Journal of the American Heart Association

BRIEF COMMUNICATION

Association Between Omega-3 Fatty Acid Levels and Risk for Incident Major Bleeding Events and Atrial Fibrillation: MESA

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BACKGROUND: Randomized trials of pharmacologic strength omega-3 fatty acid (n3-FA)–based therapies suggest a dose-dependent cardiovascular benefit. Whether blood n3-FA levels also mediate safety signals observed in these trials, such as increased bleeding and atrial fibrillation (AF), remains uncertain. We hypothesized that higher baseline n3-FA levels would be associated with incident bleeding and AF events in MESA (Multi-Ethnic Study of Atherosclerosis), which included a population free of clinical cardiovascular disease at baseline.

METHODS AND RESULTS: We examined the association between baseline plasma n3-FA levels (expressed as percent mass of total fatty acid) with incident bleeding and AF in MESA, an ongoing prospective cohort study. Bleeding events were identified from review of hospitalization *International Classification of Diseases, Ninth Revision* (*ICD-9*), and *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes, and AF from participant report, discharge diagnoses, Medicare claims data, and study ECGs performed at MESA visit 5. Separate multivariable Cox proportional hazard modeling was used to estimate hazard ratios of the association of continuous n3-FA (log eicosapentaenoic acid [EPA], log docosahexaenoic acid [DHA], log [EPA+DHA]) and incident hospitalized bleeding events and AF. Among 6546 participants, the mean age was 62.1 years and 53% were women. For incident bleeding, consistent statistically significant associations with lower rates were seen with increasing levels of EPA and EPA+DHA in unadjusted and adjusted models including medications that modulate bleeding risk (aspirin, NSAIDS, corticosteroids, and proton pump inhibitors). For incident AF, a significant association with lower rates was seen with increasing levels of DHA, but not for EPA or EPA+DHA.

CONCLUSIONS: In MESA, higher plasma levels of n3-FA (EPA and EPA+DHA, but not DHA) were associated with significantly fewer hospitalized bleeding events, and higher DHA levels (but not EPA or EPA+DHA) with fewer incident AF events.

Key Words: arrhythmia ■ atrial fibrillation ■ bleeding ■ docosahexaenoic acid ■ eicosapentaenoic acid ■ omega-3

Recent randomized control trials of omega-3 fatty acid (n3-FA)–based therapies have heralded a new era of cardiovascular preventive therapeutics.[1,2] Their benefit notwithstanding, concerns surrounding excess bleeding and n3-FA intake date back to the original observations of Dyerberg and colleagues[3] of cardioprotection yet excess bleeding among Greenland Inuits with a high intake of marine-based polyunsaturated fatty acids (FAs). These observational data were later substantiated by in vitro analyses suggesting that n3-FA inhibits platelet function via competition with arachidonic acid for incorporation into membrane phospholipids and for conversion to eicosanoids by cyclooxygenase.[4] Further, analyses within the landmark REDUCE-IT (Reduction of Cardiovascular Events With Icosapent

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For Sources of Funding and Disclosures, see page 6.

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Ethyl Intervention Trial) have suggested that much of the cardiovascular benefit of an eicosapentaenoic acid (EPA) n3-FA–based therapy may be mediated by achieved on-treatment blood EPA levels, with a recent meta-analysis corroborating a dose-dependent cardiovascular benefit.[5] Whether blood levels also mediate the safety signals observed in REDUCE-IT and other randomized trials of n3-FA–based therapies, including increased bleeding and atrial fibrillation (AF), is incompletely understood. The association between blood levels of n3-FA and outcomes such as bleeding and AF is particularly relevant as nonprescription strength n3-FA supplements are widely used in the general population and because fish intake is a guideline-endorsed tenet of a heart-healthy diet.

We sought to study the relationship between baseline n3-FA levels from MESA (Multi-Ethnic Study of Atherosclerosis) and incident major bleeding and AF, to address unanswered questions regarding whether levels of n3-FA intake mediated by lifestyle, diet, or nonprescription supplementation may mirror safety signals observed in clinical trials using pharmacologic strength agents among high-risk individuals with established cardiovascular disease. We hypothesized that similar to the findings from randomized clinical trials, higher levels of n3-FA at baseline would be associated with more major bleeding and AF events.

