American Heart Association | American Stroke Association

Prognosis in Familial Atrial Fibrillation

Laurent Fauchier, MD, PhD; Arnaud Bisson, MD; Nicolas Clementy, MD

Atrial fibrillation (AF) is a common arrhythmia associated with substantial morbidity and a markedly increased risk of ischemic stroke. It accounts for one third of all strokes in patients above the age of 65 and is also associated with an increased mortality.[1] In recent years, risk models for AF prediction have been developed based on clinical and demographic variables.[2,3] AF may also present as familial disorder. Several studies have shown an association of genetic variants with AF and indicated that familial AF increases the risk of AF.[4–10] Considering the high and increasing number of AF patients in daily practice, the clinician is interested in the clinical course of these familial forms of AF and whether familial AF patients would benefit from a different management strategy than other AF patients.

Heterogeneity of both genetic background and clinical manifestations in familial AF remains largely uncharacterized. Concomitant rhythm disorders, as well as cardiomyopathies, are common in patients with familial AF. A positive family history for AF in an apparently lone AF patient may be a marker for wider spectrum of cardiac pathology,[11] and one first message is that this should be investigated when the cardiologist identifies a patient with familial AF.

Although studies have identified several genetic loci associated with AF, it is still unclear whether genetic profiling can identify AF patients at greatest risk of cardiac events or cardioembolic stroke. One might speculate that a patient with familial AF will have earlier onset of AF and overall longer duration of AF, which might affect the risk of stroke (although this is not clearly demonstrated in other AF patients). An earlier onset and longer duration of AF might also promote a so-called cardiomyopathy in some patients, which may worsen prognosis. In the analysis of a nation-wide cohort study about familial AF in Denmark, Gundlund et al found that age difference was indeed evident with a median age at AF diagnosis of the familial AF patients of 50 years in comparison to the nonfamilial AF patients who had a median age at AF diagnosis of 77 years. However, the researchers found that long-term risks for death and thromboembolic complications were similar in familial and nonfamilial AF patients.[12] The researchers have to be congratulated given that their data set is quite unique. It has the major advantage of being nationwide, thus theoretically avoiding selection biases commonly observed in many works on these issues. Some clinical characteristics are missing and more granular data would be of interest, but the multivariable analyses seem quite robust and they are unlikely to be reproduced easily in many other cohorts. After matching the cases and the controls in a 1:1 match upon age at AF diagnosis, year at AF diagnosis, and sex, there were statistically more prevalent diabetes mellitus, coronary artery disease, and vascular disease in nonfamilial AF, but the absolute differences were relatively minimal. Importantly, matching resulted in very similar CHA_2DS_2-VASc scores, which was a key determinant for an unbiased analysis of the risk of stroke associated with familial AF per se. The lack of differences in the long-term risk of thromboembolic complications between familial and nonfamilial indicates that the perceived possible different effect of familial pattern against the risk of death and thromboembolic events seems irrelevant in AF patients when using a contemporary risk stratification scheme, the CHA_2DS_2-VASc score. As a result, this would suggest a similar antithrombotic treatment approach for familial AF patients as for the general AF population.

These results are complementary to those recently published by Lubitz et al. Using genome-wide data from an independent large-scale analysis of common variants known to be associated with AF, they found that AF genetic risk was associated with AF and cardioembolic stroke in 18 919 individuals.[9] Nevertheless, given that genetic information improved prediction minimally and afforded small improvements in discrimination of AF risk, the researchers concluded that widespread use of genetic risk profiling does not need to be incorporated into routine clinical decision making.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Service de Cardiologie, Pôle Coeur Thorax Vasculaire, Centre Hospitalier Universitaire Trousseau et Faculté de Médecine, Université François Rabelais, Tours, France.

Correspondence to: Laurent Fauchier, MD, PhD, Service de Cardiologie et Laboratoire d'Electrophysiologie Cardiaque, Centre Hospitalier Universitaire Trousseau, 37044 Tours, France. E-mail: lfau@med.univ-tours.fr

J Am Heart Assoc. 2016;5:e004905 doi: 10.1161/JAHA.116.004905.

However, familial AF may help to identify the etiology for strokes, more likely to be caused by thromboembolism from AF. This would help decision making in patients with cryptogenic stroke or, at the other end of the spectrum, for the many patients with several putative etiologies after ischemic stroke. Beyond the relatively wide aspect of familial AF, there may be a heritable component underlying ischemic stroke. AF-associated genetic variants on chromosomes 4q25 and 16q22 have been associated with cardioembolic strokes.[13,14] An AF genetic risk score has been reported for the identification of patients at highest risk for incident AF and stroke, which might be useful to target anticoagulation therapy to patients at highest risk.[15] Future works are thus needed to know whether knowing the genotype of a patient may improve risk stratification beyond the CHA_2DS_2-VASc score.

