LETTERS TO THE EDITOR

doi:10.1093/europace/euw218
Published online 27 October 2016

Performance of hand-held electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting

I read the article on the performance of two hand-held electrocardiogram devices for detecting atrial fibrillation by Desteghe *et al.*[1] with great interest. As the founder of AliveCor, I supplied the senior author Dr. Heidbuchel with the AliveCor device, as it was neither approved nor available for sale in Belgium at that time, and his group understood that it could be used only for clinical research purposes. It had been approved by the FDA and EC and was commercially available in the USA and the UK. Per email communication, the investigators downloaded the Apple iPhone App in December, 2014 but did not update the app for the duration of the study for consistency purposes. AliveCor had to voluntarily recall that version of the App in February, 2015 due to several defects which impaired diagnostic accuracy.[2] Our commercial AFib algorithm has been biased for enhanced specificity when compared with the algorithm used in two previous AFib detection studies[3,4] as our product is primarily sold directly to patients, who may not seek a physician read. The version of our AF detection algorithm utilized in the published AF screening studies[3,4] was biased to very high sensitivity because every positive result would be reviewed by a Cardiologist. The result of the 'recalled' defects in the app version used in the *Europace* study, and our enhanced specificity biasing, resulted in the very low sensitivity of 55% in the cardiology patients, and 79% in the geriatric patients and high specificity of 98% in both patient groups after exclusion of paced rhythms.[1] This was significantly different than the published performance of the research algorithm in the two previous AF studies using the AliveCor device,[3,4] and would impact the economic assessments made in the Desteghe article. Higher sensitivity (71%) compared with the 55% seen in the cardiology patients, and very high specificity (99.4%) of our commercial algorithm during AFib screening has been demonstrated in a recent presentation.[5] I contacted Drs. Desteghe and Heidbuchel to notify them of these issues after seeing the publication, and offered to re-analyse the electrocardiographic data using the currently released non-defective algorithm, or the original research AF algorithm, but the ECG data were no longer available on the iOS recording device, so this was not possible.

References

1. Desteghe L, Raymaekers Z, Lutin M, Vijgen J, Dilling-Boer D, Koopman P *et al.* Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. *Europace* 2017;**19**:29–39.
2. Class 3 Device Recall AliveECG App Version 2.1.2 used with AliveCor Heart Monitor. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRes/res.cfm?id=133315 21 (May 2016, date last accessed).
3. Lau JK, Lowres N, Neubeck L, Brieger DB, Sy RW, Galloway CD *et al.* iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke. *Int J Cardiol* 2013;**165**:193–4.
4. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J *et al.* Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014;**111**:1167–76.
5. Siu D, Wong CK, Chan PH, Poh YK, Poh M-Z. Head-to-head comparison of a camera-based smartphone application CARDIIO rhythm with ALIVECOR® heart monitor for atrial fibrillation screening in primary healthcare setting. *J Am Coll Cardiol* 2016;**67**(13_S):696.

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doi:10.1093/europace/euw237
Published online 27 October 2016

'Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting: authors' response'

We would like to thank Dr Albert, Founder and Chief Medical Officer of AliveCor, for his interpretation of our study results to the readership in the light of different software versions.[1] As one may have noted in the article, 'despite' the findings of our study, our conclusions were positive about using AliveCor (as well as MyDiagnostick) in a hospital screening setting.[2] Those conclusions only get stronger with the clarifications of Dr Albert. Improvement of the accuracy of the AliveCor algorithm will further reduce the costs for both in-hospital and out-of-hospital screening for atrial fibrillation (AF).

We confirm that we downloaded the AliveCor iPhone app at the end of December 2014 and started screening of hospitalized cardiology and geriatric patients mid-January 2015 with the latest available version of the app, as was known to and confirmed by AliveCor Inc. For the sake of consistency, all recordings in our study were performed using the same protocol without adjustments or updates to both devices. The study was carried out in a short time span of ~4 months (inclusion was finished by the end of May 2015). The 'biased' enhanced specificity of the active AliveCor algorithm was confirmed in our study with high percentages varying between 96.1 and 98.1%.