METHODS

Study Design and Participants

MESA is a longitudinal cohort study of 6814 men and women free of clinical cardiovascular disease at baseline (between 2000 and 2002). Its design, population, and methods have been previously described.[6] Between July 2000 and July 2002, 6814 participants aged 45 to 84 years were recruited from 6 US communities. Participants self-identified with 1 of 4 racial/ethnic groups: Black (28%), White (38%), Hispanic (22%), and Chinese American (12%), and 53% of participants were women. MESA was approved by the institutional review boards of all participating study sites. All participants gave informed consent. The data that support the findings of this study are available from the parent study, MESA, upon reasonable request.

Plasma FA Measurements

Fasting blood was drawn and plasma and EDTA tubes were collected and processed at the first (baseline) study visit using a standardized protocol that has been previously described.[7] Baseline plasma measurements of n3-FA were available in 6546 participants (96.1%). Participants without measurements available from the baseline examination, those with chronic anticoagulation with warfarin, and those with a prior cardiovascular event were excluded from analysis (Figure). Plasma phospholipid n3-FA measurements (expressed as a percent mass of total FA), including those of EPA, docosahexaenoic acid (DHA), and their sum (EPA+DHA), were subject to natural log-transformation to improve normality.

Primary Outcome Measures—Hospitalized Bleeding and Incident AF Events

Major bleeding events were collected from hospitalization records using *International Classification of Diseases, Ninth Revision* (*ICD-9*), and *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes (from baseline examination through 2018). *ICD* codes spanning central nervous system, gastrointestinal, genitourinary, respiratory, and postprocedural bleeding events were captured.[8] Incident AF was identified from study ECGs, *ICD-9* discharge diagnoses, and among participants enrolled in fee-for-service Medicare and inpatient and outpatient AF claims data (from baseline examination through 2015). Among participants aged ≥55 years at baseline, 86% were

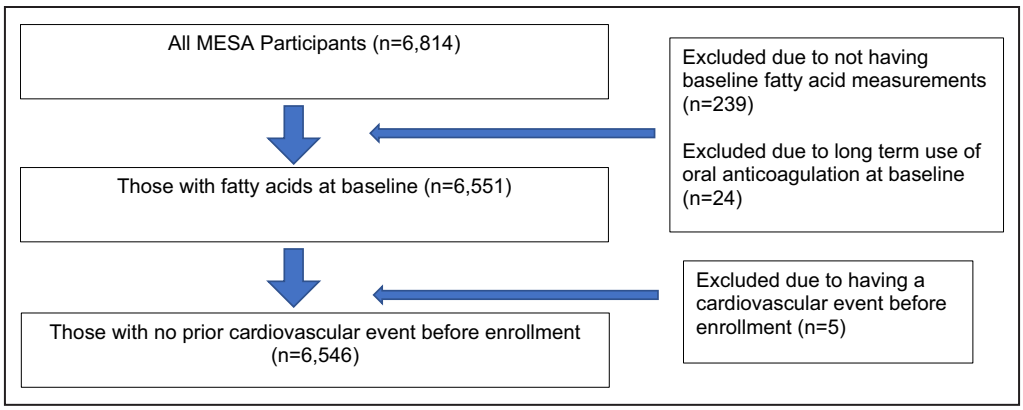

Figure. Derivation of cohort after application of exclusion criteria.
MESA indicates Multi-Ethnic Study of Atherosclerosis.

enrolled in fee-for-service Medicare at some point during follow-up. Follow-up consisted of phone calls or field center visits every 9 to 12 months to identify hospitalizations and medical records. ECGs in MESA were read at a centralized ECG reading center (Epidemiological Cardiology Research Center) at Wake Forest University. The time to AF was set as the time of study visit if AF was identified from a study ECG; otherwise, it was set as time of hospital or physician claim if identified through hospitalizations and medical records.

