2.7	3.3	<0.001
Day 3	6.0	6.7	0.005	5.0	5.2	0.24	4.9	4.8	0.80	3.8	4.7	<0.001
Day 4	7.2	7.9	0.007	5.9	6.2	0.16	5.8	5.6	0.39	4.7	5.8	<0.001
Day 5	8.1	8.8	0.01	6.7	7.0	0.20	6.5	6.4	0.48	5.4	6.4	<0.001
Day 6	8.8	9.5	0.02	7.3	7.7	0.16	7.1	7.0	0.73	6.0	7.0	<0.001
Day 7	9.4	10.1	0.03	7.8	8.3	0.04	7.6	7.7	0.87	6.6	7.5	<0.001
In-hospital	14.5	15.1	0.11	11.8	12.2	0.20	10.4	10.2	0.41	9.3	9.9	0.03
Day 14	12.5	13.2	0.03	10.4	10.9	0.09	10.2	10.2	0.86	9.4	10.4	<0.001
Day 21	13.9	14.7	0.01	11.6	12.2	0.08	11.5	11.4	0.72	10.9	11.8	0.002
Day 30	15.1	16.0	0.009	12.6	13.1	0.10	12.6	12.4	0.69	12.0	12.9	0.006
Day 180	20.5	21.5	0.01	18.0	18.5	0.14	18.1	17.8	0.38	18.9	20.0	0.005
Day 365	23.7	24.6	0.02	21.0	21.7	0.09	21.4	21.2	0.61	22.9	23.9	0.01
Hazard ratio for day 2 mortality (95% CI)		1.075 (1.032–1.121)			1.033 (0.985–1.083)			1.007 (0.958–1.057)			1.121 (1.064–1.180)	
Hazard ratio for day 7 mortality (95% CI)		1.033 (1.004–1.063)			1.044 (1.011–1.078)			1.014 (0.982–1.048)			1.080 (1.045–1.116)	
Hazard ratio for total in-hospital mortality (95% CI)		1.034 (1.009–1.059)			1.025 (0.997–1.054)			1.015 (0.986–1.045)			1.055 (1.024–1.086)	
Hazard ratio for day 30 mortality (95% CI)		1.040 (1.016–1.065)			1.038 (1.011–1.066)			1.007 (0.981–1.034)			1.048 (1.022–1.076)	
Hazard ratio for day 365 mortality (95% CI)		1.032 (1.013–1.052)			1.033 (1.012–1.054)			1.005 (0.985–1.026)			1.037 (1.017–1.056)	

* Hazard ratios are adjusted for age, sex, site of myocardial infarction, and coexisting conditions.

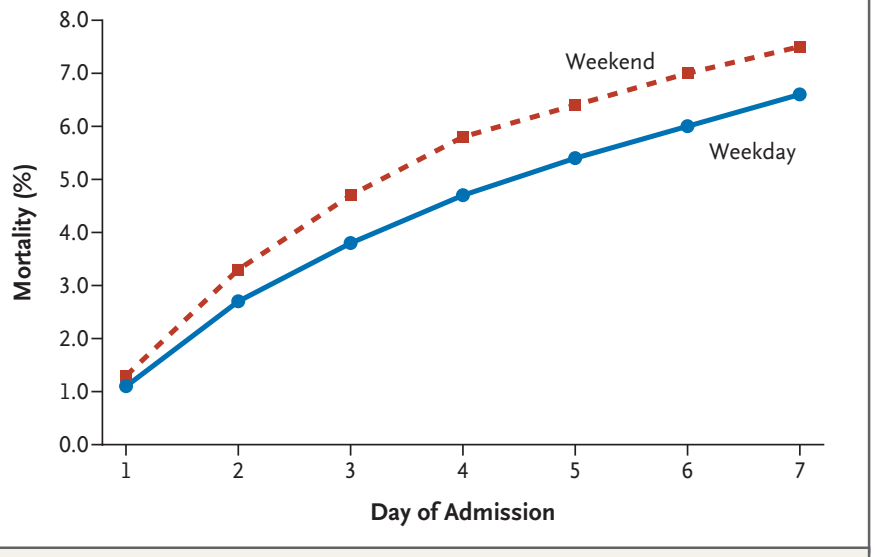

Figure 1. Mortality for Weekend versus Weekday Admissions According to Day of Admission, 1999–2002.

