Detection of atrial fibrillation

Impact

Research is driven by the urge to improve the world around us. It is usually inspired by a problem in daily life. The problem we addressed, was the occurrence of serious medical events such as a stroke, heart failure and death, as a consequence of undetected atrial fibrillation (AF). Our aim was to detect AF in an early stage, to prevent these severe consequences. We gathered knowledge by performing research, to find ways to solve the issue. Now, years after the start of our studies, when the research is finished, it is very important to look back to the problem in daily life that inspired us in the first place. How should the results be interpreted? In this chapter we reflect on how our research can influence daily life (societal impact) and science (scientific impact).

Societal impact

Research can impact society on different levels, such as climate, culture, and economy. The societal impact of this thesis can best be described in terms of policy making, industry and health. We also put our results in an international perspective.

Policy making

We initiated our trial with the intention to improve AF detection. Against our expectations, we did not pave the way for opportunistic screening. On the contrary: our results make us question dearly whether it should be done at all. Therefore, we do not recommend incorporating screening for AF in the Dutch 'NHG-standaarden', even though international guidelines already advise screening.[1-5]

In the usual care group, we found that diagnosis of AF was generally the result of an interdisciplinary process. General practitioners (GPs) most often detected the irregular pulse, whereas the cardiologists usually diagnosed it. A smooth cooperation between these physicians is therefore very important. We recommend making local working agreements to facilitate this process. These could comprise easy referral options, a possibility to share electrocardiography (ECG) recordings with a cardiologist for specialist advise, and/or protocolised care pathways.

Industry

In our diagnostic accuracy study (chapter 6) we used three AF detection methods for opportunistic screening: radial pulse palpation and measurements with two devices with built-in AF detection algorithm – an electronic blood pressure monitor

('eBPM', WatchBP Home A) and a single-lead ECG device ('handheld ECG', MyDiagnostick). The eBPM and the handheld ECG were both suitable for opportunistic screening purposes. The handheld ECG device had the best diagnostic accuracy. Being able to measure blood pressure with the eBPM can be an advantage. However, the ability to extract a rhythm strip from the handheld ECG might even be more convenient, especially if the quality is sufficient for diagnosing AF.[6] We assessed the rhythm strips of the intermittent home measurements described in chapter 7; sensitivity and specificity were lower than for single measurements in general practice. Furthermore, cardiologists judged the quality to be poor for the measurements at home. However, another study showed that AF can safely be ruled out using the rhythm strips of the same device, when the measurements are not performed at home but supervised by a GP.[7] The setting, performer, and number of measurements seem to influence both the accuracy and the quality of the recording. Ensuring a good quality of the rhythm strips under different circumstances is important when developing single-lead ECG devices. Direct feedback by means of a screen with a visible rhythm strip could facilitate this.

Ambulatory monitoring by means of a Holter or event recorder does not seem to be a popular method among professionals and patients. Performing ambulatory monitoring can be burdensome for patients; they must temporarily disconnect the device while bathing or showering, and it can be a nuisance when going to sleep. In our vignette studies in chapter 2 and 3, GPs and cardiologists chose long-term monitoring less often than recommended by the guidelines. Furthermore, in our trial we experienced a large dropout of patients before and during the two-week Holter and intermittent single-lead ECG measurements. The yield of new cases in asymptomatic patients of ≥65 years with a negative 12-lead ECG was low. This might be due to a selection bias; those that did perform the measurements at home were younger and had less comorbidity. However, consistently applying ambulatory monitoring in patients with intermittent signs or symptoms, as recommended by the guidelines, might still enhance AF detection.

Industry has already reacted to the reluctance to perform ambulatory monitoring, with the development of innovative and less obtrusive methods. Examples of these new methods are ECG patches, smartwatches, and smartphones.[8, 9] However, many of these devices still require validation. In the survey in chapter 9 we explored consumer-facing wearables, devices and apps for AF detection. Currently health care professionals around the world believe we are not ready to implement them to

screen for AF. We first need to better define suitable individuals for screening and an appropriate mechanism for managing positive results.
The results of our research can impact the development of devices. We advise to focus on the development of continuously instead of intermittently measuring devices. The challenge is to develop valid, reliable, and patient friendly devices for long-term monitoring.

Health care
The proposed opportunistic screening strategy in the Detecting and Diagnosing Atrial Fibrillation (D_2AF) study, described in chapter 4 to 8, was ineffective and cannot, as such, be implemented in everyday health care. We showed that usual care is equally effective in detecting AF, therefore, patients will not be screened for AF. We spare patients from having to undergo unnecessary testing. However, the ineffectiveness of opportunistic screening in our setting, does not mean that the investigated devices are useless. When the blood pressure needs to be taken, one might as well use a device with AF-detection function. This is in line with the advice of the Dutch College of General Practitioners to assess heart rhythm when measuring blood pressure.[1]
It is tempting to use the handheld ECG as a diagnostic tool in other situations, for instance in patients with symptoms suggestive of AF, or in home dwelling patients who cannot visit the practice for a 12-lead ECG. However, our results cannot be extended to these patient groups and previous research on the MyDiagnostick also focussed on screening settings, so we still advise caution when applying the device in other situations.[10-12] Furthermore, the AF detection algorithm of other handheld ECG and eBPM devices may differ from the devices that we used. Therefore, diagnostic accuracy can be different. As such, our results are not automatically applicable to other devices.

International collaboration
Different guidelines from various countries give advice on diagnostic procedures for AF.[1-5] International guidelines advise screening, while the Dutch guideline does not. Studies from varying countries gave contradictory results regarding the effect of screening.[13-17] It is important to look at these international differences, to uncover which factors attribute to success and which to a lack of effect. An international research agenda could facilitate the process and create cohesion.

