Contemporary Trends in Prescription of Dipeptidyl Peptidase-4 Inhibitors in the Context of US Food and Drug Administration Warnings of Heart Failure Risk

Muthiah Vaduganathan, MD, MPH[a], Avinainder Singh, MBBS, MMSc[b], Abhinav Sharma, MD[c], James L. Januzzi, Jr., MD[d], Benjamin M. Scirica, MD, MPH[a], Javed Butler, MD, MPH, MBA[e], Faiez Zannad, MD, PhD[a,f,g], Darren K. McGuire, MD, MHSc[h], Christopher P. Cannon, MD[a,i], and Deepak L. Bhatt, MD, MPH[a,*]

Dipeptidyl peptidase-4 inhibitors (DPP-4i) are one of the most widely used antihyperglycemic therapeutic classes in type 2 diabetes mellitus management. In April 2016 and August 2017, the US Food and Drug Administration (FDA) introduced sequential labelling requirements regarding heart failure risk related to DPP-4i. We explored longitudinal trends in prescription of DPP-4i before and after these FDA warnings in a multicenter health system. We identified all first-time prescriptions of DPP4i or their combinations across the Partners HealthCare system (Boston, MA) from October 2006 (FDA approval of first DPP-4i) to December 2018. Overall, 11,830 patients were newly prescribed DPP-4i during the study period. Primary care physicians (31.5%) were the most common prescribing specialty. Overall, 8.4%, 20.4%, and 11.6% had heart failure, atherosclerotic cardiovascular disease, and chronic kidney disease, respectively. Median number of background antihyperglycemic therapies was 2 [25th to 75th percentiles 1 to 2], commonly metformin (65.4%) and/or insulin (36.4%). The vast majority of prescriptions were sitagliptin (85.7%), followed by linagliptin (9.5%), saxagliptin (4.7%), and alogliptin (0.2%). Quarterly prescriptions rose gradually from 2006 to mid-2016, and have decreased consistently since then for each of the 4 DPP-4i. Declines in DPP-4i among high-risk groups and those initiated by endocrinologists were most pronounced. In conclusion, although DPP-4i remain a dominant oral antihyperglycemic therapy in clinical practice, new prescriptions have declined recently. These data may reflect relatively swift health system response to broad FDA safety communications regarding heart failure risk, which appeared to impact the entire DPP-4i class, including specific drugs that have not demonstrated any increased risk of heart failure. **(Am J Cardiol 2020;125:1577−1581)**

Dipeptidyl peptidase-4 inhibitors (DPP-4i) comprise a widely used class of oral antihyperglycemic therapies that prevent breakdown of several bioactive peptides, including glucagon-like peptide-1, thereby potentiating their activity. Four DPP-4i (alogliptin, linagliptin, saxagliptin, and sitagliptin) are approved by the US Food and Drug Administration (FDA) for glycemic control in patients with type 2 diabetes mellitus. The US FDA introduced labelling requirements regarding potential heart failure risks initially for saxagliptin and alogliptin[1−3] in April 2016, but later expanded requirements for the entire class in August 2017. Subsequent cardiovascular outcomes trials of sitagliptin and linagliptin,[4,5] each applying prospectively developed heart failure-specific statistical analysis plans, did not demonstrate excess heart failure risk, although a small mechanistic trial of vildagliptin[6] did suggest adverse effects on left ventricular volumes. We explored longitudinal trends in prescription of DPP-4i before and after these FDA warnings in a multicenter health system.

