Initiation Patterns of Statins in the 2 Years After Release of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Cholesterol Management Guideline in a Large US Health Plan

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Background—The purpose of this study was to characterize changes in statin utilization patterns in patients newly initiated on therapy in the 2 years following the release of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol management guideline in a large US health plan population.

Methods and Results—This retrospective, observational study used administrative medical and pharmacy claims data to identify patients newly initiated on statin therapy over 4 quarters prior to and 8 quarters following the release of the guideline (average N/quarter=3596). Patients were divided into the 4 statin benefit groups (SBGs) based on risk factors and laboratory lipid levels as defined in the guideline: SBG1 (with atherosclerotic cardiovascular disease [ASCVD]; N=1046/quarter), SBG2 (without ASCVD, with low-density lipoprotein cholesterol ≥190 mg/dL; N=454/quarter), SBG3 (without ASCVD, aged 40–75 years, with diabetes mellitus, low-density lipoprotein cholesterol 70–189 mg/dL; N=1391/quarter), SBG4 (no ASCVD or diabetes mellitus, age 40–75 years, low-density lipoprotein cholesterol 70–189 mg/dL, estimated 10-year ASCVD risk of ≥7.5%; N=705/quarter). Demographic variables, statin utilization patterns, lipid levels, and comorbidities were analyzed for pre- and postguideline periods. Postguideline, gradually increased high-intensity statin initiation occurred in SBG1, SBG2, and in SBG3 patients with 10-year ASCVD risk ≥7.5%. Moderate- to high-intensity statin initiation gradually increased among SBG4 patients. Recommended-intensity statin choice changed to a greater degree among patients treated by specialty care physicians. Regarding sex, target-intensity statin initiation was lower in women in all groups before and after guideline release.

Conclusions—Prescriber implementation of the guideline recommendations has gradually increased, with the most marked change in the increased initiation of high-intensity statins in patients with ASCVD and in those treated by a specialist. (J Am Heart Assoc. 2017;6:e005205. DOI: 10.1161/JAHA.116.005205.)

Key Words: American College of Cardiology/American Heart Association • cholesterol • guidelines • lipids • statins

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol management guideline suggests several significant changes to the former treatment paradigm for lipid therapy.1 One of the most controversial aspects of the guideline is the movement away from a low-density lipoprotein cholesterol (LDL-C) target attainment approach to a statin initiation strategy that selects statin intensity based on clinical trial evidence of reduction of atherosclerotic cardiovascular disease (ASCVD) events by use of statins in specific populations. The ACC/AHA guideline recommendations result from an analysis of pooled evidence from randomized clinical trials. The guideline recommends evaluating a patient’s future risk for ASCVD events; for those individuals in whom the benefit of statin treatment was likely to be greater than the risk of adverse events, statin therapy was recommended.1 With this approach, individuals should be placed on the evidence-based, preferred intensity of statin, with adjustments made, if necessary, to accommodate any tolerability issues for that individual. Monitoring LDL-C levels would then be performed to assess appropriate response to a specific intensity of statin therapy and adherence to therapy. In following this evidence-based approach, the
recommendation for many of these patients is a high-intensity statin (Figure 1).

Several studies have been conducted since the guideline was introduced in an attempt to identify the potential impact of the guideline. In studies evaluating statin prescribing in which the presence of atherosclerotic coronary artery disease was determined by coronary imaging, a greater proportion of patients were eligible for a statin based on the ACC/AHA guideline compared with the National Cholesterol Education Program Adult Treatment Panel III guideline.2,3 Chia et al compared the Pooled Cohort Risk Score with actual practice data from 1998 to 2007 and found that statin use would need to increase under the new guideline.4,5 Preguideline data from the National Cardiovascular Data Registry Practice Innovation and Clinical Excellence registry (2008–2012) and National Health and Nutrition Examination Survey data from 2005 to 2010 were assessed to estimate the impact of the guideline on statin practice patterns. This analysis found that compliance with the new guideline should result in a meaningful increase in statin use, especially in the group of patients with 10-year ASCVD risk ≥7.5%.6,7