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

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ABSTRACT

BACKGROUND

The development of a safe and effective vaccine against the human immunodeficiency virus type 1 (HIV-1) is critical to pandemic control.

METHODS

In a community-based, randomized, multicenter, double-blind, placebo-controlled efficacy trial, we evaluated four priming injections of a recombinant canarypox vector vaccine (ALVAC-HIV [vCP1521]) plus two booster injections of a recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E). The vaccine and placebo injections were administered to 16,402 healthy men and women between the ages of 18 and 30 years in Rayong and Chon Buri provinces in Thailand. The volunteers, primarily at heterosexual risk for HIV infection, were monitored for the coprimary end points: HIV-1 infection and early HIV-1 viremia, at the end of the 6-month vaccination series and every 6 months thereafter for 3 years.

RESULTS

In the intention-to-treat analysis involving 16,402 subjects, there was a trend toward the prevention of HIV-1 infection among the vaccine recipients, with a vaccine efficacy of 26.4% (95% confidence interval [CI], −4.0 to 47.9; P=0.08). In the per-protocol analysis involving 12,542 subjects, the vaccine efficacy was 26.2% (95% CI, −13.3 to 51.9; P=0.16). In the modified intention-to-treat analysis involving 16,395 subjects (with the exclusion of 7 subjects who were found to have had HIV-1 infection at baseline), the vaccine efficacy was 31.2% (95% CI, 1.1 to 52.1; P=0.04). Vaccination did not affect the degree of viremia or the CD4+ T-cell count in subjects in whom HIV-1 infection was subsequently diagnosed.

CONCLUSIONS

This ALVAC-HIV and AIDSVAX B/E vaccine regimen may reduce the risk of HIV infection in a community-based population with largely heterosexual risk. Vaccination did not affect the viral load or CD4+ count in subjects with HIV infection. Although the results show only a modest benefit, they offer insight for future research. (ClinicalTrials.gov number, NCT00223080.)

From the Department of Disease Control, Ministry of Public Health, Nonthaburi (S.R.-N., R.P., C.N., S.C., C.K., P.T., P.K.); Vaccine Trials Center (P.P.) and Data Management Unit (J.K.), Faculty of Tropical Medicine, Mahidol University, Bangkok; Thai Component (S.N.) and U.S. Army Medical Component (J.C., R.P., M.S., M.B.), Armed Forces Research Institute of Medical Sciences, Bangkok — all in Thailand; the Division of AIDS, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD (E.A.); Sanofi Pasteur, Swiftwater, PA (S.G., J.T., J.G.M.); Global Solutions for Infectious Diseases, South San Francisco, CA (D.P.F.); the Emmes Corporation, Rockville, MD (D.S.); the Global AIDS Program, Centers for Disease Control and Prevention, Atlanta (D.L.B.); U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Rockville, MD (M.L.R., N.L.M., J.H.K.); and U.S. Army Medical Materiel Development Activity, Ft. Detrick, MD (J.H.K.). Address reprint requests to Dr. Kim at the U.S. Military HIV Research Program, Walter Reed Army Institute of Research, 1600 E. Gude Dr., Rockville, MD 20850, or at jkim@hivresearch.org.

*The names and affiliations of the Ministry of Public Health–Thai AIDS Vaccine Evaluation Group (MOPH–TAVEG) investigators are listed in the Appendix.

This article (10.1056/NEJMoa0908492) was published on October 20, 2009, and was last updated on November 19, 2009, at NEJM.org.

N Engl J Med 2009;361:2209-20.