Statistical Analysis

Cox proportional hazard modeling was used to estimate hazard ratios (HRs) associated with continuous phospholipid FA on a log scale (independent variable) and incident hospitalized bleeding and AF events (dependent variable). Thus, the resultant HRs should be interpreted as corresponding to a 1-unit change in the natural log of percent plasma phospholipid n3-FA. We developed hazard models in blocks, first by including percent n3-FA (EPA, DHA, EPA+DHA) as univariate predictors; second, after adjustment for age, sex, race, study center, highest level of education, health insurance status, body mass index, diabetes mellitus status, systolic blood pressure, use of antihypertensive medications, smoking, estimated glomerular filtration rate, history of liver disease, and history of malignancy; and third, after adjustment for pharmacologic modulators of bleeding risk including self-reported use of aspirin (≥3 times weekly), NSAIDS, corticosteroids, or proton pump inhibitors. When considering incident AF as the outcome variable, hazard models were built similarly in blocks following the same stepwise adjustment, with the final model adjusting for age, sex, race, study center, highest level of education, health insurance status, body mass index, diabetes mellitus status, systolic blood pressure, use of antihypertensive medications, smoking, estimated glomerular filtration rate, heart rate, history of malignancy and self-report of moderate to vigorous exercise. Following conventional assumptions of Cox proportional hazard modeling, censoring was assumed to occur at random and independent of either outcome.

Exploratory analyses were performed considering incident malignancy and aspirin prescription (for bleeding outcome) and incident coronary heart disease (for AF outcome) as time-varying covariates. These variables were selected as a means to test the strength of any potential association baseline n3-FA and the outcomes of interest over time. Further, prespecified sensitivity analyses were performed adjusting for self-report of n3-FA supplementation at baseline. Finally, given mounting evidence regarding the pleiotropic noncardiovascular benefits of n3-FA on multiple health outcomes, and to address potential residual confounding (overall health bias), we tested the association between plasma n3-FA levels and the negative control outcome of incident hip fracture.[9] All statistical analyses were performed using STATA (version 14.2, StataCorp LLC).

RESULTS

The baseline characteristics of participants are shown in Table 1. The mean age of participants was 62.1±10.2 years, 53% were women, and 38.5% were of White, 27.5% were of Black, 22% were of Hispanic, and 12.1% were of Chinese American race/ethnicity. Median plasma n3-FA was 0.67% (interquartile range [IQR], 0.49–0.99) for EPA, 3.59% (IQR, 2.72–4.69) for DHA, and 4.26% (IQR, 3.28–5.64) for EPA+DHA. At baseline, 254 participants (4.1%) self-reported nonprescription-strength n3-FA supplementation, among whom median plasma EPA was 1.10% (IQR, 0.71–1.64), DHA was 4.40% (IQR, 3.61–5.78), and EPA+DHA was 5.66% (IQR, 4.47–7.22). In total, 225 (3.4%) patients experienced a hospitalized bleeding event and 936 (14.3%) patients had incident AF over a median of 14 years of follow-up. Further, over the same follow-up period, 687 (10.5%) patients developed incident malignancy, 2986 (47.8%) patients had a clinical indication for aspirin prescription ≥3 times per week, and 389 (5.9%) patients were diagnosed with incident coronary heart disease before experiencing either a major bleeding or AF event. Among participants experiencing a major bleeding event, the majority (37.8%) had coronary artery calcium 0, whereas among participants experiencing AF, the majority (45%) had coronary artery calcium ≥100.

A significantly reduced hazard of major bleeding was observed with higher plasma EPA and EPA+DHA, but not DHA, in both unadjusted and adjusted models (Table 2). In a prespecified sensitivity analysis adjusting for self-reported n3-FA supplementation at the baseline examination, EPA (HR, 0.69; CI, 0.53–0.91 [*P*=0.01]) and EPA+DHA (HR, 0.78; CI, 0.65–0.94 [*P*=0.01]) remained inversely associated with incident major bleeding, with no significant association observed with DHA (HR, 0.68; CI, 0.44–1.05 [*P*=0.08]). In an exploratory analysis adjusting for incident malignancy as a time-varying covariate, a similar reduction in bleeding was seen with higher plasma EPA (HR, 0.75; CI, 0.58–0.97 [*P*=0.03]) and EPA+DHA (HR, 0.81; CI 0.68–0.97 [*P*=0.02]), but not DHA alone (HR, 0.68; CI 0.45–1.04 [*P*=0.08]) (Table 3). There was no association between baseline n3-FA level and bleeding following adjustment for the development of a clinical indication for aspirin as a time-varying covariate (Table 3).