On the basis of the experience of our study, we are convinced that a hospital population creates a more challenging AF screening setting than ambulatory patients. It remains speculative in how far observed sensitivity and specificity in other populations are applicable to the in-hospital setting. Especially, hospitalized geriatric patients (with a mean age of 83 years in our study) are often very weak, have tremor, or cannot handle whatever device. Moreover, a high prevalence of implanted devices and known AF further contribute to screening complications. Nevertheless, with a properly structured approach, using handheld devices is the way to go in a hospital setting, because the detection by pulse taking (even by trained nurses) is not specific and screening using 12-lead electrocardiograms is definitely not cost-effective.[3,4]

More studies and advances in these technologies can further optimize the usability and accuracy of handheld ECG monitors, such as MyDiagnostick and AliveCor. We hope that our work provides further impetus to companies to continue development on important technological aids for screening AF. This will especially serve those patients who have the highest risk to develop AF, such as hospitalized cardiologic or geriatric patients.

Conflict of interest: none declared.

References

1. Albert DE. Performance of hand-held electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. *Europace* 2017;**19**:1408.
2. Desteghe L, Raymaekers Z, Lutin M, Vijgen J, Dilling-Boer D, Koopman P *et al.* Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. *Europace* 2017;**19**:29–39.

3. Cooke G, Doust J, Sanders S. Is pulse palpation helpful in detecting atrial fibrillation? A systematic review. *J Fam Pract* 2006;**55**:130–4.
4. Morgan S, Mant D. Randomised trial of two approaches to screening for atrial fibrillation in UK general practice. *Br J Gen Pract* 2002;**52**:373–80.

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doi:10.1093/europace/euw195
Published online 15 March 2017

Monocyte-to-HDL-cholesterol ratio and left atrial remodelling in atrial fibrillation

I was grateful to read an interesting paper by Suzuki *et al.*[1] which revealed that the ratio of circulating intermediate CD14++CD16+ monocytes was significantly higher in patients with atrial fibrillation (AF) compared with control group. Intermediate CD14++CD16+ monocytes also showed a strongly negative correlation with left atrial appendage (LAA) flow during sinus rhythm. Moreover, the ratio of circulating intermediate CD14++CD16+ monocytes was found as an independent predictor for the presence of AF.

Atrial fibrillation is initiated and maintained by a complex interaction between electrical, contractile, and structural remodelling.[2] Inflammation, oxidative stress, and subsequent atrial fibrosis are shown to be significant contributors of structural remodelling process.[3] It has been already shown that the extent of atrial fibrosis as a hallmark for structural remodelling has had a prognostic and therapeutic role in AF patients.[4] Monocytes are the most important sources of pro-inflammatory and pro-oxidant cytokines at inflammatory sites, which leads to atrial adverse electrical and/or structural remodelling and may represent a prerequisite for AF.[4] Because of its anti-inflammatory and anti-oxidant actions, the relationship between high-density lipoprotein cholesterol (HDL-C) and AF has also been investigated. In our recent study,[5] we combined both parameters as 'monocyte count-to-HDL-C ratio (MHR)' and evaluated its prognostic value among AF patients undergoing catheter ablation. For the first time in the literature, we demonstrated that MHR was found as an independent predictor of AF recurrence after cryoballoon-based AF ablation. We also showed that MHR has been significantly correlated with LA diameter and duration of AF history. These findings supported that the monocyte accumulation and reduced HDL-C may participate in atrial remodelling by the release of activated substances, including oxygen-free radicals, proteases, and pro-inflammatory cytokines. One of the important limitations of our study was using an automatically counted monocyte numbers rather than the proportion of monocyte subsets. Thus, the study by Suzuki *et al.*[1] may support and confirm our previous findings when the ratio of circulating intermediate CD14++CD16+ monocytes to HDL-C levels has been calculated and analysed. Because MHR combines the two detrimental processes like inflammation and oxidative stress, it could be used as a novel marker for prediction of the severity of atrial remodelling. However, additional large-scale prospective studies in different populations are needed to confirm the role of MHR and/or circulating intermediate CD14++CD16+ monocytes/HDL-C in the pathophysiology and prognosis of AF.

Conflict of interest: none declared.

