Novel Lipid Species for Detecting and Predicting Atrial Fibrillation in Patients With Type 2 Diabetes

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The incidence of atrial fibrillation (AF) is higher in patients with diabetes. The goal of this study was to assess if the addition of plasma lipids to traditional risk factors could improve the ability to detect and predict future AF in patients with type 2 diabetes. Logistic regression models were used to identify lipids associated with AF or future AF from plasma lipids ($n = 316$) measured from participants in the ADVANCE trial ($n = 3,772$). To gain mechanistic insight, follow-up lipid analysis was undertaken in a mouse model that has an insulin-resistant heart and is susceptible to AF. Sphingolipids, cholesteryl esters, and phospholipids were associated with AF prevalence, whereas two monosialodihexosylganglioside (GM3) ganglioside species were associated with future AF. For AF detection and prediction, addition of six and three lipids, respectively, to a base model ($n = 12$ conventional risk factors) increased the C-statistics (detection: from 0.661 to 0.725; prediction: from 0.674 to 0.715) and categorical net reclassification indices. The GM3(d18:1/24:1) level was lower in patients in whom AF developed, improved the C-statistic for the prediction of future AF, and was lower in the plasma of the mouse model susceptible to AF. This study demonstrates that plasma lipids have the potential to improve the detection and prediction of AF in patients with diabetes.

Atrial fibrillation (AF) is the most common rhythm disorder of the heart, affecting 1–4% of the general population (1,2), but ~15% of patients with diabetes (2–4). It is associated with considerable morbidity, increased mortality, and a major burden on health care resources. When AF is permanent, the pathology is typically well advanced and challenging to treat. There is an urgent need for 1) early detection of AF with strategies that are resource efficient, accessible, and scalable; and 2) strategies to predict patients at risk for AF so preventive strategies can be implemented (2).

Previous studies have highlighted the potential of proteins, genes, metabolites, and lipids to serve as potential biomarkers for AF (5). An advantage of metabolites and lipids is that they represent direct signatures of biochemical activity and a functional readout of a phenotype or disease state, capturing genetic and environmental influences (6,7). For this study, our goal was to profile the plasma lipidome (>300 lipids) from a cohort of patients with diabetes ($n = 3,772$; a subcohort of the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation [ADVANCE] trial) to ascertain if lipids are associated with AF and improve the ability to predict future AF. To gain mechanistic insight, follow-up

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lipid analysis was undertaken in a mouse model that had an insulin-resistant heart and was susceptible to AF.

RESEARCH DESIGN AND METHODS

Study Approval

The ADVANCE trial was approved by the University of Sydney Human Research Ethics Committee (Sydney, New South Wales, Australia). Analysis of archived plasma samples was approved by the Alfred Hospital Ethics Committee (Melbourne, Victoria, Australia). Animal care and experimentation were approved by the Alfred Research Alliance Animal Ethics Committee (Melbourne, Victoria, Australia). Prior to euthanasia, blood was collected and processed as described (8).

Study Populations

The ADVANCE trial ($n = 11,140$ participants with type 2 diabetes) was a randomized factorial trial (double-blind comparison of blood pressure lowering vs. placebo, and open comparison of intensive vs. standard glucose control [9]). A previously selected cohort of case patients with cardiovascular disease ($n = 3,779$) was used for these analyses (9,10). We conducted an observational cohort study within the trial on plasma samples collected at baseline (before assignment to a treatment arm) (Fig. 1). The treatment arms had no effect on AF (11).

Subset 1 (AF Baseline)

The cohort for AF detection included 3,772 participants (those without AF [hereafter, non-AF]: $n = 3,368$; AF: $n = 404$). AF was assessed by 12-lead electrocardiogram (ECG) by combining two variables: current AF at the baseline visit or previous AF within 3 months of the baseline visit.

Subset 2 (AF Future)

The cohort for the prediction of future AF included 2,238 participants (non-AF: $n = 2,054$; future AF: $n = 184$). A patient was classified as having future AF if there was no evidence of AF at baseline or within the past 3 months, and AF was detected by ECG at the 24-, 48-, or 60-month study visit. Patients without follow-up ECG data ($n = 1,534$) were excluded. Patient characteristics of non-AF groups in cohorts 1 and 2 were comparable, except for a mean age difference of 1 year (Supplementary Tables 1–3).