Methods

We identified all first-time prescriptions of DPP-4i or their combinations across the Partners HealthCare system encompassing >10 healthcare institutions (Boston, MA) from October 2006 (FDA approval of first DPP-4i) to December 2018. We tracked quarterly DPP-4i prescriptions in aggregate, by prescriber specialty, and in high-risk

[a]Brigham and Women's Hospital Cardiovascular Division and Heart & Vascular Center, Harvard Medical School, Boston, Massachusetts; [b]Department of Medicine, Yale-New Haven Hospital, New Haven, Connecticut; [c]McGill University Health Centre, Division of Cardiology, Montreal, Québec, Canada; [d]Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; [e]University of Mississippi, Department of Medicine, Jackson, Mississippi; [f]Université de Lorraine, INSERM Unite 1116, Vandoeuvre les Nancy, France; [g]Clinical Investigation Center 1433, French Clinical Research Infrastructure Network, Investigation Network Initiative−Cardiovascular and Renal Clinical Trialists, Centre Hospitalier Regional et Universitaire de Nancy, Vandoeuvre les Nancy, France; [h]Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; and [i]Cardiometabolic Trials Baim Institute for Clinical Research, Boston, Massachusetts. Manuscript received August 6, 2019; revised manuscript received and accepted January 8, 2020.

See page 1580 for disclosure information.

*Corresponding author: Tel: (857) 307-1992; fax: (857) 307-1955.
E-mail address: dlbhattmd@post.harvard.edu (D.L. Bhatt).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.01.053