Table 1. Baseline Characteristics

	All (N=6546)	Hospitalized Bleeding Event at Follow-Up (n=225)	AF at Follow-Up (n=936)
Age, y	62.1±10.2	66.7±9.7	69.5±8.5
Sex, n (%)			
Women	3468 (53.0)	111 (49.3)	150 (43.0)
Men	3078 (47.0)	114 (50.7)	199 (57.0)
Race/ethnicity, n (%)			
White	2518 (38.5)	82 (36.4)	191 (54.7)
Chinese American	793 (12.1)	26 (11.6)	27 (7.7)
Black	1798 (27.5)	65 (28.9)	70 (20.1)
Hispanic	1437 (22.0)	52 (23.1)	61 (17.5)
Aspirin use (≥3 times per wk), n (%)	1248 (19.9)	52 (24.3)	116 (35.2)
Diabetes mellitus, n (%)	812 (12.4)	35 (15.6)	52 (14.9)
Smoking status, n (%)			
Never	3285 (50.3)	103 (45.8)	152 (43.8)
Former	2383 (36.5)	90 (40.0)	161 (46.4)
Current	857 (13.1)	32 (14.2)	34 (9.8)
Antihypertensive use, n (%)	2422 (37.0)	115 (51.1)	187 (53.7)
Alcohol use, n (%)	3607 (68.7)	122 (63.9)	193 (64.8)
NSAIDs, n (%)	1137 (17.4)	38 (16.9)	55 (15.8)
Nonprescription omega-3 supplements, n (%)	254 (4.1)	12 (5.7)	8 (2.5)
Corticosteroids, n (%)	98 (1.5)	7 (3.1)	12 (3.5)
Proton pump inhibitors, n (%)	405 (6.2)	21 (9.3)	29 (8.3)
CAC categories, n (%)			
CAC 0	3288 (50.2)	85 (37.8)	90 (25.8)
CAC 1–99	1738 (26.6)	61 (27.1)	102 (29.2)
CAC ≥100	1520 (23.2)	79 (35.1)	157 (45.0)
CAC ≥400	637 (9.7)	43 (19.1)	82 (23.5)
EPA (% mass), median [IQR]	0.67 [0.49–0.99]	0.61 [0.42, 0.97]	0.67 [0.47–0.99]
DHA (% mass), median [IQR]	3.59 [2.72–4.69]	3.39 [2.71–4.55]	3.53 [2.61–4.50]
EPA+DHA (% mass), median [IQR]	4.26 [3.27–5.64]	4.09 [3.30–5.37]	4.18 [3.17–5.48]

AF indicates atrial fibrillation; CAC, coronary artery calcium; CHD, coronary heart disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; and IQR, interquartile range.

Conversely, a significantly reduced hazard of incident AF was observed with higher plasma DHA (but not EPA or EPA+DHA) following adjustment for sociodemographic and AF risk factors (Table 2). Adjusting for self-reported n3-FA supplementation at the baseline examination, the association between DHA and AF was no longer statistically significant (HR, 0.83; CI, 0.68–1.03 [*P*=0.06]). In a similar exploratory analysis as performed with the outcome of major bleeding, after adjusting for incident coronary heart disease, a reduced hazard of incident AF was observed with higher baseline plasma DHA (HR, 0.80; CI, 0.65–0.98 [*P*=0.03]), but not with EPA or EPA+DHA (Table 3).

Finally, no association was observed between plasma n3-FA levels and the negative control of incident hip fracture in similarly adjusted models as for the primary outcome measures (data not shown).

DISCUSSION

Our results show that in a cohort of community-dwelling individuals without established cardiovascular disease, higher plasma concentrations of EPA and EPA+DHA (but not DHA) at baseline were associated with less incident major bleeding events over a median of 14 years of follow-up. This association persisted following adjustment for baseline use of nonpharmacologic n3-FA supplementation and incident malignancy (but not aspirin prescription) as time-varying covariates. The absence of an independent association between DHA and bleeding suggests that the observed association between EPA+DHA and this outcome was driven by EPA, and not an additive effect of EPA+DHA. Conversely, higher plasma levels of DHA (but not EPA or EPA+DHA) at baseline were associated with less