Because of a variety of factors, changes to guidelines may not be efficiently adapted and implemented.8 With significant changes such as with the cholesterol guideline, the uptake may be delayed as well as vary greatly in extent between regions, patient populations, and physician types. From a public health perspective, the impact of a change in guideline should be evaluated. To date, 2 studies have been published that assess the impact of the guideline on statin prescribing patterns in patients with an ASCVD diagnosis. Both of these studies were limited to a single health system, and neither assessed changes in statin treatment patterns for primary prevention of ASCVD.9,10 The purpose of this study was to assess the impact of the new guideline on statin-initiating treatment patterns with regard to statin intensity for primary and secondary ASCVD prevention in the 2 years following its release. This will provide useful insight to help inform healthcare decision makers with regard to the use of moderate- and high-intensity statin therapies in the near and longer terms as this guideline becomes more thoroughly integrated into clinical practice.

Methods

Study Design and Population

This retrospective cohort study utilized administrative claims data from the HealthCore Integrated Research Environment (HIRE), which contained longitudinal pharmacy and medical claims data for 38.8 million members from 14 regionally
dispersed Anthem health plans in the Northeast, Midwest, South, and West of the United States as of December 31, 2015. In addition, the HIRE had laboratory results data for 13.2 million members receiving services from several national laboratory providers. Although the HIRE database predominantly contains commercially insured members, individuals with Medicare Advantage are also represented. The data included a wide range of commercially insured members, from those working for large national, self-insured companies to those with individual coverage. Health plan coverage type included health maintenance organizations, point of service plans, Medicare Advantage and Part D plans, preferred provider organizations, and consumer-directed health plans and indemnity plans. All data were handled in a manner that complied with federal and state laws and regulations, including those related to privacy and security of individually identifiable personal health information, such as the Health Insurance Portability and Accountability Act of 1996 Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule). As this study did not require direct patient identification, a Limited Data Set, as defined by the Privacy Rule, was used.

In order to assess the impact of the ACC/AHA cholesterol management guideline released in November 2013, the study period was divided into quarterly time periods from October 1, 2012 through December 31, 2015, 4 quarters prior to and 8 quarters following the release of the ACC/AHA guideline (Figure 2). Inclusion criteria for eligible patients were assessed separately for each of the 12 quarter cohorts; patients could be included in more than 1 cohort. Eligible patients were health plan members aged 21 years or older at the beginning of the study quarter with continuous medical and pharmacy benefit coverage beginning 12 months prior to and for the entire quarter of their enrollment and who were newly initiated on a statin. “Newly initiated on a statin” was defined as the absence of a statin in the 12 months prior to the first statin claim in a quarter. For the purpose of assignment to a statin benefit group (SBG), patients were required to have laboratory results available for at least 1 lipid panel (LDL-C, high-density lipoprotein cholesterol [HDL-C], and total cholesterol) during the 12 months prior to the beginning of the quarter. Women with a diagnosis of pregnancy during the study quarter were excluded.

### Study Cohorts

Eligible patients were divided into the 4 SBGs as defined in the 2013 ACC/AHA guideline (Figure 1).1 SBG1 included patients with clinical ASCVD. According to the ACC/AHA cholesterol management guideline, ASCVD includes acute coronary syndromes, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease, all of presumed atherosclerotic origin.1 For this study, ASCVD was identified based on medical claims during the 12-month period prior to the start of each quarter period with International Classification of Diseases, 9th Revision diagnosis and procedure codes for coronary atherosclerosis, myocardial infarction, unstable and stable angina, angina pectoris, coronary catheterization, coronary revascularization, ischemic stroke, peripheral artery disease, and carotid endarterectomy. SBG2 included patients without clinical ASCVD and with LDL-C ≥190 mg/dL. SBG3 included patients without clinical ASCVD aged 40 to 75 years with diabetes mellitus and LDL-C 70 to 189 mg/dL. Diabetes mellitus was identified as either with ≥2 medical claims with International Classification of Diseases, 9th Revision diagnosis codes for type 2 diabetes mellitus, or with ≥1 medical claim with International Classification of Diseases, 9th Revision diagnosis codes for type 2 diabetes mellitus and ≥1 pharmacy

**Figure 2.** Study time frame diagram. ACC/AHA indicates American College of Cardiology/American Heart Association.
claim for diabetes mellitus medications during the 12-month period prior to the start of each quarter period. SBG4 included patients without clinical ASCVD or diabetes mellitus, aged 40 to 75 years with LDL-C 70 to 189 mg/dL and an estimated 10-year ASCVD risk of ≥7.5%.