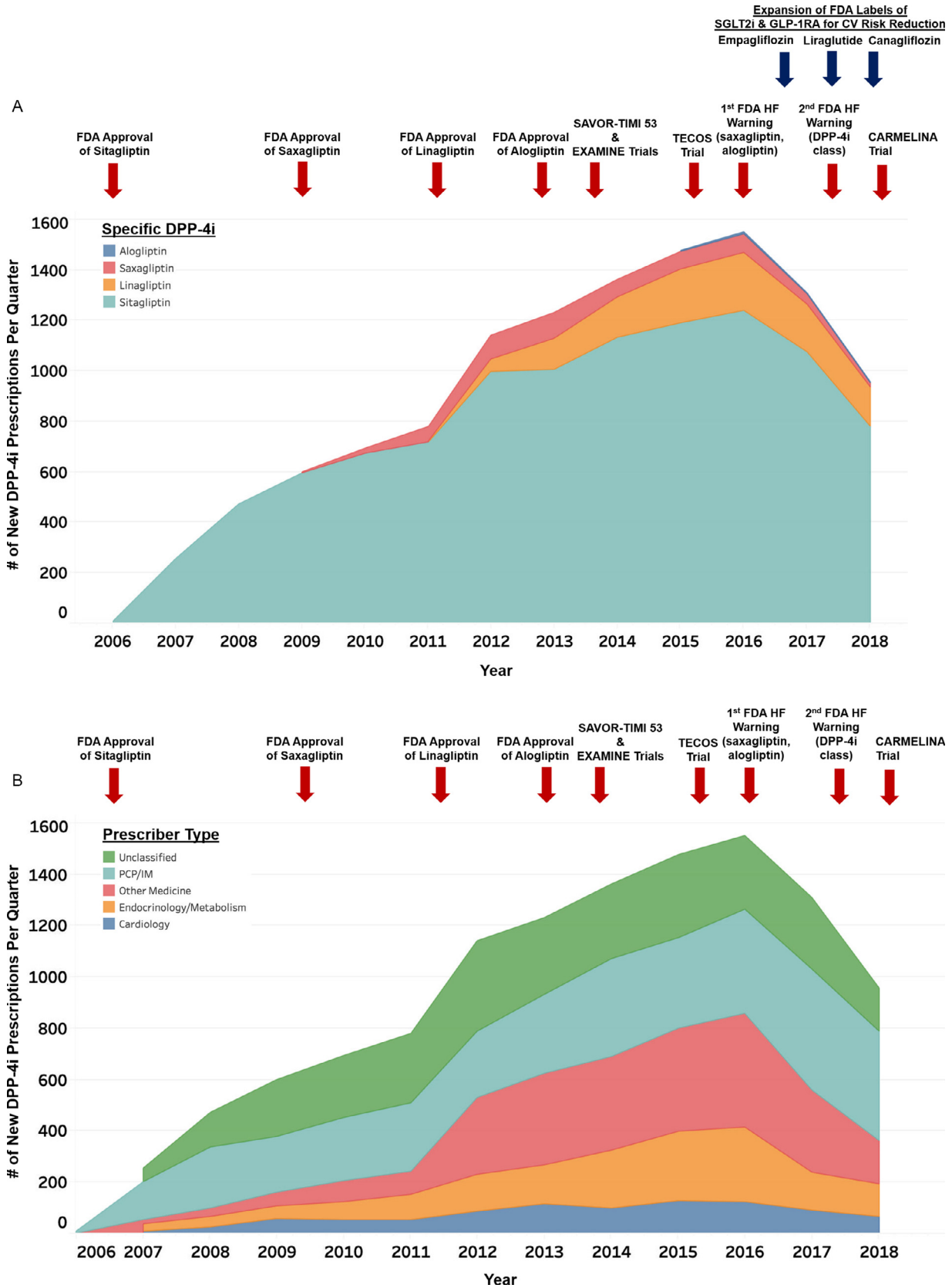

Figure 1. New dipeptidyl peptidase-4 inhibitors (DPP-4i) quarterly prescriptions by specific drug within class (Panel A), prescriber type (Panel B), and in high-risk subgroups (Panel C). Red arrows indicate key US FDA regulatory approvals, warnings, or publication of landmark cardiovascular outcomes trials. ASCVD = atherosclerotic cardiovascular disease; CARMELINA = The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; CKD = chronic kidney disease; CV = cardiovascular; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HF = heart failure; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; IM = internal medicine; PCP = primary care physician; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