Heart-Specific Mouse Model With Reduced Phosphoinositide 3-Kinase (PI3K) and an Insulin-Resistant Heart

Lipid profiling was performed on plasma from adult (10–13 weeks old) male and female, heart-specific, dominant negative PI3K transgenic mice (dnPI3K-reduced cardiac PI3K activity of $\sim 77\%$ [12]) and nontransgenic control mice (Fig. 1).

Lipidomic Profiling

Lipids were extracted from 10 μL of human plasma and abundances measured in our previous study; information regarding batch effects and inter- and intra-assay

coefficients of variation are described (10). Lipids were extracted from 10 μL of mouse plasma and analyzed as described (8,13).

Statistics

Mann-Whitney U test and χ^2 tests were used for continuous and categorical variables, respectively. Lipid data were log10-transformed and scaled by SD. Logistic regression models that were adjusted for 12 covariates (Supplementary Table 1; clinical lipids, covariates selected by the CHARGE-AF Consortium [14]) were used to determine the association of individual lipids with the prevalence and prediction of AF. Logistic and linear regression P values were corrected for multiple comparisons using the Benjamini-Hochberg method ($P < 0.05$). Cluster analysis was performed in R. Ranking of lipids was performed using Akaike information criterion-based forward selection of lipids into multivariate models (10) and assessed using the C-statistics for 5-year risk, continuous and categorical net reclassification index (NRI), integrated discrimination indexes (IDI) and relative IDI with fivefold cross-validation ($n = 200$ repeats). Categorical NRI was calculated on the basis of 5-year risk categories of $<2.5\%$, $2.5\text{--}5\%$, and $>5\%$.

Data and Resource Availability

All data generated and analyzed during this study are included here and in the Supplementary Material. No applicable resources were generated or analyzed during this study.

RESULTS

Baseline Characteristics

Characteristics of patients in subset 1 (AF Baseline) ($n = 3,368$ participants in the non-AF group and $n = 404$ in the AF group at baseline) (Fig. 1) are provided in Supplementary Table 1. Older age and obesity are risk factors for AF, and patients with AF were significantly older and heavier.

Subset 2 (AF Future) ($n = 2,238$ participants) represented participants from subset 1 who did not have AF at baseline and for whom an ECG was performed at a follow-up time point (24, 48, and/or 60 months). AF was subsequently identified in 184 patients (Supplementary Table 2).

Lipids Associated With Baseline and Future AF

Logistic regression analysis was conducted on data from subsets 1 and 2 (Supplementary Tables 4 and 5) after adjusting for 12 covariates (Supplementary Table 1). For subset 1 (AF Baseline), 42 lipids ($n = 14$ sphingolipids, 10 neutral lipids, 6 lysophospholipids, and 12 phospholipids) were associated with the presence of AF ($n = 8$ negative; $n = 34$ positive) (Fig. 2A). Although univariate analysis showed that total cholesterol was associated with prevalent AF (Supplementary Table 1), because clinical lipids were included in the multivariate model, the 42 lipids identified were independent of clinical lipids (Supplementary Table 6). All six dihexosylceramide species were positively associated with the prevalence of AF (Fig. 2A).

Figure 1—CONSORT diagram for lipidomic profiling and subsequent analyses of subsets 1 and 2 of the ADVANCE cohort, and lipid assessment in plasma from a dnPI3K transgenic mouse model. A total of 7,376 baseline samples were available from the ADVANCE study; of these, 3,779 samples were selected and used for lipidomic profiling previously. In this study, subset 1 (AF Baseline; $n = 3,772$) samples were selected after excluding samples ($n = 7$) because of missing values (from the covariates used [Q waves] [for assessment of prior myocardial infarction], $n = 5$; weight, $n = 1$; height, $n = 1$). Subset 2 (AF Future) was selected from the 3,772 for analyses of future AF. Patients without follow-up ECG data ($n = 1,534$) were excluded. There was some attrition due to death ($n = 355$), but this did not result in bias between cohorts 1 and 2. The dnPI3K mouse model is a cardiac-specific mouse model.