A question is that AF related to a genetic disease may be primarily electric (possibly overlapping channelopathies) or secondary to any other familial cardiac condition. This may be familial hypertension or cardiomyopathies, but this did not appear in the study by Gundlund et al. There was a lower prevalence of ischemic heart disease in patients with familial AF, whereas they had the same rate of heart failure. A higher prevalence of dilated cardiomyopathy would have been expected and be confirmatory of a genetic predisposition for at least some of the patients with familial AF. There were actually no differences between the familial and the nonfamilial AF patients regarding nonischemic dilated cardiomyopathy. These data can neither clearly support nor invalidate any theory regarding whether genetic AF may be predominantly caused by channelopathies or structural cardiac conditions. Considering the more specific subgroup of patients with so called lone AF, Jurkko et al found that familial AF may account for 20% of the patients, and they were able to show that the arrhythmia triggers for lone AF were heterogeneous (premature atrial contractions, vagal or sympathetic related), but were often family specific.[11] Overall, it seems that associated rhythm disorders, as well as cardiomyopathies, are not uncommon in patients with familial AF. A family history for AF may be the indicator of a variety of cardiac pathologies, which may actually be the main determinant of prognosis.

An element to be taken into account (and a possible bias) is that families with long life expectancy for any reason may be at higher risk for familial AF attributed to older age of relatives. Other researchers defined familial AF as premature when the first detected occurrence is at age 65 years or younger in a first-degree relative.[16] Similarly, Oyen et al performed their analysis in patients with lone AF before age 60 years.[17] Consequently, the researchers performed a sensitivity analysis in which familial AF was restricted to patients with a first-degree family member diagnosed with AF before the age of 70 years. Whereas this conservative approach should decrease the bias selecting patient with a longer life expectancy, the researchers actually found a lower risk of death in this subgroup of patients with familial AF. Maybe the study in 4329 cases still lacks some power for definite conclusions and the researchers acknowledge this point, but a 17% lower risk of death has to be considered beyond statistical significance. This is a quite intriguing result, which is uneasy to explain at this stage. Maybe a better awareness about AF may lead to an earlier and holistic management in patients with familial AF. This would be an interesting part of a general strategy of AF screening in the population, advocating that an early detection and treatment of patients with asymptomatic AF before the first complications occur is a recognized priority for the prevention of cardiovascular events.[18]

Disclosures

Fauchier reports consulting and/or lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, and Novartis. Clementy reports consulting and/or lecture fees from Medtronic. Bisson reports no COI.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; Authors/Task Force Members, Document Reviewers. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC endorsed by the European Stroke Organisation (ESO). *Eur Heart J*. 2016. Available at: http://eurheartj.oxfordjournals.org/content/ehj/early/2016/08/26/eurheartj.ehw210.full.pdf. Accessed November 18, 2016.
2. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasan RS, Benjamin EJ. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;373:739–745.
3. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens ACJW, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kääb S, Couper D, Harris TB, Soliman EZ, Stricker BHC, Gudnason V, Heckbert SR, Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc*. 2013;2:e000102 doi: 10.1161/JAHA.112.000102.
4. Everett BM, Cook NR, Conen D, Chasman DI, Ridker PM, Albert CM. Novel genetic markers improve measures of atrial fibrillation risk prediction. *Eur Heart J*. 2013;34:2243–2251.
5. Hong K, Xiong Q. Genetic basis of atrial fibrillation. *Curr Opin Cardiol*. 2014;29:220–226.
6. Lubitz SA, Lunetta KL, Lin H, Arking DE, Trompet S, Li G, Krijthe BP, Chasman DI, Barnard J, Kleber ME, Dörr M, Ozaki K, Smith AV, Müller-Nurasyid M, Walter S, Agarwal SK, Bis JC, Brody JA, Chen LY, Everett BM, Ford I, Franco OH, Harris TB, Hofman A, Kääb S, Mahida S, Kathiresan S, Kubo M, Launer LJ, Macfarlane PW, Magnani JW, McKnight B, McManus DD, Peters A, Psaty BM, Rose LM, Rotter JI, Silbernagel G, Smith JD, Sotoodehnia N, Stott DJ, Taylor KD, Tomaschitz A, Tsunoda T, Uitterlinden AG, Van Wagoner DR, Völker U, Völzke H, Murabito JM, Sinner MF, Gudnason V, Felix SB, März W, Chung M, Albert CM, Stricker BH, Tanaka T, Heckbert SR, Jukema JW, Alonso A, Benjamin EJ, Ellinor PT. Novel genetic markers

associate with atrial fibrillation risk in Europeans and Japanese. *J Am Coll Cardiol*. 2014;63:1200–1210.

