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Discontinuation of Warfarin Therapy for Patients With Atrial Fibrillation: The Michigan Anticoagulation Quality Improvement Initiative Experience.

Geoffrey D. Barnes

Scott Kaatz
Henry Ford Health, skaatz1@hfhs.org

Alexis Lopez

Xiaokui Gu

Jay Kozlowski

See next page for additional authors

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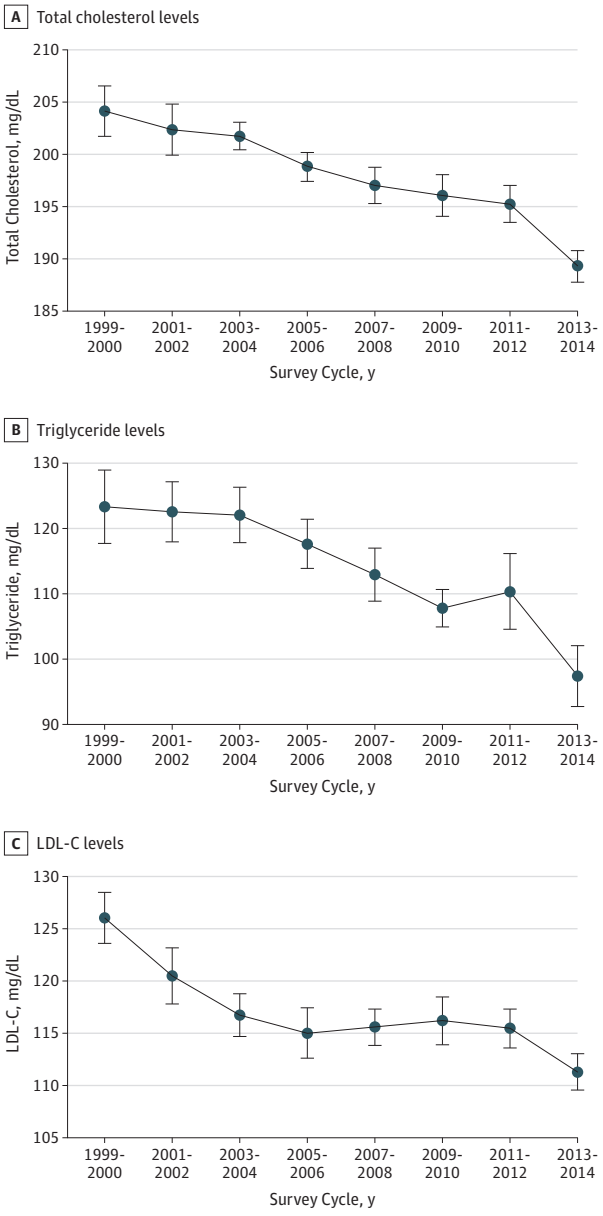
Figure. Age-Adjusted Total Cholesterol, Triglyceride, and Low-Density Lipoprotein Cholesterol (LDL-C) Trends for US Adults Aged 20 Years and Older, 1999 to 2014



A, Predicted total cholesterol levels and 95% confidence intervals in a sample size of 39 049. B, Predicted log-transformed triglyceride levels and 95% confidence intervals; log-transformed values were exponentiated after the regression, sample size of 17 406. C, Predicted LDL-C levels and 95% confidence intervals in a sample size of 17 096. Figure generated using marginal standardization from age-adjusted linear regression models. Data source: Centers for Disease Control and Prevention/National Center for Health Statistics, the National Health and Nutrition Examination Survey.

SI conversion factors: To convert LDL-C to micromoles per liter, multiply by 0.0259; to convert total cholesterol to micromoles per liter, multiply by 0.0259; to convert triglycerides to micromoles per liter, multiply by 0.0113.

Author Contributions: Dr Rosinger had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Rosinger, Carroll, Ogden.
Acquisition, analysis, or interpretation of data: Rosinger, Lacher, Ogden.
Drafting of the manuscript: Rosinger, Carroll.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Rosinger, Carroll.
Administrative, technical, or material support: Lacher.

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Center for Health Statistics, Centers for Disease Control and Prevention.