References

1. Suzuki A, Fukuzawa K, Yamashita T, Yoshida A, Sasaki N, Emoto T *et al.* Circulating intermediate CD14++CD16 + monocytes are increased in patients with atrial fibrillation and reflect the functional remodelling of the left atrium. *Europace* 2016;**19**:40–7.
2. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;**54**:230–46.
3. Canpolat U, Oto A, Yorgun H, Sunman H, Sahiner L, Kaya EB *et al.* Association of plasma fibronectin level with left atrial electrical and structural remodelling in lone paroxysmal atrial fibrillation: a cross-sectional study. *Turk Kardiyol Dern Ars* 2015;**43**:259–68.
4. Friedrichs K, Klinke A, Baldus S. Inflammatory pathways underlying atrial fibrillation. *Trends Mol Med* 2011;**17**:556–63.
5. Canpolat U, Aytemir K, Yorgun H, Sahiner L, Kaya EB, Cay S *et al.* The role of preprocedural monocyte-to-high-density lipoprotein ratio in prediction of atrial fibrillation recurrence after cryoballoon-based catheter ablation. *Europace* 2015;**17**:1807–15.

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doi:10.1093/europace/euw197
Published online 5 October 2016

Monocyte-to-HDL-cholesterol ratio and left atrial remodelling in atrial fibrillation: author's reply

We thank Dr Canpolat[1] for his interest in our recent study.[2] Many studies have established a strong association between inflammation, oxidative stress, and atrial fibrillation (AF); the pathogenesis and progression of AF seem to be simultaneously influenced by multiple factors.[3–5] Canpolat *et al.* showed in their study that among commonly measured clinical factors, the 'monocyte to high-density lipoprotein cholesterol (HDL-C) ratio (MHR)'—a combined inflammatory and oxidative stress marker—was independently associated with AF recurrence after cryoenergy ablation and correlated with the left atrial (LA) diameter.[6] In our study, we investigated the role of intermediate CD14++CD16+ monocytes in the pathogenesis of AF and showed that a monocyte subgroup, intermediate CD14++CD16+ monocytes, was independently associated with the presence of AF. In addition, intermediate CD14++CD16+ monocytes reflected LA functional remodelling. Of note, the total monocyte count in healthy controls and AF patients without any other obvious co-morbidities was not predictive for the AF status.[2]

In their letter to the editor, Canpolat *et al.* now hypothesize that the 'intermediate CD14++CD16+ monocytes to HDL-C ratio' is able to predict severity of LA remodelling. To this end, we performed a sub-analysis of our data including MHR and intermediate CD14++CD16+ MHR (iMHR). In addition, for a complete analysis, we looked at classical CD14++CD16– MHR (cMHR) as well as non-classical CD14+CD16++ MHR (nMHR). Univariate logistic regression analysis revealed that the MHR [odds ratio (OR): 1.041; 95% confidence interval (CI): 1.004–1.078, $P = 0.027$] and iMHR (OR: 2.057; 95% CI: 1.301–3.251, $P = 0.002$) both influenced the presence of AF. Furthermore, parameters such as body mass index, diastolic blood pressure (dBP), total cholesterol (T-chol), HDL-C, triglycerides (TG) and proportion of classical CD14++CD16– monocytes, and intermediate CD14++CD16+ monocytes also influenced the AF status. There was no statistical significant association of cMHR and nMHR values with AF (OR: 1.040; 95% CI: 0.997–1.085, $P = 0.070$ and OR: 1.259; 95% CI: 0.976–1.623, $P = 0.076$, respectively). Although iMHR was strongly associated with the presence of AF ($P = 0.002$), the cell proportion of intermediate CD14++CD16+ monocytes (collinear to MHR and iMHR) of all parameters had the strongest association with the presence of AF in univariate analysis ($P = 0.001$).

In contrast to intermediate CD14++CD16+ monocytes, the iMHR did not show significant correlation with any clinical and laboratory parameters including the duration of AF, echocardiogram parameters, BNP level, and LA volume in AF patients.

There are several limitations inherent to the different design of our present study and in the study of Canpolati *et al.* First, to avoid bias of other systemic diseases, our study population was limited to patients without any co-morbidities. Secondly, mean HDL-C level in our study