Does Distance Modify the Effect of Self-Testing in Oral Anticoagulation?

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ABSTRACT

Objectives: Patient self-testing (PST) improves anticoagulation control and patient satisfaction. It is unknown whether these effects are more pronounced when the patient lives farther from the anticoagulation clinic (ACC). If the benefits of PST are limited to a subset of patients (those living farther from care), selectively providing PST to that subset could enhance cost-effectiveness.

Study Design: This is a secondary analysis of a randomized trial of PST versus usual ACC care, which involved 2922 patients of the Veterans Health Administration (VHA).

Methods: Our 3 outcomes were the primary composite clinical end point (stroke, major hemorrhage, or death), anticoagulation control (percent time in therapeutic range), and satisfaction with anticoagulation care. We measured the driving distance between the patient's residence and the nearest VHA facility. We divided patients into quartiles by distance and looked for evidence of an interaction between distance and the effect of the intervention on the 3 outcomes.

Results: The median driving distance was 12 miles (interquartile range = 6-21). Patients living in the farthest quartile had higher rates of the primary composite clinical end point in both groups compared with patients living in the nearest quartile. For PST, the hazard ratio (HR) was 1.77 (95% CI, 1.18-2.64), and for usual care, the HR was 1.81 (95% CI, 1.19-2.75). Interaction terms did not suggest that distance to care modified the effect of the intervention on any outcome.

Conclusions: The benefits of PST were not enhanced among patients living farther from care. Restricting PST to patients living more than a certain distance from the ACC is not likely to improve its cost-effectiveness.

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Oral anticoagulants are received by millions of patients each year to treat or prevent thromboembolic disease.[1] Despite the introduction of novel anticoagulants, warfarin is likely to remain in widespread use for years to come, in part due to concerns about the cost-effectiveness of the novel agents[2] and their safety and efficacy in real-world settings. The effective use of warfarin, however, presents several important challenges. First, excellent anticoagulation control can improve patient outcomes,[3-5] but it can be difficult to achieve[6,7]; therefore, there is a great need to find effective strategies to improve anticoagulation control.[8-10] Second, the burden and cost of frequent clinic visits for monitoring the International Normalized Ratio (INR) can fall heavily on patients and their caregivers.[11-13]

Patient self-testing (PST), the use of a point-of-care device to monitor INR at home, has the potential to address both challenges. Several meta-analyses have suggested that PST generally reduces rates of adverse events (defined here as stroke, major hemorrhage, and all-cause mortality) and improves percent time in therapeutic range (TTR), although the effects were relatively small.[14-16] In one large study of PST, The Home INR Study (THINRS), PST was associated with small but significant improvements in TTR and satisfaction with anticoagulation care; the difference in adverse event rates seemed to favor PST, but did not reach statistical significance.[17] It is generally assumed that the causal pathway for these effects involves test frequency and the ease of testing.[18] Patients may find it difficult to test INR frequently under usual care and, in fact, may test less frequently than would be optimal. Since PST makes it easier to test more frequently, patients are less likely to resist requests to test more frequently when their INR has been unstable. Indeed, the general practice with PST is to test weekly, regardless of the stability of INR, because the burden associated with frequent testing is minimal. Because it reduces the burden of testing, PST should improve satisfaction with care and contribute to

Take-Away Points

Self-testing of anticoagulation improves outcomes, but is expensive. Because its main impact is to enable frequent testing, it could have greater benefit for patients living farther from care.

- We examined data from a randomized trial of self-testing, stratified by distance to care.
- The benefit of self-testing over usual care did not increase with distance from care for patient satisfaction, anticoagulation control, or adverse events.
- However logical it may seem, payers and healthcare managers should not assume that limiting this expensive technology to patients living more than a certain distance from care would enhance its cost-effectiveness.

improved anticoagulation control,[18] which in turn would prevent adverse events.[3-5]

This implies that the benefits of PST should be magnified among patients who have the greatest difficulty visiting the anticoagulation clinic (ACC). These patients would be the most likely to delay needed INR testing, to the detriment of their anticoagulation control and outcomes.[19] Also, these patients would tend to have low baseline levels of satisfaction, due to the burden of frequent visits to the ACC. This raises the possibility that limiting PST to patients with the greatest difficulty accessing care might realize a disproportionate share of its benefits at a fraction of the cost of providing it for all patients. This conjectured causal pathway has not been empirically examined.