Table 2. HRs for Incident Hospitalized Bleeding and AF Events

	HR	Major Bleeding	
		CI	*P* Value
Log EPA			
Unadjusted	0.75	0.60–0.94	0.01
Model 1	0.74	0.58–0.94	0.02
Model 2	0.76	0.59–0.98	0.03
Model 3	0.75	0.53–0.91	0.01
Log DHA			
Unadjusted	0.79	0.57–1.10	0.17
Model 1	0.66	0.44–0.98	0.04
Model 2	0.72	0.48–1.08	0.12
Model 3	0.69	0.45–1.05	0.08
Log EPA+DHA			
Unadjusted	0.84	0.73–0.98	0.03
Model 1	0.80	0.68–0.95	0.01
Model 2	0.83	0.69–0.98	0.03
Model 3	0.82	0.68–0.97	0.03
		AF	
Log EPA			
Unadjusted	1.09	0.98–1.21	0.09
Model 1	0.98	0.87–1.09	0.70
Model 2	0.99	0.89–1.12	0.96
Log DHA			
Unadjusted	1.05	0.89–1.23	0.57
Model 1	0.78	0.64–0.95	0.01
Model 2	0.81	0.67–0.99	0.04
Log EPA+DHA			
Unadjusted	1.05	0.98–1.13	0.17
Model 1	0.95	0.88–1.03	0.20
Model 2	0.97	0.89–1.05	0.40

Models for bleeding include model 1: age, sex, race/ethnicity, and MESA (Multi-Ethnic Study of Atherosclerosis) site adjusted; model 2: model 1 plus education, insurance, body mass index (BMI), diabetes mellitus, systolic blood pressure (SBP), blood pressure (BP) medications, smoking status, estimated glomerular filtration rate (eGFR), history of cancer, and history of liver disease; model 3: model 2 plus aspirin, NSAIDS, oral steroids, or proton pump inhibitors. Models for atrial fibrillation (AF) include model 1: age, sex, race/ethnicity, and MESA site adjusted; and model 2: model 1 plus education, insurance, BMI, diabetes mellitus, SBP, BP medications, smoking status, eGFR, heart rate, history of cancer, and moderate to vigorous exercise. DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; and HR, hazard ratio.

incident AF following adjustment for age, sex, race, and other established AF risk factors. This association persisted following adjustment for incident coronary heart disease as a time-varying covariate, but not following adjustment for nonpharmacologic n3-FA supplementation at baseline.

The differential associations between EPA and DHA with bleeding and AF are of interest and may reflect intrinsic structural differences between the two. DHA has an additional double bond and 2 more carbons compared with EPA. These biophysical properties may impact the nature of their interactions with surrounding membrane lipids, with implications on lipid raft formation and downstream signal transduction pathways.[10] These, in turn, may impact their respective antithrombotic and membrane-stabilizing effects.[11] Our results are consistent with reports from CHS (Cardiovascular Health Study) demonstrating an inverse association between baked fish (containing higher relative concentrations of DHA versus EPA) and incident AF, as well as observational data from the surgical literature reporting that nonpharmacologic-strength n3-FA supplementation was not associated with an increased incidence of perioperative bleeding or abnormal coagulation parameters.[12] An important limitation of our study, however, is that neither bleeding nor AF events were prospectively adjudicated in MESA.

Overall, despite being consistent with prior observational studies, our results may be seen as conflicting with prior randomized studies of high-dose n3-FA supplementation. Excess bleeding has been reported in JELIS (Japan EPA Lipid Intervention Study) and REDUCE-IT, and excess AF in REDUCE-IT, STRENGTH (Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridemia), and the OMEMI (Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction) trial.[2,13,14] A direct comparison between the achieved blood levels among MESA participants and trial participants is limited by differing techniques used in their measurement. However, the blood concentrations among MESA participants are almost assuredly lower than those in clinical trials, given the significantly higher n3-FA concentrations in prescription formulations. Furthermore, the concentrations we report in MESA are consistent with those reported from other longitudinal community-based cohorts.[15] Thus, the discrepancy between our observational findings and those from the randomized trials likely relates to the low absolute plasma levels among MESA participants compared with the on-treatment levels of trial participants, as well as inherent differences in interpreting baseline n3-FA levels in healthy community-dwelling individuals versus high-risk patients enrolled in trials with an active n3-FA intervention. One rationale for our findings in the context of the clinical trial data is a potential J-shaped association, wherein a threshold of n3-FA concentrations exists beyond which the balance of antiaggregatory and antiarrhythmic properties shifts toward increased bleeding and arrhythmia.