In subset 2 (AF Future), two species of monosialodihexosylganglioside (GM3) ganglioside were negatively associated with future AF (Fig. 2B). Given the positive association of dihexosylceramide (Hex2Cer) species with AF in subset 1 (Fig. 2A) and the inverse association of GM3 species in subset 2 (Fig. 2B), we evaluated the ratio of Hex2Cer to GM3 because Hex2Cer is a precursor substrate for GM3 (Supplementary Fig. 1A). Five of six Hex2Cer-to-GM3 ratios were significantly associated with AF in subset 1 (Supplementary Fig. 1B), whereas two of the six Hex2Cer-to-GM3 ratios were associated with the development of future AF in subset 2 (Supplementary Fig. 1C).

Cluster analysis (Supplementary Fig. 2) identified other species from the same class, which correlated with individual lipids associated with AF at baseline (Fig. 2A). By contrast, only GM3 species were correlated for the prediction of future AF (Supplementary Fig. 2).

Multivariate Models Identified Lipids That Improved on Traditional Risk Factors for the Detection and Prediction of AF

Sequential addition of ranked lipids to the base model led to an increase in the C-statistic for both the detection of AF at baseline and prediction of future AF (Fig. 2C and D). There was an inflection point after the addition to the model of six lipids (AF detection) and three lipids (future AF). To prevent overfitting, we limited the models to 12 covariates and six and three lipids for the baseline AF and future AF models, respectively. This improved the C-statistics, categorical and continuous NRI, IDIs, and relative IDIs (Table 1).

Depressed Plasma GM3 Lipids in a Heart-Specific Mouse Model With Reduced PI3K and an Insulin-Resistant Heart

To examine whether the insulin-resistant heart in a setting of diabetes has the potential to contribute to the lipid

Figure 2—Association and predictive modeling of plasma lipids in detecting AF in ADVANCE subset 1 ($n = 3,772$) (A and C), and patients in whom AF developed in the future (ADVANCE subset 2; $n = 2,238$) (B and D). A and B: Logistic regression model of individual lipid species against prevalence of AF at baseline (subset 1, AF Baseline) and future AF (subset 2, AF Future) adjusting for 12 covariates (namely, age, weight, height, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, myocardial infarction, antihypertensive medication used, current smoking status, and hospital admission for heart failure). Odds ratios and 95% CIs are shown. Lipid levels in red (A) and blue (B) were significant ($P < 0.05$) after applying the Benjamini-Hochberg correction. C and D: Logistic regression models used to determine improvement in the C-statistic to detect or predict the incidence of AF by adding lipids to the base model, consisting of the 12 covariates. Logistic regression models were developed using forward stepwise feature selection by Akaike information criterion reduction. Analysis was conducted in a fivefold cross-validated framework (repeated 200 times). Ranked lipids are shown sequentially as features added to the base model. CE, cholesteryl ester; Cer, ceramide; DG, diacylglycerol; dhCer, dihydroceramide; GM3, monosialodihexosylganglioside; HexCer, monohexosylceramide; Hex2Cer, dihexosylceramide; Hex3Cer, trihexosylceramide; LPC, lysophosphatidylcholine; LPC(O), lysoalkylphosphatidylcholine; LPI, lysophosphatidylinositol; PC, phosphatidylcholine; PC(O), alkylphosphatidylcholine; PC(P), alkenylphosphatidylcholine; PE, phosphatidylethanolamine; PE(O), alkylphosphatidylethanolamine; PG, phosphatidylglycerol; PI, phosphatidylinositol; SM, sphingomyelin; TG, triacylglycerol.

Table 1—Reclassification and discrimination statistics of detecting and predicting AF in the ADVANCE dataset

Feature	C-Statistic	Continuous NRI	Categorical NRI	IDI	Relative IDI
Detecting incidence of AF					
Base model*	0.661 (0.653–0.668)	Reference	Reference	Reference	Reference
Base model + six lipid species#	0.725 (0.720–0.730)	0.477 (0.450–0.504)	0.124 (0.108–0.141)	0.044 (0.043–0.046)	0.881 (0.839–0.922)
Predicting incidence of AF					
Base model*	0.674 (0.662–0.685)	Reference	Reference	Reference	Reference
Base model + three lipid species†	0.715 (0.705–0.725)	0.434 (0.372–0.495)	0.084 (0.049–0.119)	0.017 (0.015–0.019)	0.439 (0.386–0.492)