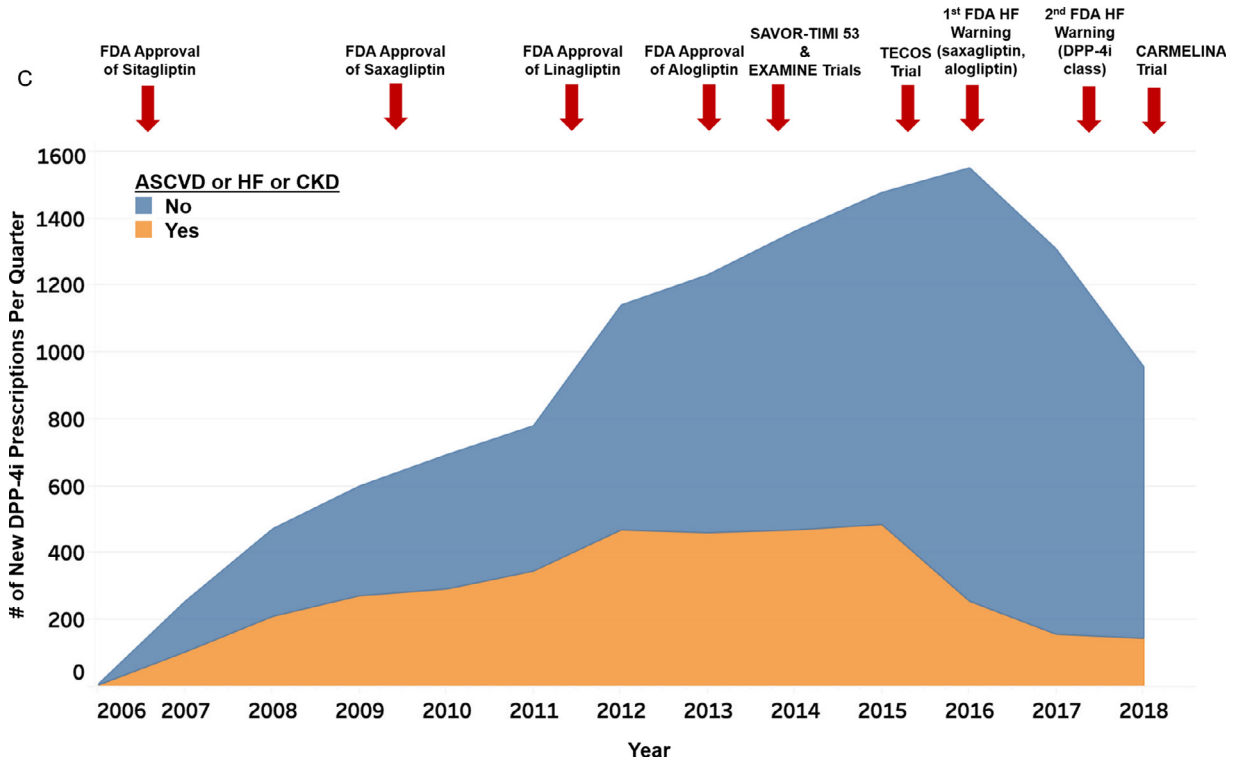

Figure 1. Continued

subgroups, including prevalent heart failure, atherosclerotic cardiovascular disease, and chronic kidney disease. To inform temporal changes in prescriber practices, we ascertained new prescriptions rather than prevalent use. The study was approved by the Partners HealthCare Institutional Review Board. Statistical analyses were performed with STATA 14.1 (College Station, TX).

Results

From 2006 to 2018, 11,830 patients were newly prescribed DPP-4i (median age 70 [25th to 75th percentiles 61 to 78] years, 44.6% women, 74.7% white). Primary care physicians (31.5%) were the most common prescribing specialty. Overall, 8.4%, 20.4%, and 11.6% had heart failure, atherosclerotic cardiovascular disease, and chronic kidney disease, respectively. Median number of background antihyperglycemic therapies was 2 (25th to 75th percentiles 1 to 2), commonly metformin (65.4%) and/or insulin (36.4%), and infrequently sodium-glucose cotransporter 2 inhibitors (SGLT2i; 1.7%) and/or glucagon-like peptide-1 receptor agonists (GLP-1RA; 2.9%).

The vast majority of prescriptions were sitagliptin (85.7%), followed by linagliptin (9.5%), saxagliptin (4.7%), and alogliptin (0.2%). Quarterly prescriptions rose gradually from 2006 to mid-2016 and have decreased consistently since then for each of the 4 DPP-4i (Figure 1). Declines in prescriptions by endocrinologists and other medical specialties were most pronounced (Figure 1). In high-risk groups, declines in new prescriptions started earlier in mid-2015 (Figure 1).

Discussion

We describe contemporary patterns of use of DPP-4i in a multicenter academic health system over 14 years. Sitagliptin, which was the first FDA-approved DPP-4i, remained the most commonly prescribed agent within the class. DPP-4i use continued to increase, even in high-risk groups, after initial publication of potential heart failure risk with saxagliptin in October 2013. New prescription of DPP-4i declined starting in mid-2016, which coincides with the first FDA communication regarding heart failure risk.[7] Temporal declines appeared consistent for specific DPP-4i therapies with or without potential heart failure risk signals.

Recent declines in DPP-4i may also reflect concurrent increases in SGLT2i or GLP-1RA,[8,9] 2 classes of therapies with known cardiovascular and renal benefits. We observed marked declines in new prescription of DPP-4i in patients with cardiovascular or renal disease. Upfront selection or switching from DPP-4i to 1 of these classes in appropriately selected high-risk patients represents an opportunity for care optimization.

This retrospective analysis is subject to certain limitations. Although we tracked initial prescriptions, we were unable to determine discontinuations or adherence given limitations of the database. Similarly, although we were unable to assess temporal changes in volume of encounters, increasing use of other antihyperglycemic therapies during a similar timeframe[8,9] suggests that a lower number of evaluated patients with diabetes mellitus are unlikely to explain recent trends in DPP-4i use. High-risk subgroups were identified using administrative coding, which may introduce

misclassification. DPP-4i initiation outside the integrated health system would not have been captured.

Although DPP-4i remain a dominant oral antihyperglycemic therapy in clinical practice, new prescriptions have declined recently. These data may reflect relatively swift health system response to broad FDA safety communications regarding heart failure risk, which appeared to impact the entire DPP-4i class, including specific drugs that have not demonstrated any increased risk of heart failure.