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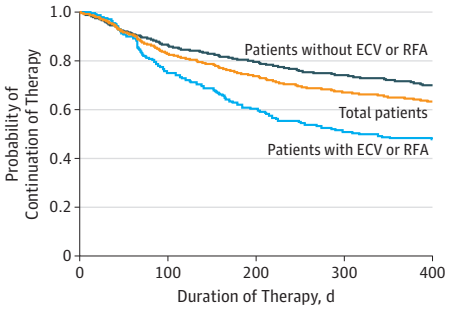
Discontinuation of Warfarin Therapy for Patients With Atrial Fibrillation: The Michigan Anticoagulation Quality Improvement Initiative Experience

The use of warfarin significantly reduces the risk of stroke among patients with atrial fibrillation (AF). Unfortunately, up to 60% of patients discontinue therapy within the first year.[1] Prior studies did not assess the quality of warfarin therapy or the occurrence of electrical cardioversion (ECV) or radiofrequency ablation (RFA) as predictors of discontinuation of warfarin therapy.

Methods | Within the Michigan Anticoagulation Quality Improvement Initiative, a 6-center Blue Cross Blue Shield of Michigan/Blue Care Network-sponsored collaborative of anticoagulation management services, we explored the discontinuation rate of warfarin therapy among a randomly sampled, diverse inception cohort of unselected patients with AF. Institutional review board approval was gained at all 6 Michigan Anticoagulation Quality Improvement Initiative sites, and informed consent was waived because the data was collected retrospectively. For each patient, we calculated the Rosendaal time in the therapeutic range and the Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus Stroke or Systemic Embolism, Vascular Disease, and Sex Characteristic (CHA_2DS_2-VASc) score for stroke risk.[2,3] The statistical significance for all *P* values was set at .05. We explored the predictive ability of these measures and the scheduling of an ECV or RFA based on discontinuation rates among patients enrolled in warfarin therapy from August 2011 to December 2013 and followed up through June 2015.

Figure. Kaplan-Meier Estimates for Discontinuation of Warfarin Therapy



No. at risk

Patients without ECV or RFA	516	440	404	376	350
Patients with ECV or RFA	218	159	125	105	97
Total patients	734	599	529	481	447

Kaplan-Meier curves for the discontinuation of warfarin therapy among patients with nonvalvular atrial fibrillation who did or did not undergo electrical cardioversion (ECV) or radiofrequency ablation (RFA). The estimated 1-year discontinuation rates are 51.2% for patients who underwent ECV or RFA and 27.8% for patients who did not.

Table. Unadjusted and Multivariable Predictors of Discontinuation of Warfarin Therapy Within 1 Year

Predictors	All Patients With AF HR (95% CI)	*P* Value
Unadjusted		
ECV or RFA planned	2.14 (1.68-2.72)	<.001
Male	1.42 (1.10-1.82)	.01
Diabetes	0.72 (0.54-0.96)	.03
Coronary artery disease	0.91 (0.70-1.19)	.50
Hypertension	0.63 (0.48-0.83)	<.001
Heart failure	0.97 (0.73-1.29)	.84
Chronic liver disease	1.13 (0.46-2.74)	.79
Chronic renal insufficiency	1.04 (0.72-1.50)	.85
Prior Stroke	0.47 (0.29-0.75)	.002
Heavy alcohol use	1.05 (0.66-1.69)	.83
Peripheral artery disease	0.98 (0.61-1.58)	.92
NSAID/antiplatelet use	1.19 (0.93-1.53)	.18
$CHADS_2$ risk group[a]	3.0 (2.14-4.20)	<.001
CHA_2DS_2-VASc risk[b]	3.99 (2.69-5.91)	<.001
HAS-BLED risk group[c]	2.51 (1.43-4.43)	.001
TTR, per 10% decrease	1.44 (1.32-1.56)	<.001
Multivariable		
ECV or RFA planned	1.86 (1.32-2.61)	<.001
CHA_2DS_2-VASc risk[b]	3.89 (2.05-7.36)	<.001
TTR, per 10% decrease	1.45 (1.33-1.58)	<.001

Abbreviations: AF, atrial fibrillation; CHA_2DS_2-VASc, Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus Stroke or Systemic Embolism, Vascular Disease, and Sex characteristic; ECV, electrical cardioversion; HAS-BLED, Hypertension, Abnormal Renal and Liver Function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or Alcohol; HR, hazard ratio; NSAID, nonsteroidal antiinflammatory drug; RFA, radiofrequency ablation; TTR, time in the therapeutic range.

