

Ethnic Variability in Warfarin Maintenance in the Community Setting: A Population-Based Study in a Managed Care Environment in Israel

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Abstract

Background: Ethnicity has been associated with variance in warfarin treatment regimens in various settings.

Objectives: To determine whether ethnicity is associated with variance in patient management in Israel.

Methods: Data were extracted from the electronic patient records of Clalit Health Services clinics in the Sharon Shomron region. The study group comprised all patients treated with warfarin who performed international normalized ratio tests for at least 6 months in 2003. The proportion of tests of each patient within the target range was calculated, as was the crude average rates and 95% confidence intervals for Jewish and Arab patients. The data were then stratified by patient's gender and age, specialty of the attending physician, and the country where the physician studied medicine.

Results: We identified 2749 Jews and 293 Arabs who met the inclusion criteria of the study. The crude average rate of patients' INR tests within the target range was 62.3% among Jews (95% CI 61.5–63.1) and 52.7% (95% CI 49.9–55.5) among Arabs. When stratified by gender, age, and the treating physician's specialty and country of education, the stratum-specific rates among Jewish patients were consistently higher than among Arabs.

Conclusions: These results suggest that cultural differences regarding adherence to recommendations for drug therapy in addition to genetic factors may be associated with this variance.

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international normalized ratio laboratory testing to determine clotting time is required for patients treated with this drug [4,5]. Accordingly, in order to achieve an optimal therapeutic outcome and to avoid the drug-induced morbidity that elevated doses may cause, proper monitoring of warfarin therapy is essential for maintaining patients within the therapeutic range.

When treating with warfarin, a single, indication-specific, target INR value should be used as an endpoint [6]. Current guidelines for oral anticoagulant therapy recommend a target INR of 2.5 (range 2.0–3.0) for most indications except for some types of mechanical prosthetic heart valves or for the prevention of recurrent myocardial infarction for which the recommended target INR is 3.0 (range 2.5–3.5) [3,7]. Despite the hazards associated with non-adherence to these recommendations, it has been reported that INR values in some patients were within the recommended target range less than 50% of the time [8]. Furthermore, recent studies have reported ethnic variation in dose requirements for warfarin maintenance [9,10] and an association between warfarin sensitivity and gene variants [11,12] in a number of different clinical settings. The purpose of this study was to evaluate the distribution of the proportions of individual warfarin-treated patients' INR values within the therapeutic range in the Israeli community setting and to determine whether ethnicity is associated with suboptimal patient maintenance in this population.

Patients and Methods

This study was conducted in the Sharon Shomron region of the Clalit Health Services, the largest of the four health management organizations in Israel, providing coverage to over 3.5 million members nationwide including approximately 535,000 members in the region studied (70.6% Jews and 29.4% Arabs). This region, which is located in the center of Israel in proximity to many of the country's major medical centers, provides treatment to all patients at full-service clinics located in their communities. This setting was therefore chosen for analysis since it provided a setting without the confounding factors related to disparities in access to care that we wished to avoid. All patients receiving warfarin during the 12 month period, January to December 2003, were identified from electronic patient records and dispensed prescription data using the in-house data processing program

Thrombosis is a major cause of death and disability due to the obstruction of arteries, leading to myocardial infarction, stroke and peripheral ischemia, or the occlusion of veins causing deep vein thrombosis and pulmonary embolism [1]. In order to prevent thrombotic episodes, particularly stroke, patients at risk are often treated with an oral anticoagulant agent such as sodium warfarin, which reduces the risk of thrombosis by interfering with the hemostatic pathways [2]. However, since the major side effect of this class of drugs is bleeding, either from supratherapeutic effect or by accentuating the blood loss in patients with an existing source of bleeding, oral anticoagulants must be used with great caution [3]. Furthermore, since warfarin has a narrow therapeutic-toxic index with high inter-individual variability, frequent