Data are reported as No. (95% CI) unless otherwise indicated. CE, cholesteryl ester; DG, diacylglycerol; GM3, monosialodihexosyl-ganglioside; HexCer, monohexosylceramide; LPC(O), lysoalkylphosphatidylcholine; PC(O), alkylphosphatidylcholine; PC(P), alkenyl-phosphatidylcholine; PE(O), alkylphosphatidylethanolamine. *The base model consisted of the following 12 covariates: age, weight, height, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, myocardial infarction, antihypertensive medication used, current smoking status, and hospital admission for heart failure. #Ranked lipids for the detection of AF were SM(d18:1/24:0), LPI(18:2), PG(36:1), PC(O-16:0/16:0), SM(d18:1/20:0)/SM(d16:1/22:0), and TG(50:3). †Ranked lipids for the prediction of AF incidence were CE(17:0), GM3(d18:1/24:1), and PC(P-16:0/18:1).

profile in the plasma, we undertook lipid profiling in a cardiac-specific dnPI3K transgenic mouse model. The mouse model is characterized as a heart-specific model of type 2 diabetes because it has defective cardiac insulin signaling due to depressed PI3K and develops severe cardiomyopathy and increased susceptibility to AF in response to cardiac stress (15–19). GM3, sphingomyelin (SM), phosphatidylserine, and oxidized species classes were decreased in plasma from dnPI3K mice (Supplementary Fig. 3). Here, we focused on levels of GM3 lipids, which were lower and clustered together in patients in whom AF subsequently developed (Figs. 2B and 3A and B and Supplementary Fig. 2). Levels of three of five GM3 lipids were lower in plasma from dnPI3K mice (Fig. 3C).

DISCUSSION

New strategies and biomarkers are urgently required to identify those at risk for AF, but these strategies and biomarkers are likely to differ on the basis of underlying conditions, including diabetes. The key findings of this study were: 1) 42 lipids were associated with the presence of AF, and the addition of six lipids improved the accuracy of a base model ($n = 12$ covariates and conventional risk factors for AF), and 2) two lipids were associated with the development of future AF, and the inclusion of three lipids improved the ability to predict future AF development. Finally, by assessing plasma lipids in a mouse model with an insulin-resistant heart, we gained insight as to how insulin resistance may contribute to altered plasma lipids.

Diabetes increases the risk for AF (3). Approximately 16% of patients in this study ($n = 588$ of 3,772 patients) either had AF at baseline or AF developed in these patients over the following 60 months. To our knowledge, this is the first study to undertake comprehensive lipidomic profiling ($n > 300$ lipids) in a large cohort of patients with diabetes screened for AF. Previous studies focused on smaller subsets of lipids, conventional lipids (e.g., HDL,

LDL, triacylglycerides), or much smaller cohorts of patients with AF (5,20–24).

Lipids Associated With AF

Of the 42 lipids associated with AF, the two largest groups of lipids were cholesteryl esters and dihexosylceramides (Fig. 2A). Dihexosylceramides are a derivative of ceramides and serve as a precursor to GM3 gangliosides. Increased levels of circulating dihexosylceramides in the absence of an increase in GM3 gangliosides may indicate dysregulation within the sphingolipid pathway converting dihexosylceramide to GM3 ganglioside in patients with AF (Supplementary Fig. 1A).

Previous plasma lipidomic studies identified associations of specific lysophosphatidylcholine (LPC), LPE, phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol and alkenylphosphatidylethanolamine species with AF (20,21). Although we did not observe associations with the same specific species, there were associations in lipids from the same lipid classes (i.e., LPC, PC, and PE) (Fig. 2A). A major difference between our cohort and previous work was that the ADVANCE cohort consisted entirely of patients with type 2 diabetes.