The 10-year ASCVD risk was calculated by using the new Pooled Cohort Risk Assessment Equations from the new guideline in a series of steps using age, sex, race, total cholesterol, HDL-C, systolic blood pressure, use of antihypertensive medications, current smoking status, and diagnosis of diabetes mellitus. As the HIRE does not contain specific values for race, systolic blood pressure, or smoking status, several assumptions were made. All patients were assumed to be white, which is reflective of the majority of the HIRE commercially insured population. Optimal systolic blood pressure (110 mm Hg) was assumed. Patients were classified as current smokers if claims for smoking dependence or smoking cessation counseling were present, or as nonsmokers if these claims were absent. This method provided the most conservative risk estimates. The natural log of age, total cholesterol, HDL-C, and systolic blood pressure was first calculated with systolic blood pressure being either a treated or untreated value. Interaction terms were then calculated. These values were then multiplied by the coefficients from the equation for the specific race-sex group of the individual. The sum of the “Coefficient × Value” was then calculated for the individual. The estimated 10-year risk of a first hard ASCVD event was formally calculated as 1 minus the survival rate at 10 years (“Baseline Survival”), raised to the power of the exponent of the “Coefficient × Value” sum minus the race- and sex-specific overall mean “Coefficient × Value” sum. The equation is presented here:

$$1 - S_0(t) = \exp((\text{individual score} - \text{mean score}) \times \text{Coefficient} \times \text{Value})$$

### Variables of Interest

Demographic and clinical variables were examined for preguideline and postguideline periods. Demographic variables included patient age, sex, health plan type (health maintenance organization, preferred provider organization, consumer-directed health plan, other commercial), geographic region (Northeast, Midwest, South, West), and index year (2007–2015).

The primary outcome variable—statin utilization patterns with regard to intensity of dosing for newly initiated patients—was reported for each of the 4 SBGs and described for each of the 12 quarterly time periods. Statin utilization was described by intensity as defined by the 2013 ACC/AHA guideline, with a focus on high-intensity statin use (atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg), and moderate-intensity statin use (atorvastatin 10 or 20 mg, rosuvastatin 5 or 10 mg, simvastatin 20 or 40 mg, pravastatin 40 or 80 mg, lovastatin 40 mg, fluvastatin XL 80 mg, fluvastatin 40 mg twice daily, and pitavastatin 2 or 4 mg). As a subgroup analysis, changes in statin initiation patterns in each SBG were also stratified based on provider specialty type and sex. Provider specialty type was categorized as primary care (family medicine, general practice, obstetrics and gynecology, geriatrics, and internal medicine without any subspecialties) versus subspecialty care (cardiology and endocrinology). The provider specialty variable was taken as the prescribing physician for the first statin fill in each quarter. If the prescribing physician was missing, the prescribing physician was obtained from the statin fill in the 12 months prior to the quarter (closest to the quarter if there were multiple fills).

Other clinical variables included lipid levels and comorbid conditions. Lipid levels examined within each quarter included total cholesterol, triglycerides, LDL-C, HDL-C, and non-HDL-C. Comorbidities of interest, defined by the presence of at least 1 International Classification of Diseases, 9th Revision diagnosis code in any position of a claim, included cardiovascular disease (myocardial infarction, unstable angina, ischemic stroke, peripheral artery disease, atrial fibrillation, abdominal aortic aneurysm, and hypertension), hyperlipidemia (dyslipidemia), type 2 diabetes mellitus, chronic kidney disease, and obesity. Deyo-Charlson Comorbidity Index, a measure of comorbidity burden, was calculated for each patient during the 12-month period prior to specific quarter.