Author Contribution

Muthiah Vaduganathan: Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing

Avinainder Singh: Methodology, Software, Formal Analysis, Writing – Review & Editing

Abhinav Sharma: Conceptualization, Writing – Review & Editing

James L. Januzzi Jr.: Writing – Review & Editing

Benjamin M. Scirica: Writing – Review & Editing

Javed Butler: Writing – Review & Editing

Faiez Zannad: Writing – Review & Editing

Darren K. McGuire: Writing – Review & Editing

Christopher P. Cannon: Writing – Review & Editing

Deepak L. Bhatt: Supervision; Writing – Review & Editing

Disclosures

Dr. Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (NIH/NCATS Award UL 1TR002541), serves on advisory boards for Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, & Relypsa, and participates on clinical endpoint committees for studies sponsored by Novartis and the NIH. Dr. Singh reports no disclosures. Dr. Sharma has received support from Bayer-Canadian Cardiovascular Society, Alberta Innovates Health Solution, Bristol-Myers Squibb-Pfizer, Boehringer Ingelheim, Roche Diagnostics, and Takeda. Dr. Januzzi is supported in part by the Hutter Family Professorship; has received grant support from Abbott, Cleveland Heart Labs, Singulex, and Prevencio; has received consulting income from Roche Diagnostics, Critical Diagnostics, and Novartis; and has participated in clinical endpoint committees/data or safety monitoring boards for Novartis, Amgen, GE, Janssen, Pfizer, and Boehringer Ingelheim. Dr. Scirica reports research grants via Brigham and Women's Hospital from AstraZeneca, Eisai, Novartis, and Merck. Consulting fees from AstraZeneca, Biogen Idec, Boehringer Ingelheim, Covance, Dr. Reddy's Laboratory, Eisai, Elsevier Practice Update Cardiology, GlaxoSmithKline, Lexicon, Merck, NovoNordisk, Sanofi, St. Jude's Medical, and equity in Health [at] Scale. Dr. Butler has received research support from the NIH and European Union; and has been a consultant for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, Janssen, Luitpold Pharmaceuticals, Medtronic, Merck, Novartis, Relypsa, Vifor Pharma, and ZS Pharma. Dr. Zannad reports personal fees from Janssen Research & Development LLC and Bayer during the conduct of the study; personal fees from AstraZeneca, Boehringer Ingelheim, LivaNova, GE Healthcare, Amgen, Novartis, Quantum Genomics, Cardior Pharmaceuticals, CardioRenal, CVCT, Merck, CVRx, Vifor Fresenius Medical Care Renal Pharma, NovoNordisk, and MundiPharma outside the submitted work; fees for serving on a steering committee or a safety and data monitoring board from Actelion, Amgen, Bayer, Boehringer Ingelheim, Boston Scientific, CVRx, GE Healthcare, Janssen Research & Development LLC, Novartis, and ResMed; and consulting fees from AstraZeneca, Cardior Pharmaceuticals, CardioRenal, Quantum Genomics, and Vifor Fresenius Medical Care Renal Pharma. Dr. McGuire reports honoraria for trial leadership from Astra Zeneca, Sanofi Aventis, Janssen, Boehringer Ingelheim, Merck & Co, Pfizer, Novo Nordisk, Lexicon, Eisai, GlaxoSmithKline, Esperion, Lilly US; and honoraria for consulting for Astra Zeneca, Sanofi Aventis, Lilly US, Astra Zeneca, Boehringer Ingelheim, Merck & Co, Pfizer, Novo Nordisk, Metavant, Applied Therapeutics. Dr. Cannon reports research grants from (all >10K) Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb (BMS), Daiichi Sankyo, Janssen, Merck; and consulting fees from Alnylam, Amarin, Amgen, Boehringer-Ingelheim, BMS, Eisai, Janssen, Kowa, Merck, Pfizer, Regeneron, and Sanofi. Dr. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, 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 trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), 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 clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-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), 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), NCDR-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 Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.

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