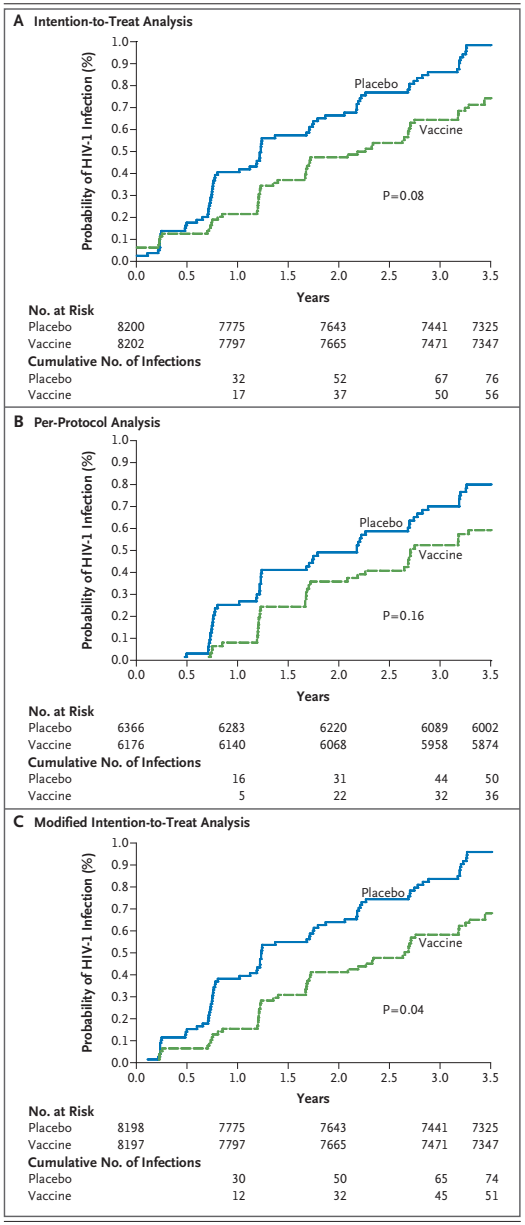


Figure 2. Kaplan–Meier Cumulative Rates of Infection, According to Type of Analysis.

The vaccination regimen was completed approximately 6 months after the first dose was administered. In the intention-to-treat analysis involving 16,402 subjects, the vaccine efficacy was 26.4% (95% confidence interval [CI], −4.0 to 47.9; P=0.08) (Panel A). In the per-protocol analysis involving 12,542 subjects, the vaccine efficacy was 26.2% (95% CI, −13.3 to 51.9; P=0.16) (Panel B). In the modified intention-to-treat analysis involving 16,395 subjects (excluding 7 subjects who were found to have had HIV infection at baseline), the vaccine efficacy was 31.2% (95% CI, 1.1 to 51.2; P=0.04) (Panel C).

be seropositive for HIV-1 on the first test after vaccination were determined by RNA testing to have been infected at enrollment and were not included in the modified intention-to-treat analysis, leaving 16,395 volunteers: 8197 in the vaccine group and 8198 in the placebo group. This group consisted of 10,064 men (61.4% of the subjects) and 6331 women (38.6%). Baseline characteristics were similar for selected variables, and there was no imbalance between the two groups in self-described risk behavior (Table 1).

There were no substantive changes in serial self-reports of risk behavior during the trial. No data were collected on the status of male circumcision or on serologic analyses for adenovirus type 5 or herpes simplex virus type 2.

There were 52,985 person-years of follow-up (15% more than planned). At 42 months, 14,672 of the volunteers (89.5%) had completed the trial and were HIV-seronegative.

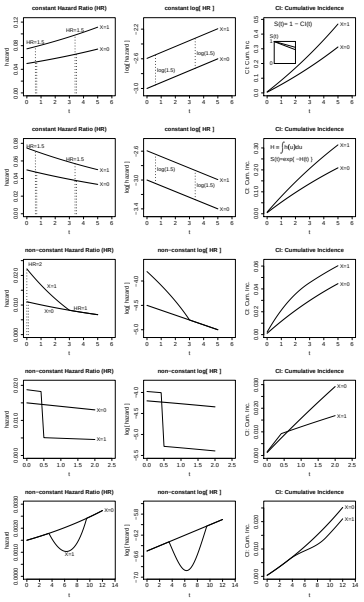
ADVERSE EVENTS

Most local and systemic reactions to the vaccine were mild to moderate and reflected the findings of studies on the safety of these products that have been reported previously[12,17,27-29] (Fig. 1 in the Supplementary Appendix). Most reactions were mild to moderate and resolved within 3 days after vaccination. At least one adverse event was reported in 69.4% of subjects in the two study groups. The number of deaths and the frequency and severity of adverse events and serious adverse events were similar in the two groups (Table 1 in the Supplementary Appendix).