### Statistical Analysis

Descriptive statistics were used to summarize the characteristics of each cohort and patterns of statin initiation. For categorical and dichotomous variables, the frequency and proportion of each category within each of these variables are presented. For continuous variables, the means and SDs are presented.

### Results

An average of 3596 patients newly initiated on a statin met the eligibility requirements and were identified across the 4 SBGs during each quarter. Newly initiated statin patients had a mean age of 61 years, and 41% were women. The average numbers of patients per quarter in each SBG were as follows: SBG1—1046, SBG2—454, SBG3—1391, and SBG4—705.

Statin initiation results are shown in Figure 3. In SBG1 (patients with clinical ASCVD), initiation of high-intensity statins in patients ≤75 years old increased from an average of 19.4% per quarter prior to the guideline release to 23.6% in the first year’s quarters and 31.1% in the second year’s quarters following the guideline release. Among patients...
>75 years old, there was a slight decrease in moderate-intensity statin initiation (from an average of 67.1% per quarter prior to the guideline release to 63.9% per quarter in the first year and 62.9% per quarter in the second year following), which coincides with an increase in high-intensity statin initiation (from an average of 15.1% per quarter prior to the guideline release to 20.2% and 25.0% per quarter, respectively, in the first and second years following).

In SBG2 (no clinical ASCVD, and LDL-C ≥190 mg/dL), there was a gradual increase in high-intensity statin use following the introduction of the guideline, from an average of 14.8% of patients per quarter in the year prior to the guideline publication to 17.1% in the first year and 19.0% in the second year postguideline release. In SBG3 (no clinical ASCVD, with diabetes mellitus, aged 40–75 years, and LDL-C 70–189 mg/dL), among patients with a 10-year ASCVD risk ≥7.5%, high-intensity statin use increased during the postguideline period (from an average of 10.8% per quarter prior to the guideline release to 14.8% per quarter in the first year and 15.8% in the second year following the guideline release); among patients with a 10-year ASCVD risk <7.5%, very little change was seen for moderate-intensity statin use (67.2% per quarter prior to the guideline release versus 67.0% per quarter in the first year and 67.2% in the second year following the guideline release). In SBG4 (no clinical ASCVD or diabetes mellitus, who were 40–75 years of age and had LDL-C 70–189 mg/dL and an estimated 10-year ASCVD risk of ≥7.5%), an increase in combined moderate- to high-intensity statin use was observed (80.3% per quarter prior to the guideline release versus 83.5% in the first year and 85.0% in the second year after the guideline release). The increase in this group was primarily from increased initiation of high-intensity statins.

An average of 23.0% of SBG1 patients, 6.8% of SBG2 patients, 12.9% of SBG3 patients, and 9.8% of SBG4 patients were seen by specialists (cardiologists and endocrinologists) during the 4 preguideline quarters and the 8 postguideline quarters. As shown in Figure 4, in all SBGs, the change in high-intensity statin initiation in the first and second year after the guideline release appeared to be greater in patients seen by specialty care physicians than in those seen by primary care physicians. In SBG1, the initiation of high-intensity statins increased from an average of 17.3% to 20.8% in the first year and 25.5% in the second year in the primary care group, while it increased from 20.8% to 27.6% in the first year and 37.4% in the second year among those in the specialty group. In SBG2, the initiation of high-intensity statins increased from 14.8% to 17.3% in the first year and 18.9% in the second year in the primary care group, while it increased from 20.8% to 27.6% in the first year and 37.4% in the second year among those in the specialty group. In SBG3, the primary care high-intensity statin initiation increased from 9.6% to 10.7% in the first year and 12.5% in the second

Figure 3. Pre- and postguideline statin intensity use among new statin users by statin benefit group (SBG). Each graph depicts the percentage of patients newly prescribed a high- or moderate-intensity statin by SBG per quarter. In reflecting the guidelines, the percentage of patients in SBG1 newly prescribed a statin is displayed by age (≤75 and >75 years of age) and intensity and for SBG3 is displayed by ASCVD risk (≥7.5% and <7.5%) and intensity. SBG groups are defined per the 2013 ACC/AHA guidelines for cholesterol management. ACC/AHA indicates American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease.