[a] Low score (0) vs high score (2-6).

[b] Low score (0) vs high score (2-9).

[c] Low score (0) vs high score (3-7).

Results | Of the 734 patients initiating warfarin therapy for nonvalvular AF between August 2011 and December 2013, 270 (36.8%) discontinued therapy within 1 year of initiation (118 of 218 patients [54.1%] with ECV or RFA and 152 of 516 patients [29.5%] without ECV or RFA; $P < .001$). The Kaplan-Meier estimated probability that a patient would discontinue warfarin therapy within the first year was 34.8% and was greater for patients with ECV or RFA ($P < .001$) (**Figure**).

Patients who discontinued warfarin therapy within the first year were more likely than patients who continued therapy to have undergone ECV or RFA (43.7% vs 21.6%; $P < .001$), a lower CHA_2DS_2-VASc score (mean [SD] score, 3.0 [1.9] vs 3.7 [1.6]; $P < .001$), and a lower time in the therapeutic range in the first year (mean [SD], 51.2% [22.7%] vs 65.5% [15.2%]; $P < .001$). Race/ethnicity was not a statistically significant predictor of discontinuation of warfarin therapy. In the multivariable model (**Table**), predictors of discontinuation of warfarin therapy within the first year include having undergone ECV or RFA (hazard ratio, 1.86; 95% CI, 1.32-2.61), CHA_2DS_2-VASc risk group (hazard ratio, 3.89; 95% CI, 2.05-7.36 for low score [0] vs high score [2-9]), and low time in the therapeutic range (hazard ratio, 1.45; 95% CI, 1.33-1.58 for each 10% decrease).

Discussion | The association of ECV or RFA with discontinuation of warfarin therapy is an important consideration given the lack of consensus around long-term stroke risk following ECV or RFA. Guidelines suggest at least 4 to 8 weeks of anticoagulation following ECV but do not specify if stopping anticoagulation is appropriate after that initial period.[4] Conclusive data are needed regarding the efficacy of extended prophylaxis with warfarin beyond 4 to 8 weeks after a successful ECV or RFA.

Identifying poor-quality warfarin control as a predictor of discontinuation has important implications given the abundance of alternative therapies. For some clinicians, poor warfarin therapy control indicates a need to change anticoagulant therapy. While it may seem appealing to use a direct oral anticoagulant for patients with poorly controlled warfarin therapy, there are many situations in which switching is not recommended. Early reports indicate that patients with AF prescribed direct-acting oral anticoagulants for stroke prevention have rates of discontinuation similar to those of warfarin-treated patients.[5]

The strengths of this analysis include using an unselected inception cohort of warfarin-treated patients at 6 health centers and medical record-abstracted data instead of billing codes for analysis. Our study's limitations include the potential for unmeasured confounders in observational studies, the inability to characterize index AF diagnoses (eg, postoperative and paroxysmal), and the single-state location of all of the clinics.

Despite these limitations, our study demonstrates a high rate of discontinuation of warfarin therapy within the first year, especially among patients undergoing ECV or RFA. This suggests a need to better define which patients with AF undergoing ECV or RFA should continue anticoagulation. Additionally, we identified poor-quality warfarin care as a strong predictor of medication discontinuation, without transition to another oral anticoagulant. Further efforts are needed to increase the use and

persistence of anticoagulation therapy among patients with nonvalvular AF and to understand the implications of ECV or RFA as an indication for anticoagulation therapy.