In this study, we used data from THINRS to examine whether PST would be more effective among patients living farther from the nearest Veterans Health Administration (VHA) facility. We expected to find, among the usual ACC group, that patients living farther from care would have less frequent INR testing, lower satisfaction with care, lower TTR, and higher rates of adverse events. Among the PST group, however, we expected all these parameters would be unaffected by distance to care. We consequently expected to find that PST would have a greater impact on these outcomes among patients living farther from care.

METHODS

The Home INR Study

THINRS was a randomized trial of PST versus high-quality usual ACC care, funded by the Veterans Affairs (VA) Cooperative Studies Program (CSP 481). The methods and main results of THINRS have been discussed elsewhere.[17,18] Briefly, THINRS recruited VHA patients with atrial fibrillation and/or mechanical heart valves who required chronic warfarin therapy. Those deemed competent to perform PST were randomized in a 1:1 ratio to usual ACC care (with testing once every 4 weeks) or PST (with most patients testing once a week). Follow-up visits were scheduled approximately every 3 months after randomization to collect information about medical events and other data, and to check whether PST patients were still competent to use the meter. The primary clinical end point was time to first major event (stroke, major hemorrhage, or death). The study was approved by the institutional review boards of all VHA medical centers where patients were enrolled or research was conducted.

Driving Distance to Nearest VHA Facility

We used the VHA's centralized file that contains the driving distance for each patient to the nearest VHA facility. These driving distances are calculated using ESRI StreetMap Premium for ArcGIS (ESRI Corporation, Redlands, California) and we used these distances for THINRS patients as a proxy measure for their likely burden of transportation to each ACC visit. We linked information for each of the 2922 patients randomized in the THINRS study to these records and found 2903 with distance information (of the 19 nonmatches, most were due to a missing address). We classified these 2903 patients into quartiles based on driving distance for addresses at the time of randomization. We excluded data for 89 patients who moved to a different distance quartile during the 2-year follow-up period, leaving 2814 patients. Of these, 2755 (1360 in the usual ACC group and 1395 in the PST group) had INR values during the 2-year follow-up period and comprised the analytic population for this study.

Outcomes

Patient-level outcomes included the composite primary clinical end point, anticoagulation control, and satisfaction with care. All outcomes were measured during the 2-year period following randomization. The composite primary clinical end point included stroke, major hemorrhage, or death. These outcomes were confirmed by chart review and adjudicated by an independent committee blinded to treatment assignment.[17]

Anticoagulation control was measured using percent TTR, computed according to the method of Rosendaal.[20] TTR summarizes anticoagulation control over time by using linear interpolation to assign an INR value to each day between successive observed INR values. After interpolation, the percentage of time during which the interpolated INR values lie within the patient's target INR range (from 0%-100%) is calculated.[20]

Satisfaction with anticoagulation care was measured using the Duke Anticoagulation Satisfaction Scale,[21] a

Table 1. Demographics and Baseline Health Status at Randomization

	Usual ACC Group n = 1360 (%)	PST Group n = 1395 (%)	*P*
Male sex	1335 (98%)	1373 (98%)	.60
Race			
White	1258 (93%)	1283 (92%)	.60
Black	70 (5%)	89 (6%)	.17
Other	32 (2%)	25 (2%)	.30
Age, years			.19
<60	303 (22%)	352 (25%)	
60-74	721 (53%)	715 (51%)	
≥75	336 (25%)	328 (24%)	
Health conditions			
Atrial fibrillation	1144 (84%)	1142 (82%)	.12
Angina	233 (17%)	225 (16%)	.48
Heart failure	403 (30%)	383 (27%)	.21
Hypertension	939 (69%)	987 (71%)	.33
Mechanical heart valve	305 (22%)	337 (24%)	.28
Other arrhythmias	152 (11%)	151 (11%)	.77
Transient ischemic attack	133 (10%)	137 (10%)	.97
Complicating factors			
Bleeding disorder	8 (0.6%)	6 (0.4%)	.56
Dementia	7 (0.5%)	6 (0.4%)	.75
Diabetes	457 (34%)	449 (32%)	.43
Frequent falls	36 (3%)	47 (3%)	.27
Homebound	17 (1%)	11 (1%)	.23
Psychosis	13 (1%)	8 (0.6%)	.25
Other medications			
Amiodarone (Cordarone)	105 (8%)	113 (8%)	.72
Aspirin	365 (27%)	377 (27%)	.92
Clopidogrel (Plavix)	16 (1%)	22 (2%)	.37
Driving distance to nearest VHA facility			.37
Shortest (≤6 miles)	343 (25%)	391 (28%)	
Shorter (>6 to ≤12 miles)	353 (26%)	345 (25%)	
Longer (>12 to ≤21 miles)	324 (24%)	311 (22%)	
Longest (>21 miles)	340 (25%)	348 (25%)	