In our previous lipidomics study from the ADVANCE trial, for the prediction of cardiovascular events, the addition of seven lipids to the base model increased the C-statistic from 0.680 to 0.700 (10). Using a similar approach here, the addition of six lipids [SM(d18:1/24:0), lysophosphatidylcholine (LPI)(18:2), phosphatidylglycerol (PG)(36:1), PC(O-16:0/16:0), SM(d18:1/20:0)/SM(d16:1/22:0), and triacylglycerol (TG)(50:3)] improved the C-statistic even more (from 0.661 to 0.725). Three of the six lipids were also associated with AF at baseline [SM(d18:1/24:0) level decreased; LPI(18:2) and PC(O-16:0/16:0) levels increased] (Fig. 2A). We previously identified a decrease in plasma SM(d18:1/24:0) levels in a mouse model with substantial cardiac pathology due to severe pressure overload (8). These mice had enlarged atria, which predispose the heart to AF.

Figure 3—GM3 lipid species in plasma from patients in subset 2 (AF Future) and dnPI3K mice. **A**: Lipids clustered with GM3 lipids from Fig. 2B (cluster 3 from complete heat map presented in Supplementary Fig. 2). Color scale: cyan (correlation [corr] = -1) to blue to black (corr = 0) to red to magenta (corr = 1); diagonal (self corr = 1) shown in white. **B** and **C**: GM3 lipid levels that were significantly changed in ADVANCE subset 2 and dnPI3K mice. * $P < 0.05$ vs. non-AF. For mouse lipidomic data, the Shapiro-Wilk test was used to check for normality before additional testing. * $P < 0.05$ vs. nontransgenic (Ntg) via Mann-Whitney test. Non-AF, $n = 2,054$; AF Future, $n = 184$. Animal numbers: Ntg, $n = 42$ ($n = 25$ male; $n = 17$ female); dnPI3K, $n = 39$ ($n = 21$ male; $n = 18$ female).

Lipids Associated With the Future Development of AF

The ability to better identify people at risk for AF, and provide interventions to prevent AF, would have enormous health and economic benefits. Two GM3 lipids were inversely associated with the development of AF at a later time (Fig. 2B). The addition of three lipids improved the ability to predict future AF (C-statistic: from 0.674 to 0.715); GM3(d18:1/24:1) increased the C-statistic the most. In settings of type 2 diabetes and obesity, GM3 gangliosides have been implicated mechanistically via a disruption in insulin signaling inducing insulin resistance (25). Numerous studies have identified associations between lipids and various diseases. Mechanistic insight into how these lipids reflect and/or contribute to pathology are important to assess which lipids have the most potential as biomarkers or drug targets. In our study, levels of several GM3 lipids were decreased in patients in whom AF subsequently developed (Fig. 3A and B), and GM3 lipid levels also decreased in the plasma of dnPI3K mice, which have an insulin-resistant heart and are susceptible to AF in cardiac-stress settings (Fig. 3C). Collectively, these data provide a potential mechanism whereby the insulin-resistant diabetic heart might contribute to the differential levels of lipids in the circulation.

Limitations and Future Directions

It will be important to validate our lipid markers and modeling in independent cohorts of patients with diabetes. AF can be missed in patients with paroxysmal or intermittent AF. However, any misclassification of patients

in our cohort has been estimated to represent ~3% of the group (11) and will not change the associations identified. From mechanistic and therapeutic perspectives, it will be important to assess whether reduced circulating levels of GM3 contribute to the development of AF or are a consequence of dysregulated cardiac metabolism due to cardiac insulin resistance.

In summary, we identified circulating lipids that were associated with the presence of AF and the development of future AF in patients with type 2 diabetes. We have also shown that lipids can improve the detection and prediction of AF over and above traditional risk factors in this setting. Incorporation of lipids into risk assessment could have a significant impact on improving patient outcomes.

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Author Contributions. J.R.M. conceived the study. J.R.M. and P.J.M. designed the study. K.S.J. developed the statistical analysis protocols with input from P.J.M. The ADVANCE trial was conducted by S.Z., G.S.H., and J.C. The lipidomic analysis and data processing of the ADVANCE samples were performed previously by Z.H.A. C.G. and K.H. contributed to lipidomic methodology. C.G., K.H., and A.A.T.S. assisted with statistical analyses. Y.K.T. and J.Y.Y.O. performed mouse experiments. Y.K.T. performed lipidomic experiments, and analyses of mouse samples and lipid results from the ADVANCE trial in relation to atrial fibrillation. Y.K.T. and J.R.M. wrote the manuscript. All authors critically edited the manuscript. P.J.M. and J.R.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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