INR = international normalized ratio

CI = confidence interval

“Business Object.” In addition to the drug utilization data, the program provided data for all patients included in the study, including age, gender, ethnicity (Arabs or Jews), location of clinic, laboratory tests, hospitalization and mortality. Physician data included age, gender, specialty, and country in which he/she attended medical school. All relevant data on patients receiving warfarin were integrated into a data file. Data collection and processing were conducted according to the data security and patient privacy requirements of the region of the HMO in which the study was conducted. For each patient the total number of months throughout 2003 in which INR tests were performed, the aggregate number of tests, and the number of these tests whose results were within the target range of 2.0–3.5 were calculated. In order to exclude patients receiving sporadic therapy and to avoid confounding factors such as lack of adherence to laboratory test requirements, the study was limited to patients for whom an INR test was recorded for at least 6 months within the study period. The proportion of tests in each patient that were within the target range was calculated. The crude average rates and 95% confidence intervals were calculated for the Jewish and Arab populations as well as the distribution of the individual proportions of tests within range for both subpopulations. The data were then stratified by patient’s age and gender, specialty of attending physician, and the country where the physician attended medical school. The stratum-specific data were compared between the two relevant ethnicities (Jew or Arab). The proportion of sub-therapeutic vs. supra-therapeutic test results found to be outside of the target range was calculated for both subpopulations. Furthermore, a subset analysis of both Jewish and Arab patients for whom INR tests were recorded during each of the 12 months of the study period was then performed in order to validate the findings from the initial larger population studied and to diminish possible biases caused by variance in frequency of test performance in the two groups.

Results

During the 12 month study period 2749 Jews and 293 Arabs who met the inclusion criteria of the study were identified. The patient characteristics of the two subpopulations are presented in Table 1. Among Jewish patients, the largest age group (79.4%) was above 65, whereas among Arabs this age group accounted for only 38.9% of the population, with the largest group being 46–65 years old (40.3%) compared to 18.4% among Jews ($P < 0.001$). Differences in the distributions of specialties and of countries where the attending physicians studied were also noted. Variance in the gender distribution of the two subpopulations was not found to be significant.

The case distributions of rates of patients’ tests within target range for both subpopulations are presented in Figures 1 and 2. The crude average rate of patients’ INR tests within the target range was 62.3% among Jews (95% CI 61.5–63.1) versus 52.7% (95% CI 49.9–55.5) among Arabs. In univariate analysis, variances were not significant with regard to patient’s gender, specialty

Table 1. Patient characteristics

| | Jewish (n=2749) | Arab (n=293) | P |
|--|--------------------|-----------------|---------|
| Gender | | | |
| Male | 1349 (49.1) | 133 (45.4) | 0.243 |
| Female | 1400 (50.9) | 160 (54.6) | |
| Physician specialty (by patient) | | | |
| Non-specialists + other | 1162 (42.3) | 191 (65.2) | < 0.001 |
| Internist | 231 (8.4) | 15 (6.1) | |
| Family | 1356 (49.3) | 87 (29.7) | |
| Patient age (yrs) | | | |
| 0–18 | 2 (0.1) | 3 (1.0) | < 0.001 |
| 19–45 | 60 (2.2) | 58 (19.8) | |
| 46–65 | 505 (18.4) | 118 (40.3) | |
| > 65 | 2182 (79.4) | 114 (38.9) | |
| Physician’s country of education (by patient) | | | |
| Other + unknown | 460 (16.7) | 43 (14.7) | < 0.001 |
| East Europe | 965 (35.1) | 81 (27.6) | |
| West Europe, South Africa, USA, Canada | 506 (18.4) | 154 (52.6) | |
| South America | 153 (5.6) | 0 | |
| Israel | 665 (22.4) | 15 (5.1) | |