ACC indicates anticoagulation clinic; PST, patient self-testing; VHA, Veterans Health Administration.

validated instrument for assessing health-related quality of life (HRQoL) specifically related to long-term oral anticoagulation. For this study, we dichotomized patients into those who were "highly satisfied" with anticoagulation care (the highest tertile of satisfaction) versus all others.

The frequency of INR testing was also examined as a possible link in the causal pathway between PST and improved TTR. For each patient, we calculated the number of INR tests per patient-year. We hypothesized that test frequency would be lower with increased distance to care in the usual care group, but unaffected by distance in the PST group.

Statistical Analyses

We compared baseline characteristics between PST and usual ACC patients, including distance to care. We compared PST and usual ACC patients regarding our main outcomes of interest (primary composite clinical end point, TTR, and satisfaction with care) overall, and by quartiles of distance to care. We performed tests of increasing or decreasing trends by distance within each treatment group, using the Cochran-Armitage test for categorical outcomes[22,23] and the Jonckheere-Terpstra test for continuous outcomes.[24,25] For comparisons of study outcomes, all 2755 patients were involved in the analyses; however, only 1977 provided data for satisfaction with anticoagulation care at 2 years of follow-up.

Finally, we looked for evidence of a statistical interaction between group assignment and distance quartile for each outcome. For these formal tests of interaction, we used linear or logistic regression, as appropriate, and structured the distance quartiles as a class variable, rather than forcing its levels into a single linear function. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Baseline Characteristics

Among the 2755 patients included in our study, 1395 received PST and 1360 received usual ACC care. Characteristics were generally balanced between groups (Table 1). Enrollees were overwhelmingly male (98%) and white (92%), with an average age of 67 years. The mean distance to care was 16 miles (SD = 17); the median was 12 miles

Table 2. Effect of Intervention on INR Test Frequency and Percent Time in Therapeutic Range, Overall and by Distance From Care

Driving Distance (Quartiles)	INR Tests per Year[a]		Percent TTR[b]	
	Usual ACC Group (n = 1360)	PST Group (n = 1395)	Usual ACC Group (n = 1360)	PST Group (n = 1395)
All patients, mean ± SD	16.5 ± 7.1	47.2 ± 18.6	63.0 ± 17.4	65.7 ± 14
Shortest (≤6 miles)	16.7 ± 5.7	46.3 ± 16.5	62.1 ± 18.0	66.2 ± 13.2
Shorter (>6 to ≤12 miles)	16.6 ± 9.2	47.4 ± 17.5	63.3 ± 17.1	66.7 ± 13.2
Longer (>12 to ≤21 miles)	15.9 ± 5.7	48.1 ± 22.4	63.4 ± 16.6	64.5 ± 15.4
Longest (>21 miles)	16.8 ± 7.3	47.4 ± 17.9	63.3 ± 18.1	65.2 ± 14.4
P test for linear trend across quartiles	.23	.59	.40	.18

ACC indicates anticoagulation clinic; INR, International Normalized Ratio; PST, patient self-testing; TTR, time in therapeutic range.
[a]Measured in units of number of tests per year.
[b]Percent time in range ranges from 0%-100%, those are the units.
Test of interaction between distance quartile and group (3 degrees of freedom) from linear regression: for INR tests per year, *P* = .42; for TTR, *P* = .26.

(interquartile range = 6-21). Ten percent of patients lived more than 38 miles from the nearest VHA facility. As with other patient characteristics, distance to care was balanced between groups.