There are several strengths to our study, foremost of which is that MESA is a unique study population

Table 3. HRs for Incident Hospitalized Bleeding and AF Events, With Incident Aspirin Prescription, Malignancy, and CHD Considered as Time-Varying Covariates

Major Bleeding						
	Aspirin Prescription*			Malignancy*		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Log EPA	0.81	0.63–1.04	0.11	0.75	0.58–0.97	0.03
Log DHA	0.79	0.52–1.21	0.28	0.68	0.45–1.04	0.08
Log (EPA+DHA)	0.86	0.72–1.03	0.12	0.81	0.68–0.97	0.02

AF			
	CHD*		
	HR	95% CI	*P* Value
Log EPA	0.99	0.88–1.12	0.96
Log DHA	0.80	0.65–0.98	0.03
Log (EPA+DHA)	0.96	0.88–1.04	0.39

CHD indicates coronary heart disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; and HR, hazard ratio.

*Aspirin prescription and malignancy considered as time-varying covariates for the primary outcome measures of either major bleeding or atrial fibrillation (AF).

for this particular analysis, given the large number of participants with baseline n3-FA measurements (>6000), in addition to other features such as ethnic diversity, long duration of follow-up, and contemporary medical therapy. Other important limitations to our study in addition to the lack of formally adjudicated end points include residual confounding that may persist beyond multivariate adjustment. To this end, the lack of significant association between baseline n3-FA level and the negative control of hip fracture suggests that our findings are likely specific to our outcome measures and not a reflection of pleiotropic benefit. Another limitation is that our findings lack generalizability to higher-risk populations who may not be receiving pharmacologic strength n3-FA supplementation but may still have augmented blood levels resulting from dietary or nonpharmacologic strength supplementation.

CONCLUSIONS

We report an inverse association in incident hospitalized bleeding events with higher baseline plasma levels of EPA and EPA+DHA, and in incident AF with higher baseline levels of DHA in a multiethnic population free of baseline cardiovascular disease. We hypothesize that a threshold of n3-FA concentrations exists, likely in the context of pharmacologic dosing, beyond which a predisposition toward increased bleeding and arrhythmia is incurred. As indications for n3-FA–based therapies continue to expand, future studies should focus on whether the dose-dependency of cardiovascular benefit is also manifested in safety signals such as bleeding and AF.

ARTICLE INFORMATION

Received February 27, 2021; accepted April 12, 2021.

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Acknowledgments

The authors thank the other investigators, the staff, and the participants of MESA for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Sources of Funding

This research was supported by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences.

Disclosures

Dr Blaha discloses the following relationships—advisory board/consulting: Amgen, Sanofi, Regeneron, Novartis, Novo Nordisk, Bayer, Akcea Therapeutics, 89Bio, Zogenix, Tricida, Gilead; grants: National Institutes of Health; American Heart Association; Aetna Foundation, and Amgen Foundation. Dr Bhatt discloses the following relationships—advisory board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; board of directors: Boston VA Research Institute, Society of

Cardiovascular Patient Care, TobeSoft; chair: American Heart Association Quality Oversight Committee; data monitoring committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO (Macitentan for the Treatment of Portopulmonary Hypertension) trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED [Efficacy of Secukinumab Compared to Adalimumab in Patients With Psoriatic Arthritis] trial, funded by Edwards), Contego Medical (chair, PERFORMANCE II [Protection Against Emboli During Carotid Artery Stenting Using the Neuroguard IEP System]), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; honoraria: American College of Cardiology (senior associate editor, Clinical Trials and News, ACC.org; vice chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran Versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II (ApoA-I Event Reducing in Ischemic Syndromes II) executive committee funded by CSL Behring), Belvoir Publications (editor in chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (editor in chief, *Journal of Invasive Cardiology), Journal of the American College of Cardiology* (guest editor; associate editor), K2P (co-chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), WebMD (CME steering committees); other: *Clinical Cardiology* (deputy editor), the National Cardiovascular Data Registry's ACTION Registry steering committee (chair), VA CART Research and Publications Committee (chair); research funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; royalties: Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); site coinvestigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; trustee: American College of Cardiology; unfunded research: FlowCo, Merck, Novo Nordisk, and Takeda. Dr Miller discloses the following relationships—advisory board/consulting: Amarin, 89bio, Pfizer: he also serves on AstraZeneca HealthCare Foundation's Board of Trustees on behalf of the Connections for Cardiovascular Health program. ENVISAGE trial: Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation. Dr Shapiro discloses the following relationships – advisory board/consulting: Alexion, Amgen, Esperion, Novartis. The remaining authors have no disclosures to report.

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