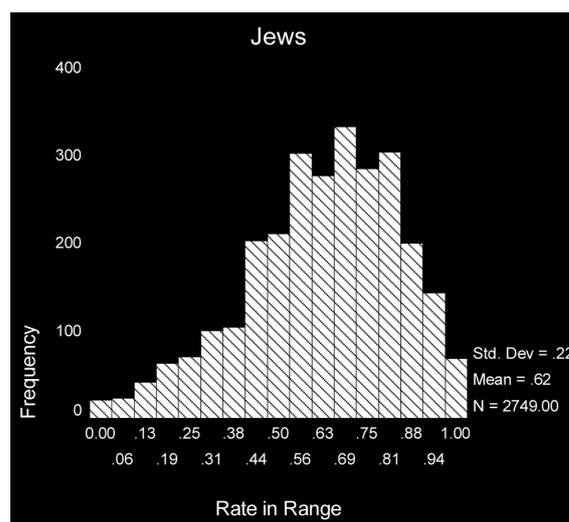


Figure 1. Distribution of rate of INR tests of Jewish patients within target range

of attending physician, patient’s age category, and the country where the attending physician studied. In the stratified analysis with these variables, the rates observed among Jewish patients were consistently higher than those among Arabs of the parallel substratum [Table 2]. The test results that were out of the therapeutic range were predominately in the sub-therapeutic range of INR < 2.0 (72.5% and 73.5% among Jewish and Arab patients respectively). In the subset analysis, 922 Jewish and 61 Arab patients who performed tests at least once during the 12 months of the study were identified. The average rate was 67.1%

HMO = health management organization

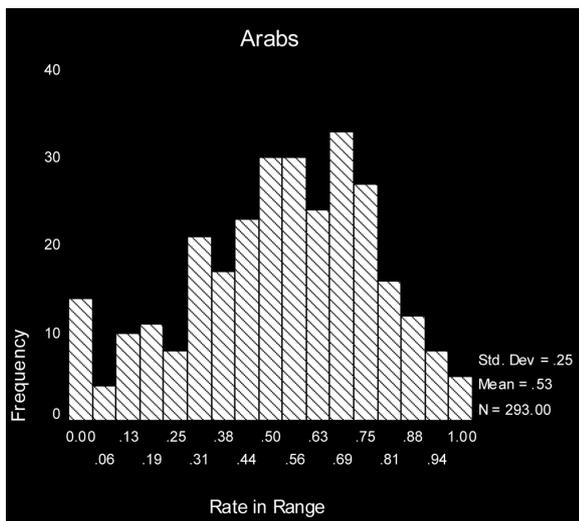


Figure 2. Distribution of rate of INR tests of Arab patients within target range

Table 2. Average rate of tests within range

| | Average rate in range (95% CI) | |
|--|--------------------------------|------------------|
| | Jewish | Arab |
| Gender | | |
| Male | 63.4 (62.3–64.5) | 53.7 (49.6–57.9) |
| Female | 61.2 (60.0–62.3) | 51.8 (47.9–55.7) |
| Physician specialty | | |
| Non-specialists + other | 61.7 (60.4–62.9) | 51.3 (47.8–54.8) |
| Internist | 61.3 (58.5–64.1) | 53.0 (37.7–68.3) |
| Family | 63 (61.8–64.1) | 55.6 (50.4–60.8) |
| Patient age (yrs) | | |
| 0–18 | – | – |
| 19–45 | 56.5 (50.5–62.5) | 51.6 (44.8–58.4) |
| 46–65 | 62.3 (61.0–64.8) | 51.4 (47.1–55.7) |
| > 65 | 62.3 (61.4–63.2) | 54.4 (49.8–59) |
| Physician's country of education (by patient) | | |
| Other + unknown | 62.4 (60.6–64.3) | 52.7 (44.7–60.8) |
| East Europe | 60.2 (58.7–61.6) | 50.0 (44.1–55.9) |
| West Europe, South Africa, USA, Canada | 64.3 (62.4–66.1) | 53.7 (49.9–57.4) |
| South America | 62.9 (59.3–66.4) | – |
| Israel | 63.5 (62–65.1) | 56.9 (45.3–68.6) |
| Crude | 62.3 (61.5–63.1) | 52.7 (49.9–55.5) |

(95% CI 66–68.3) for Jewish patients and 55.7% (95% CI 49.4–61.8) for Arabs.