Satisfaction with Anticoagulation Care

For the entire study, the PST group had a nonsignificantly higher proportion of patients reporting that they were "highly satisfied" with their anticoagulation care (32% vs 28%; OR, 1.21; 95% CI, 0.99-1.47; *P* = .06). We did not find evidence of an increasing or decreasing trend for satisfaction in the usual ACC group based on distance to care (see eAppendix Table 1 [eAppendices available at **www.ajmc.com**]), although the interaction term between distance quartile and treatment group was close to being statistically significant (*P* = .06). If anything, distance seemed to impact satisfaction more in the PST group (test for trend, *P* = .028) than in the usual ACC group (*P* = .41), which was not what we had hypothesized.

Anticoagulation Control

Using the sample for the present study, the PST intervention was associated with a small, but statistically significant overall improvement in TTR (65.7% vs 63.0%; 95% CI for difference, 1.5%-3.8%; *P* <.001).We did not find evidence of an increasing or decreasing trend in TTR by distance to care within either group (Table 2). The interaction term between distance to care and group assignment was not statistically significant for the outcome of TTR (*P* = .26).

INR Test Frequency

By design, the PST intervention was associated with an almost 3-fold increase in INR test frequency (Table 2) (47.2 vs 16.5 tests/year; *P* <.001). We did not find evidence of a trend for test frequency in the usual ACC group by distance to care, and the interaction term between distance and group assignment was not significant (*P* = .42). Thus, we did not have any evidence that patients who live farther from care were postponing needed INR tests under usual ACC care.

Primary Composite Clinical End Point

Figure 1 is the Kaplan-Meier curve comparing time to first event within the first 2 years of follow-up for the usual ACC group by distance quartile, and Figure 2 is a similar curve for the PST group. The hazard ratio, its 95% CI, and the *P* value for the treatment comparison within each distance quartile are in Table 3. Tabular presentation of the data underlying Figures 1 and 2 can be found in eAppendix Table 2.

Within each treatment group, the comparison across distance quartiles was statistically significant (indicating that the hazard for the composite outcome was not the same across all 4 distance quartiles; see Figures 1 and 2). Specifically, there was an increased hazard for the composite outcome in the group living farthest from care compared with the group living closest. For the comparison between usual ACC and PST groups within each distance quartile, the only statistically significant difference found was for the second closest distance group (Table 3). The interaction term between distance quartile and treatment group using the Cox proportional hazards regression model did not reach statistical significance (*P* = .07).

Sensitivity Analyses

We also divided distance to care into deciles rather than quartiles to ensure that patients living great distances from care (≥38 miles in the farthest decile) did not show

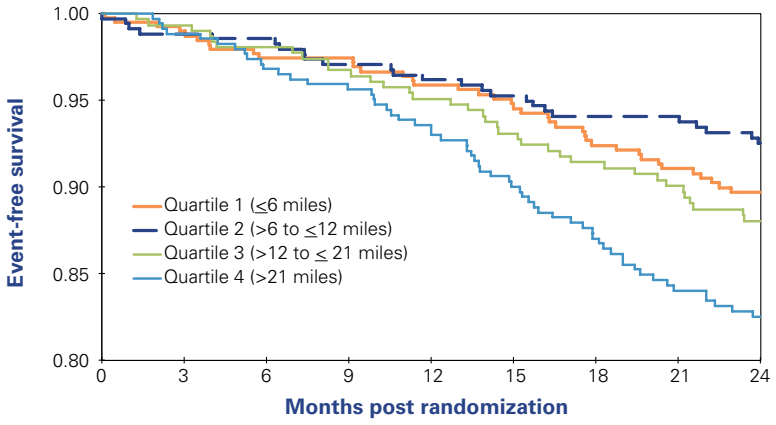
effects that were obscured within larger groups. Findings were similar to those seen with distance quartiles and are not shown.