PRIMARY END POINTS

HIV-1 Infection

HIV-1 infection was diagnosed in 132 subjects (56 in the vaccine group and 76 in the placebo


constant Hazard Ratio (HR)
HR=1.5
X=1
X=0
hazard
t
constant log[HR]
log(1.5)
log(hazard)
CI: Cumulative Incidence
S(0)= 1 − CI(0)
Cir Cum. Inc
non−constant Hazard Ratio (HR)
HR=2
HR=1
non−constant log[HR]
log(hazard)

Comments

History Corner: JASA 1947

TUMBLER MORTALITY

GEORGE W. BROWN
Statistical Laboratory, Iowa State College
AND
MERRILL M. FLOOD
Princeton, New Jersey

I. INTRODUCTION

1. *The statistical problem.* Life tables are constructed for certain types of equipment, under specified conditions of use, from records of experience with the equipment in service. Items such as electric lamps, glass tumblers, and silk stockings, under the normal conditions of use, in effect may be said to "die" when they "burn out," "crack," or "run." The data and analysis necessary to obtain an estimate of the mortality distribution, life expectancy, and other similar characteristics of such equipment, are exactly analogous to the more familiar techniques applied in the case of human mortality experience. This paper presents the results of an analysis of a service test that was conducted in order to estimate the mean lengths of life for each of two types of glass tumbler when used in a particular cafeteria, and discusses statistical techniques that proved to be well-suited for the treatment of the problem. Technological considerations of a model for tumbler breakage are given, leading to familiar mortality curves of Makeham-Gompertz type.

2. *The service test.** A fixed number of tumblers of each of two types, called "annealed" and "toughened," were kept in service at all times in the test cafeteria. At the end of each week, each broken tumbler was replaced by a new one of the same type. A record was kept of the date each tumbler was introduced into service and of the week each broken tumbler was removed from service. The test was continued for 78 weeks employing 60 annealed tumblers and 120 toughened tumblers.

TABLE 1

ANNEALED CASE ($\lambda = 0.183$, $\mu = 1.60$)

Week	Exposed N	Broken n	n/N	F_i	P_i^c	σ	δ	δ/σ
1	549	23	.042	.0410	.041	.0086	.001	.12
2	521	38	.073	.1127	.075	.0115	−.002	−.17
3	470	48	.102	.1934	.091	.0133	.011	.83
4	415	40	.096	.2763	.103	.0149	−.007	−.47
5	371	36	.097	.3564	.111	.0163	−.014	−.86
6	331	42	.127	.4317	.117	.0177	.010	.56
7	285	35	.123	.5008	.122	.0194	.001	.05
8	247	33	.134	.5638	.126	.0211	.008	.38
9	210	26	.124	.6199	.129	.0231	−.005	−.22
10	182	17	.093	.6698	.131	.0250	−.038	−1.52
11	163	22	.135	.7145	.134	.0267	.001	.04
12	139	16	.115	.7537	.136	.0291	−.021	−.72
13	123	8	.065	.7876	.138	.0311	−.073	−2.35
14	114	19	.167	.8174	.140	.3026	.027	.83
15	95	17	.179	.8432	.141	.0357	.038	1.06
16	78	13	.167	.8656	.143	.0396	.024	.61
17	65	8	.123	.8850	.144	.0436	−.021	−.48
18	56	7	.125	.9016	.145	.0470	−.020	−.43
19	49	12	.245	.9161	.146	.0504	.099	1.96
20	37	5	.135	.9284	.147	.0582	−.012	−.21
21–25	31	17	.548	.9680	.553	.0893	−.005	−.06
26–30	14	10	.714	.9860	.563	.1325	.151	1.14

$\chi^2 = \Sigma(\delta/\sigma)^2 = 18.3$

$F_i = \int_0^i f(x)dx$ (From tables of the incomplete gamma function)

$\sigma\sqrt{\dfrac{P_i^c(1-P_i^c)}{N}}$

$P_i^c = \dfrac{F_i - F_{i-1}}{1 - F_{i-1}}$

$\delta = \dfrac{n}{N} - P_i^c$