Discussion

Since its discovery in the 1920s by researchers working under the sponsorship of the Wisconsin Alumni Research Fund (hence the name “warfarin”), its initial use in the 1940s as rat poison and then a decade later as a therapeutic anticoagulant agent

[13], this highly potent substance has persistently intrigued researchers and clinicians alike. Although indisputably recognized as a life-saving drug, the high inter-individual variance observed with warfarin therapy coupled with its narrow therapeutic index present a major clinical challenge to ensure that its use is safe and effective. Recently, after concentrating on possible behavioral and physiologic factors such as diet, gender and smoking to explain this inter-individual variance, researchers have redirected their focus to ethnic-genetic variances which may elucidate this phenomenon. It is within this context that the results of this study are significant.

The approximate 10% inferiority in management rates among Arab as compared to Jewish patients was observed in all but one of the substrata analyzed. Initially, we postulated that the higher prevalence of smoking among Israeli Arabs may partially explain these results. However, the inferior management rates observed among Arab women as compared to Jewish women weaken this explanation since the prevalence of smoking in the former is relatively low [14]. We also ruled out variances that may be associated with the profile of attending physicians since these factors were not found to be contributory in univariate analysis, nor were significant differences detected in the stratified data. Furthermore, this study was conducted in a managed care setting that provides coverage to a large multicultural population in the center of Israel in proximity to many of the country's major medical centers. All patients were treated in full-service clinics in their communities by physicians and dispensing pharmacists fluent in their mother languages. Accordingly, all patients studied, regardless of their ethnic background, had equal access to modern western medical care provided in a familiar community setting where there was no language barrier between patient and caregiver. We therefore rule out disparities often observed between rural and urban populations as being relevant to these findings. The ethnic disparity in the subset analysis of patients who performed INR tests on a monthly basis for 12 consecutive months verifies this assumption since these patients obviously had access to care on a regular basis. However, possible variance in test frequency between the two populations was a factor we could not investigate due to limitations in data availability. Additionally, since we relied on HMO electronic data sources, we were able to study the population as a whole without having to rely on sampling techniques which may bias results. This study therefore demonstrates the potential of the available data sources in managed care settings to monitor quality of care and patient outcomes in the populations they serve. Furthermore, these data capabilities should facilitate future interventions that may require cooperation with the individual prescribing physicians who will receive audits of their patients' progress in reaching therapeutic goals.

A factor that may have contributed to these results is that during 2003, warfarin tablets were available in Israel in 5 mg strength only. Consequently, dose titration was only possible through the breaking of tablets. The inferior outcomes observed among Arab patients may have been the result of lower adher-

ence to instructions for breaking tablets to achieve the required dose. This factor constitutes a limitation of this study. Eligible patients were identified through pharmacy claims data, which do not include the daily regimen that often involves ingestion of fractions of tablets. Due to this limitation, comparing the distribution of daily doses between the two populations was unfeasible. With the subsequent introduction of 1, 2, and 2.5 mg tablets into the Israeli market, it is expected that physicians, patients and pharmacists will achieve dosage precision with these new products.

Additionally, observed differences in polymorphisms of enzymes responsible for the metabolism of certain drugs in various Israeli ethnic groups, including the Bedouin [15], suggest that warfarin metabolism may differ between Arabs and Jews. However, the limitations posed by the retrospective design of this study preclude the testing of this hypothesis. Likewise, since this study did not include analyses of polymorphisms, we cannot rule out that the variance observed may be attributable to inferior patient adherence in the Arab population. With the recent increase in the migration from Arab countries to other parts of the world, these findings may be relevant to other clinical settings internationally.

Conclusions

Arab patients were less likely than Jews in this setting to reach target INR endpoints. Cultural differences regarding adherence to recommendations for drug therapy may explain part of these results. Future research is needed to verify whether polymorphisms of liver enzymes may have contributed to these findings. This study therefore illustrates that healthcare systems and providers that serve multiethnic populations should be cognizant of potential ethnic variance in patient response to drug therapy. Furthermore, this study demonstrates the potential value of electronic patient records in monitoring drug therapy precision in large and diverse populations in the community setting.

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