DISCUSSION

Patient self-testing has some proven benefits for patients, particularly in terms of improved anticoagulation control and improved satisfaction with care.[17] However, PST is costly and it would be logical to think that selectively providing it to patients living farther from the ACC could target a smaller group who are more likely to benefit. In this study, we examined this logical, but unproven, supposition. We had expected to find that among the usual ACC group—who did not receive PST—patients living farther from care would have less frequent INR testing because patients would tend to resist suggestions to follow up sooner. Consequently, we also expected to find that patients living farther from the ACC would have worse TTR as a result of testing their INR less frequently than recommended.[19] However, we found no empirical evidence to support any step in our hypothesized causal pathway; namely, that patients living father from care would have decreased frequency of INR testing, leading to poor anticoagulation control[19] and thus to an increased incidence of adverse events.[5]

Based on our findings with regard to test frequency, TTR, and the primary combined clinical end point, it would not be possible to argue that limiting PST to patients living farther from the ACC would enhance its cost-effectiveness. Somewhat surprisingly, we also did not find that patients living farther from the ACC had lower anticoagulation-specific HRQoL under usual ACC care, nor

Figure 1. Time to First Adjudicated Primary Outcome Within 2 Years Post Randomization by Distance Quartile From VHA ACC for Usual ACC Patients

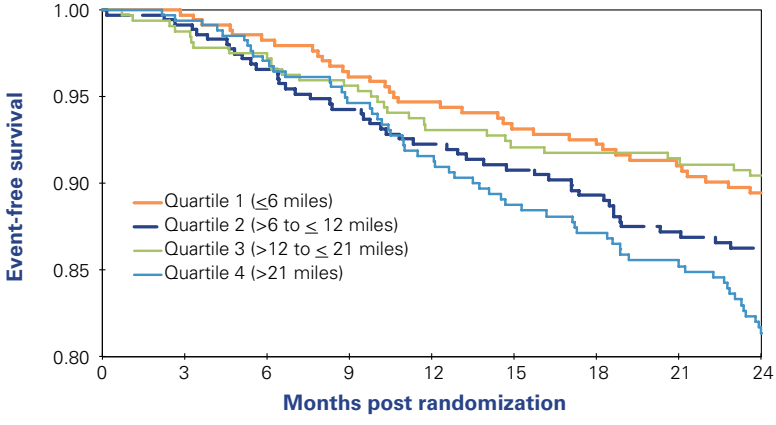


Number at risk:									
Quartile 1	391	387	379	375	364	356	343	337	319
Quartile 2	345	340	335	327	321	317	312	309	295
Quartile 3	311	306	300	293	286	280	273	267	253
Quartile 4	348	342	332	325	315	304	290	278	264

Log-rank = 4.09 *P* value = .0008 Total events = 159
Quartile 2 HR (95% CI) relative to Quartile 1 = 0.72 (0.44-1.19)
Quartile 3 HR (95% CI) relative to Quartile 1 = 1.17 (0.75-1.84)
Quartile 4 HR (95% CI) relative to Quartile 1 = 1.77 (1.18-2.64)

ACC indicates anticoagulation clinic; HR, hazard ratio; VHA, Veterans Health Administration.

Figure 2. Time to First Adjudicated Primary Outcome Within 2 Years Post Randomization by Distance Quartile From VHA ACC for PST Patients



Number at risk:									
Quartile 1	343	342	331	322	314	308	299	291	277
Quartile 2	353	350	337	326	315	308	297	282	267
Quartile 3	324	320	312	302	285	281	275	273	265
Quartile 4	340	338	326	310	294	282	274	265	249

Log-rank = 3.53 *P* value = .0059 Total events = 172
Quartile 2 HR (95% CI) relative to Quartile 1 = 1.34 (0.87-2.08)
Quartile 3 HR (95% CI) relative to Quartile 1 = 0.92 (0.57-1.50)
Quartile 4 HR (95% CI) relative to Quartile 1 = 1.81 (1.19-2.75)

ACC indicates anticoagulation clinic; HR, hazard ratio; PST, patient self-testing; VHA, Veterans Health Administration.

