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Ectopy and Expectations: Can We Predict Atrial Fibrillation, and Should We Try?

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Despite advances in diagnostics and therapy, atrial fibrillation (AF) continues to place an enormous burden on patients and public health (1). Recent work aimed at reducing the morbidity and costs of AF include genetic insights into the substrate for AF (2), ablation-guided mechanistic studies (3), and striking advances in anticoagulant therapy (4). Yet strategies for predicting and preventing AF in routine outpatient practice remain elusive.

In this issue, Dewland and colleagues (5) advance this discussion by presenting results from a substudy of the Cardiovascular Health Study, a large prospective cohort of more than 5000 Medicare beneficiaries drawn from 4 academic medical centers between 1989 to 1990. From that group, 1429 participants were randomly selected to receive 24-hour Holter monitoring at baseline assessment, of whom 1260 were included in the current study after exclusions for prevalent AF. The study evaluated the ability of hourly premature atrial contraction (PAC) count at baseline to predict incident AF, determined through annual electrocardiograms out to 10 years and hospital discharge diagnosis codes. Risk prediction was determined in several ways, including by adapted c-statistic of hourly PAC count compared with the Framingham AF risk algorithm both alone and with the PAC count, reclassification of intermediate-risk (10-year risk of 15% to 20%) participants in the Framingham model into high- (>20%) and low- (<15%) risk groups, and sensitivity and specificity of hourly PAC count.

Overall, at a median of 13.0 years of follow-up, 343 (27%) participants developed incident AF, whereas 573 (45%) died without a known new diagnosis of AF. Compared with patients who had a median PAC count of 2.5 beats/h, those with and without incident AF had median PAC counts of 5.3 and 1.8 beats/h, respectively. Although PAC count alone only trended toward improved AF risk discrimination compared with the Framingham model, adding PAC count to this model improved the c-statistic from 0.65 (95% CI, 0.61 to 0.67) to 0.72 (CI, 0.68 to 0.74). The proportion of intermediate-risk participants reclassified into high- or low-risk categories was 31.8% (CI, 4.1% to 59.6%; $P = 0.025$) and was driven by improved prediction for case participants rather than noncase participants. The relationship between hourly PAC count and incident AF risk was nonlinear, with specificity exceeding 90% at

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PAC counts greater than 32 beats/h and 95% at 100 beats/h. In a prespecified secondary analysis, PAC count was also associated with cardiovascular death and all-cause mortality.

This study was elegantly designed and extends prior work (6) by anchoring the importance of PAC count in a growing list of clinical variables shown to contribute additively to AF risk prediction (7). Several important limitations, however, diminish our enthusiasm for routine or targeted hourly PAC estimation in clinical practice. First, the long time horizon in this study (5 to 15 years depending on the analysis) may be a strength from an epidemiologic standpoint but weakens the case for PAC screening as a useful clinical tool. Second, the underlying mechanisms for developing and sustaining AF remain obscure and probably vary between AF phenotypes. Whether PACs represent modifiable triggers of arrhythmia or “herald beats” of a proarrhythmic substrate remains unproven. Thus, the work by Dewland and coworkers remains under the long shadow of past trials targeting ventricular ectopy to prevent sudden death. It is perhaps premature to assume that strategies designed to treat or prevent PACs will minimize future AF risk or will do so in all at-risk populations.

These 2 concerns coalesce as follows: Should we devote increasingly scarce health care resources to screen for PACs to predict incident (if distant) AF, or should we simply screen for prevalent AF in persons most likely to benefit from treatment? Prompt identification of incident AF in select populations will immediately impact treatment and presumably outcomes through rapid initiation of therapeutic anticoagulation. A recent study screening older adults with risk factors for thromboembolism found that 9% of previously undiagnosed patients met criteria for starting systemic anticoagulation (8). Further advances in ambulatory monitoring may make this the preferred strategy, even as parallel work strives to broaden our understanding of potentially modifiable substrates and triggers for AF.

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References

1. Lubitz SA, Bauer KA, Benjamin EJ, Besdine RW, Forman DE, Gurol ME, et al. Stroke prevention in atrial fibrillation in older adults: existing knowledge gaps and areas for innovation: a summary of an American Federation for Aging Research seminar. *J Am Geriatr Soc.* 2013; 61:1798–803. [PubMed: 24083473]
2. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, et al. Meta-analysis identifies 6 new susceptibility loci for atrial fibrillation. *Nat Genet.* 2012; 44:670–5. [PubMed: 22544366]
3. Narayan SM, Krummen DE, Clopton P, Shivkumar K, Miller JM. Direct or coincidental elimination of stable rotors or focal sources may explain successful atrial fibrillation ablation: on-treatment analysis of the CONFIRM trial (Conventional ablation for AF with or without focal impulse and rotor modulation). *J Am Coll Cardiol.* 2013; 62:138–47. [PubMed: 23563126]
4. Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation.* 2012; 126:2381–91. [PubMed: 23071159]
5. Dewland TA, Vittinghoff E, Mandayam MC, Heckbert SR, Siscovick DS, Stein PK, et al. Atrial ectopy as a predictor of incident atrial fibrillation. A cohort study. *Ann Intern Med.* 2013; 159:721–8. [PubMed: 24297188]

6. Binici Z, Intzilakis T, Nielsen OW, Køber L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. *Circulation*. 2010; 121:1904–11. [PubMed: 20404258]
7. Lubitz SA, Husser D. Genomic risk scores in atrial fibrillation: predicting the unpredictable? [Editorial]. *Eur Heart J*. 2013; 34:2227–9. [PubMed: 23585492]
8. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention. *Circulation*. 2013; 127:930–7. [PubMed: 23343564]