7. Hobbelt AH, Siland JE, Geelhoed B, Van Der Harst P, Hillege HL, Van Gelder IC, Rienstra M. Clinical, biomarker, and genetic predictors of specific types of atrial fibrillation in a community-based cohort: data of the PREVEND study. *Europace*. 2016. Available at: http://europace.oxfordjournals.org/content/early/2016/03/07/europace.euw016. Accessed November 18, 2016.
8. Tucker NR, Clauss S, Ellinor PT. Common variation in atrial fibrillation: navigating the path from genetic association to mechanism. *Cardiovasc Res*. 2016;109:493–501.
9. Lubitz SA, Yin X, Lin H, Kolek M, Smith JG, Trompet S, Rienstra M, Rost NS, Teixeira P, Almgren P, Anderson CD, Chen LY, Engström G, Ford I, Furie KL, Guo X, Larson MG, Lunetta K, Macfarlane PW, Psaty BM, Soliman EZ, Sotoodehnia N, Stott DJ, Taylor KD, Weng L-C, Yao J, Geelhoed B, Verweij N, Siland JE, Kathiresan S, Roselli C, Roden DM, van der Harst P, Darbar D, Jukema JW, Melander O, Rosand J, Rotter JI, Heckbert SR, Ellinor PT, Alonso A, Benjamin EJ; AFGen Consortium. Genetic risk prediction of atrial fibrillation. *Circulation*. 2016. Available at: http://circ.ahajournals.org/content/early/2016/10/27/CIRCULATIONAHA.116.024143. Accessed November 18, 2016.
10. Gundlund A, Christiansen MN, Hansen ML, Olesen JB, Zahir D, Køber L, Gislason GH, Piccini JP, Peterson ED, Torp-Pedersen C, Fosbøl EL. Familial clustering and subsequent incidence of atrial fibrillation among first-degree relatives in Denmark. *Europace*. 2016;18:658–664.
11. Jurkko R, Palojoki E, Huttunen H, Holm C, Lehto M, Heliö T, Swan H, Toivonen L. Characteristics of atrial fibrillation and comorbidities in familial atrial fibrillation. *J Cardiovasc Electrophysiol*. 2013;24:768–774.
12. Gundlund A, Olesen JB, Staerk L, Lee C, Piccini JP, Peterson ED, Køber L, Torp-Pedersen C, Gislason GH, Fosbøl EL. Outcomes associated with familial vs. non-familial atrial fibrillation: a matched nationwide cohort study. *J Am Heart Assoc*. 2016;5:e003836 doi: 10.1161/JAHA.116.003836.
13. Gretarsdottir S, Thorleifsson G, Manolescu A, Styrkarsdottir U, Helgadottir A, Gschwendtner A, Kostulas K, Kuhlenbäumer G, Bevan S, Jonsdottir T, Bjarnason H, Saemundsdottir J, Palsson S, Arnar DO, Holm H, Thorgeirsson G, Valdimarsson EM, Sveinbjörnsdottir S, Gieger C, Berger K, Wichmann H-E, Hillert J, Markus H, Gulcher JR, Ringelstein EB, Kong A, Dichgans M, Gudbjartsson DF, Thorsteinsdottir U, Stefansson K. Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. *Ann Neurol*. 2008;64:402–409.
14. Gudbjartsson DF, Holm H, Gretarsdottir S, Thorleifsson G, Walters GB, Thorgeirsson G, Gulcher J, Mathiesen EB, Njølstad I, Nyrnes A, Wilsgaard T, Hald EM, Hveem K, Stoltenberg C, Kucera G, Stubblefield T, Carter S, Roden D, Ng MCY, Baum L, So WY, Wong KS, Chan JCN, Gieger C, Wichmann H-E, Gschwendtner A, Dichgans M, Kuhlenbäumer G, Berger K, Ringelstein EB, Bevan S, Markus HS, Kostulas K, Hillert J, Sveinbjörnsdóttir S, Valdimarsson EM, Løchen M-L, Ma RCW, Darbar D, Kong A, Arnar DO, Thorsteinsdottir U, Stefansson K. A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. *Nat Genet*. 2009;41:876–878.
15. Tada H, Shiffman D, Smith JG, Sjögren M, Lubitz SA, Ellinor PT, Louie JZ, Catanese JJ, Engström G, Devlin JJ, Kathiresan S, Melander O. Twelve-single nucleotide polymorphism genetic risk score identifies individuals at increased risk for future atrial fibrillation and stroke. *Stroke*. 2014;45:2856–2862.
16. Lubitz SA, Yin X, Fontes JD, Magnani JW, Rienstra M, Pai M, Villalon ML, Vasan RS, Pencina MJ, Levy D, Larson MG, Ellinor PT, Benjamin EJ. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *JAMA*. 2010;304:2263–2269.
17. Oyen N, Ranthe MF, Carstensen L, Boyd HA, Olesen MS, Olesen S-P, Wohlfahrt J, Melbye M. Familial aggregation of lone atrial fibrillation in young persons. *J Am Coll Cardiol*. 2012;60:917–921.
18. Lip GYH, Fauchier L, Freedman SB, Van Gelder I, Natale A, Gianni C, Nattel S, Potpara T, Rienstra M, Tse H-F, Lane DA. Atrial fibrillation. *Nat Rev Dis Primers*. 2016;2:16016.

Key Words: Editorials • atrial fibrillation • genetics • stroke