Table 3. Effect of Group Assignment (PST or Usual ACC care) on Time to First Event,[a] by Distance Quartile

	Usual ACC Group		PST Group			
	Patients at Risk, n	With Adverse Event, n (%)	Patients At Risk, n	With Adverse Event, n (%)	HR[b] (95% CI)	*P*
Shortest	343	35 (10%)	391	39 (10%)	0.97 (0.61-1.53)	.89
Shorter	353	47 (13%)	345	25 (7%)	0.52 (0.32-0.85)	.007
Longer	324	30 (9%)	311	36 (12%)	1.23 (0.76-2.00)	.40
Longest	340	60 (18%)	348	59 (17%)	0.94 (0.65-1.34)	.72

ACC indicates anticoagulation clinic; HR, hazard ratio; PST, patient self-testing.
[a]Stroke, major hemorrhage, or death.
[b]Hazard ratio compares PST group with usual ACC group within each distance quartile; a hazard ratio less than 1 means that there were fewer events in the PST group.

did we find that PST had a particular benefit for HRQoL among such patients. Therefore, we also cannot argue for selective use of PST with patients living farther from care based on considerations of patient satisfaction or HRQoL.

Perhaps our most striking finding was that patients living farther from the nearest VHA site of care had higher rates of the combined primary clinical end point of stroke, major hemorrhage, or death—a finding observed in both the PST and the usual ACC groups. Clearly, distance from care is important, but was not operating as we had anticipated. Little has been written about the impact of distance to care for patients receiving warfarin; the one study of which we are aware showed that patients living farthest from care had a small decrement in TTR (approximately 1%), but only during the first 6 months of warfarin therapy.[26] A difference of this magnitude is unlikely to explain a meaningfully higher rate of adverse events.

The findings of the present study appear to be novel and deserving of further investigation. Although this finding remains to be replicated in a second study, a dose-response gradient—as was seen here with distance to care—argues fairly strongly that the finding is real and not merely an artifact. The mechanism of this finding is not immediately clear, although one possibility is that patients living farther from the nearest hospital may have some degree of hesitancy in seeking emergency or inpatient care,[27] possibly delaying the onset of treatment when serious adverse events occur.

Strengths and Limitations

Our study has considerable strengths. In particular, nesting this analysis within the setting of a well-conducted randomized trial ensures a balance of both measured and unmeasured confounders. In addition, the ascertainment of adverse events was extremely rigorous. However, our study also has some noteworthy limitations, such as our use of driving distance as a proxy for the burden of transportation to the ACC, because driving distance may not always reflect actual travel time, although studies have shown that they are highly correlated.[28] Nevertheless, for urban patients, driving distance may fail to capture added travel time associated with using public transportation.[11] In addition, VHA patients are overwhelmingly male and mostly Caucasian, which may impact generalizability to the general population.

CONCLUSIONS

We did not find any evidence that patients living farther from the ACC receive a disproportionate benefit from PST in terms of satisfaction with anticoagulation care, anticoagulation control, or preventing adverse events. Therefore, our study does not support the notion that limiting PST to patients living farther from care would enhance its cost-effectiveness.

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eAppendix Table 1. Effect of Intervention on Proportion Reporting Satisfaction With Anticoagulation Care, Overall and by Distance From Care

	Usual ACC Group	**PST Group**
	(n = 900), %	**(n = 1077), %**
All Patients	249/900, 28%	340/1077, 32%
Shortest (≤6 miles)	56/233, 24%	104/302, 34%
Shorter (>6 to ≤12 miles)	69/226, 31%	89/276, 32%
Longer (>12 to ≤21 miles)	63/227, 28%	83/236, 35%
Longest (>21 miles)	61/214, 29%	64/263, 24%
P value, test for linear trend across quartiles	.41	.028

ACC indicates anticoagulation clinic; PST, patient self-testing.
Test of interaction between distance quartile and group (3 degrees of freedom) from logistic regression: $P = .06$.

eAppendix Table 2. Effect of Distance From Care on Time to First Event,[a] by Intervention

	Usual ACC Group	**PST Group**
HR (95% CI)		
Shorter relative to shortest distance quartile	1.34 (0.87-2.08)	0.72 (0.44-1.19)
Longer relative to shortest	0.92 (0.57, 1.50)	1.17 (0.75-1.84)
Longest relative to shortest	1.81 (1.19-2.75)	1.77 (1.18-2.64)
P value comparing distance quartiles[b]	.006	.001

ACC indicates anticoagulation clinic; HR, hazard ratio; PST, patient self-testing.
[a]Stroke, major hemorrhage, or death.
[b]A statistically significant result rejects the null hypothesis that the hazard is the same across all 4 quartiles.
Test of interaction between distance quartile and group (3 degrees of freedom) from Cox proportional hazards regression: $P = .07$.