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year; specialty care high-intensity statin use increased from 11.5% to 18.9% in the first year and 16.7% in the second year. In SBG4, primary care moderate- to high-intensity statin initiation increased from 79.1% to 83.1% in the first year and 84.2% in the second year, and specialty care moderate- to high-intensity statin initiation increased from 82.8% to 86.3% in the first year and 89.3% in the second year.

In all SBGs, target intensity statin initiation was generally much lower in female than male patients before the guideline and in the first year after release of the guideline (shown in Figure 5). High-intensity statin initiation in SBG1 was 15.4% in women and 20.2% in men before the guideline release, 18.6% in women and 25.6% in men in the first year after the guideline, and 24.5% in women and 33.7% in men for the second year after guideline. In SBG2, high-intensity statins were initiated before the guideline in 12.7% of women and 17.7% of men and after the guideline in 13.7% of women and 21.8% of men in the first year, and 16.2% in women and 22.7% in men in the second year. In SBG3, preguideline high-intensity statin initiation was 8.9% in women and 11.4% in men, and after the guideline, it was 10.3% in women and 14.3% in men for the first year, and 11.4% in women and 15.5% for the second year. Similarly, in SBG4, moderate- to high-intensity statin initiation was lower in women (75.6%) than in men (81.4%) preguideline, and the trend stayed the same after the guideline (78.8% and 84.5%, respectively, for the first year; 80.0% and 85.7%, respectively, for the second year).

Discussion
This is the first large-scale, geographically diverse descriptive study of real-world data in the United States on the use of statins prior to and following the release of the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults in the 4 benefit groups defined in the guideline. Other analyses of the guideline used populations of patients during the years leading up to the release of the guideline. Using National Health and Nutrition Examination Survey data from 2005 to 2010, Pencina et al estimated the impact of the new guideline on the number of adults (aged 40–75 years) in the US population who would be eligible for statin therapy. They found that the guideline would result in an increase of statin recommendation from 37.5% of this population to 48.6%, with the greatest impact occurring in adults without cardiovascular disease but with $\geq 7.5\%$ 10-year risk of developing ASCVD. Although Pencina et al did not make a distinction between intensity levels of statins and did not evaluate actual statin utilization, their work is helpful in estimating the expected magnitude and direction of the impact of the guideline. Maddox et al made a similar assessment of the estimated impact of the guideline in...
the NCDR Pinnacle (National Cardiovascular Data Registry Practice Innovation and Clinical Excellence) population of US cardiovascular practice clinics from 2008 to 2012 and found that in this population, 96.1% were statin-eligible, but 32.4% were not currently receiving statins, and 29.3% were not receiving any lipid-lowering therapy. Among the 4 statin treatment groups in the ACC/AHA guideline, 69.9% of patients with ASCVD, 65.5% of patients in the LDL-C ≥190 mg/dL risk group, 59.6% of patients in the diabetic risk group, and 59.7% of patients in the 10-year ASCVD risk ≥7.5% group were receiving statins or statins in combination with nonstatin lipid-lowering therapy. Like Pencina and colleagues, Maddox et al made no distinction between intensity levels of statins, as the NCDR Pinnacle registry does not contain medication dose information, but their results do show that there is a great opportunity to optimize statin treatment within each risk group.

Where the present study differs from the other published research that analyzed the uptake of the ACC/AHA guideline is in the evaluation of adherence to the guideline recommendations regarding choice of statin intensity at initiation of therapy in a broad and geographically diverse US population, rather than analyzing eligibility for statin initiation based on the ACC/AHA guideline using preguideline data or assessing adherence to the guideline in a relatively small, single-health-system population. Both Zupec et al and Bellows et al evaluated adherence to the guideline in a single-health-system population limited by ASCVD diagnosis. Zupec et al observed treatment pattern changes for 1 year postguideline, and found a significant increase in the initiation of high-intensity statins from 26.0% to 45.0% ($P=0.01$) in ASCVD patients 18 to 75 years of age within primary care practices. Bellows observed treatment patterns for 6 months postguideline, and found that initiation of high-intensity statin increased from 16.3% in the historical cohort to 23.7% postguideline ($P<0.001$). The results of the present research show that the ACC/AHA guideline appeared to have a moderate effect on initiation of high-intensity statins in the period immediately following its release among patients who were previously naive to statin medications and who were in the high-intensity statin recommendation categories. In patients who were in the moderate-intensity statin recommendation categories, the initiation of moderate-intensity statins was essentially unchanged before and after the guideline was released. Overall, prescriber implementation of the new guideline during the 2-year postguideline period shows a gradual trend in adoption of the recommendations, as reflected by the new statin initiation rates observed in this study. This is not surprising because of the inherent challenges of introducing new guidelines and overcoming medical practice inertia. Compliance with clinical practice guidelines tends to be low in general, because of the passive dissemination of guidelines, complexity of implementation, and potential negative economic impact to medical practices. In the present study, the guideline produced the most marked change in the increased initiation of high-intensity statins.