Geoffrey D. Barnes, MD, MSc
Scott Kaatz, DO, MSc
Alexis Lopez, MD
Xiaokui Gu, MD, MA
Jay Kozlowski, MD
Gregory D. Krol, MD
James B. Froehlich, MD, MPH

Author Affiliations: Frankel Cardiovascular Center, University of Michigan Health System, Ann Arbor (Barnes, Lopez, Gu, Froehlich); Henry Ford Hospital, Detroit, Michigan (Kaatz, Krol); Huron Valley Sinai-Cardiology and Vascular Associates, Commerce Township, Michigan (Kozlowski).

Corresponding Author: Geoffrey D. Barnes, MD, MSc, Frankel Cardiovascular Center, University of Michigan Medical Health System, 2800 Plymouth Rd, Bldg 14, Room G101, Ann Arbor, MI 48109-2800 (gbarnes@umich.edu).

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COMMENT & RESPONSE

Atrial Fibrillation and Cancer—Validation in the Real World

To the Editor We read with interest the article by Conen et al[1] published in the April issue of *JAMA Cardiology*. In an analysis of the Women's Health Study, the authors found an association between incident atrial fibrillation (AF) and cancer. While the study cohort was large, the incidences of AF and cancer were low, placing the findings at risk of a type II error. In addition, this association was not generalizable to men. Therefore, we sought to validate these findings in a larger real-world cohort among both sexes.

Using the Explorys platform,[2] an aggregated electronic database spanning inpatient and outpatient records from 26 major integrated health care systems across the United States, we identified 11 207 890 women and 9 003 530 men with characteristics similar to the population in the study by Conen et al[1] (ie, 45 years or older and free of major cardiovascular disease and cancer at baseline). These cohorts were examined for new-onset AF or cancer between June 2011 and May 2016 and analyzed using logistic regression.

There were 388 270 and 833 520 patients with incident AF and cancer, respectively. The crude incidence of AF was 0.31% per year for women and 0.42% per year for men, similar to the 0.22% reported by Conen et al.[1] Among those with new-onset AF, the age-adjusted odds ratio (age-OR) for incident cancer was 1.66 (95% CI, 1.62-1.71) for women and 1.66 (95% CI, 1.62-1.70) for men, comparable with the age-adjusted hazard ratio of 1.58 (95% CI, 1.34-1.87) reported by Conen et al.[1] The risk of incident cancer following new-onset AF was highest during the first year (women: age-OR, 2.58; 95% CI, 2.50-2.66; men: age-OR, 2.58; 95% CI, 2.51-2.65) and returned to baseline risk by the following year, in accordance with the findings by Conen et al.[1]

For patients with new cancer, we observed an annual incidence of 0.78% per year in women and 0.85% per year in men, consistent with the 0.77% per year rate reported by Conen et al.[1] Among those with new cancer, the risk of incident AF was highest during the first year (women: age-OR, 4.46; 95% CI, 4.35-4.58; men: age-OR, 4.37; 95% CI, 4.27-4.47), which was comparable with the age-adjusted hazard ratio of 4.67 (95% CI, 2.85-7.64) during the first 3 months reported by Conen et al[1]. Finally, we confirmed that the risk of incident AF in those with new cancer was persistently elevated beyond 1 year (women: age-OR, 1.30; 95% CI, 1.25-1.36; men: age-OR, 1.22; 95% CI, 1.17-1.27), a finding not statistically significant in the study by Conen et al.[1]

Thus, we validate the association between AF and cancer among women and men in a real-world cohort more than 500-fold larger than that used by Conen et al.[1] Further studies are needed to better delineate and validate these findings in a prospective manner.

Chang H. Kim, MD
Sadeer G. Al-Kindi, MD
Guilherme H. Oliveira, MD

Author Affiliations: Department of Medicine, University Hospitals Cleveland Medical Center, Cleveland, Ohio (Kim, Al-Kindi, Oliveira); School of Medicine, Case Western Reserve University, Cleveland, Ohio (Kim, Al-Kindi, Oliveira); Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, Cleveland, Ohio (Al-Kindi, Oliveira).

Corresponding Author: Guilherme H. Oliveira, MD, Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, 11100 Euclid Ave, Lakeside 3012, Cleveland, OH 44106 (guilherme.oliveira@uhhospitals.org).