Figure 5. Pre- and postguideline annual statin use by sex in each statin benefit group (SBG). Each graph depicts the percentage of patients newly prescribed a high- or moderate-intensity statin by SBG and specialty per year. SBG groups are defined per the 2013 ACC/AHA guidelines for cholesterol management. ACC/AHA indicates American College of Cardiology/American Heart Association.
intensity statins in patients with ASCVD and in patients treated by specialists.

Generally, high-intensity statin use according to the guideline was much lower in women than in men. Despite evidence of the benefit of preventive statin use in women in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) and Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trials, prescriber perception of a lower risk of cardiovascular disease for women has been shown to be a major barrier to the use of preventive strategies.14–16 Perceived or actual inconsistency in published cardiovascular disease prevention guidelines and lack of provider agreement with guidelines may also have contributed to the decreased use of statins in women.17

Limitations
Limitations of this study are primarily attributable to the data source of administrative claims. Administrative claims data from commercially insured populations cannot be generalized to the entire US population. In particular, because eligibility was limited to members of a commercially insured population, the full Medicare population was underrepresented, as only Medicare Advantage members were included, and Medicaid patients were not included. Administrative claims data are primarily collected for billing and reimbursement purposes rather than for research purposes. In general, claims data are subject to potential coding errors and inconsistencies. Administrative claims data contain limited clinical information; therefore, certain cardiovascular risk factors, such as family history, blood pressure, smoking status, and weight, were not available for analysis. Other characteristics, such as race and education, are not captured in claims data and are therefore not observed, but may have an impact on measures of interest. Because of lack of data for blood pressure, smoking status, and race, the most conservative responses in terms of risk were selected for these variables for the Pooled Cohort Risk Assessment Equation risk estimation, which resulted in a systematic underestimation of risk for SBG3 and SBG4. This undoubtedly excluded patients from the study who would have met the 10-year ASCVD risk thresholds for statin therapy, but ensured that all patients in the analysis met the appropriate threshold. Full lipid laboratory panel values were available for only a subset of members in the HIRE population and limited the sample size. The study focused on intensity of statins in patients newly initiating therapy, and not those already taking statins, as it was thought that the guidelines may have a more meaningful impact on those being newly prescribed a statin. Inpatient administered pharmacy medications are not present in the claims data; it is possible that some patients may have been initiated on statin therapy during a hospitalization, and these data would not be captured for the analysis until the statin prescription was filled in the outpatient setting.

Conclusion
In the period immediately following the release of the 2013 ACC/AHA guideline, initiation of high-intensity statins appears to have moderately increased among patients who were previously statin naive. Specialist physicians appeared to more aggressively implement the guideline, and initiation of guideline-approved therapy remains lower in women compared with their male counterparts. More research and/or more follow-up time postguideline is needed to understand to what degree the new guideline will be incorporated into practice patterns, and if the new guideline is implemented fully, how effective the change in practice will be in reducing LDL-C and cardiovascular risk among patients in the 4 statin benefit groups.

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Olufade is an employee of AstraZeneca. Zhou is an employee of HealthCore. Anzalone is an employee of AstraZeneca. Kern is an employee of HealthCore. Tunceli is an employee of Janssen Scientific Affairs, LLC. Willey is an employee of HealthCore. Cziraky is an employee of HealthCore.

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