The publication of the D_2AF study protocol aroused the interest of the AF-SCREEN international collaboration, a group promoting discussion and research about screening for AF. Steven Uittenbogaart and I were invited to attended an AF-SCREEN meeting in Rome in 2016.[18] During this gathering, we took part in a consensus procedure on recommendations on screening for AF, resulting from a Delphi process. The two of us and the 49 other attendents voted and proposed changes, which were worked out further in a smaller group the next day. This resulted in the publication of a white paper.[19] With our vote we were able to have an impact on these international recommendations.

In 2019 the members of the collaboration distributed a survey among their colleagues, on the use of wearables and devices.[20] The results were presented in chapter 9. It is because of the collaboration, that the survey could be distributed widely, reaching different kinds of health care professionals internationally.

In the future, the collaboration may be used to perform larger international studies, or facilitate the exchange of data. However, as scientists devoted to screening for AF, we must ensure not to develop tunnel vision. Keeping an open mind is important, because – as we showed in our trial – screening for AF is not always effective.

Scientific impact

We now have a look at how our results impact science. However, what defines scientific impact? To clarify that, we go back to the first randomised controlled trial (RCT), conducted by Bradford Hill.[21] He laid the foundations for modern medical research in 1948, when he successfully showed that streptomycin was more effective than only bedrest in treating tuberculosis. Ever since, RCTs represent a high methodological quality in evidence-based medicine, with great scientific impact.

Trials with a significant positive effect, such as the trial of Bradfort Hill, usually get the most attention.[22] They lead to new treatments or diagnostic strategies and provide a clear path to improve current practice. In contrast, negative trials are often regarded as failures. They were (and still are) underrepresented; it is more difficult to get the results published, they have a lower citation index, are less often presented at conferences, and get less attention in the media than positive trials.[23] Measuring scientific impact by the attention a study gets, however, is unjust. The importance of negative trials – if they are not underpowered – is underrated. The results show us what *not* to do and can lead to valuable hypotheses for new research. Furthermore, highlighting positive trials at the expense of negative trials

can create a distorted view of reality, especially when results of trials are bundled in systematic reviews or meta-analyses.

Screening for AF

Let us focus on our research field. In 2007 Fitzmaurice et al. published the 'Screening For AF in the Elderly' (SAFE) study. This RCT on screening for AF showed a positive effect of screening.[13] After this, AF detection became a hot topic. In the past two decades, many studies were performed in different settings, looking at various aspects of screening. Which device should be used?[24-26] In which setting and which population should we screen?[27-31] The European Society of Cardiology (ESC) recommended opportunistic screening in the updated guideline on management of AF in 2016.[32] In 2017 Halcox et al. confirmed the positive effect of screening in the 'Assessment of REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation' (REHEARSE-AF) trial.[14] Small systematic reviews on screening for AF were performed in 2018 and 2019, favouring screening.[33, 34] But then, in 2020, two Dutch RCTs, our own D_2AF study (chapter 8) and the 'Improving DEtection of Atrial fibriLlation in Primary Care With the MyDiagnostick' (IDEAL-MD) study, showed no effect of screening for AF.[15] While we all thought screening for AF was effective, now doubt arose. Even though our trial was negative, it was ever so important: it made us question the benefit of screening, which was previously assumed to be certain.

The conflicting results on the effect of screening for AF could inspire other scientists. In future systematic reviews on the effect of screening for AF, the inclusion of our study might shift the balance. Future research could focus on screening in populations with a low incidence of AF or select patients based on risk factors for development of AF, for instance heart failure and hypertension. More research is needed to uncover which factors lead to an effective intervention.

Conclusion

We demonstrated that opportunistic screening for AF is not effective in Dutch patients ≥65 years of age. We show that a change of course is necessary in research on AF detection. Hopefully our research will impact the direction of future research, like a pebble in the pond.

References

1. NHG-werkgroep Atriumfibrilleren. NHG-Standaard Atriumfibrilleren (Derde partiële herziening). Huisarts Wet. 2017;60(9):2-27.
2. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2020.
3. National Institute for Health and Care Excellence. Lead-I ECG devices for detecting symptomatic atrial fibrillation using single time point testing in primary care. London: National Institute for Health and Care Excellence; 2019. p. 40.
4. National Institute for Health and Care Excellence. WatchBP Home A for opportunistically detecting atrial fibrillation during diagnosis and monitoring of hypertension: guidance, MTG 13. London: National Institute for Health and Care Excellence; 2013.
5. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2020;36(12):1847-948.
6. Witvliet MP, Karregat EPM, Himmelreich JCL, de Jong J, Lucassen WAM, Harskamp RE. Usefulness, pitfalls and interpretation of handheld single-lead electrocardiograms. J Electrocardiol. 2021;66:33-7.
7. Karregat EPM, Himmelreich JCL, Lucassen WAM, Busschers WB, van Weert H, Harskamp RE. Evaluation of general practitioners' single-lead electrocardiogram interpretation skills: a case-vignette study. Fam Pract. 2021;38(2):70-5.
8. Barrett PM, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, et al. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. Am J Med. 2014;127(1):95.e11-7.
9. Al-Alusi MA, Ding E, McManus DD, Lubitz SA. Wearing Your Heart on Your Sleeve: the Future of Cardiac Rhythm Monitoring. Curr Cardiol Rep. 2019;21(12):158.
10. Tieleman RG, Plantinga Y, Rinkes D, Bartels GL, Posma JL, Cator R, et al. Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. Europace. 2014;16(9):1291-5.
11. Battipaglia I, Gilbert K, Hogarth AJ, Tayebjee MH. Screening For Atrial Fibrillation In The Community Using A Novel ECG Recorder. J Atr Fibrillation. 2016;9(2):1433.
12. 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. 2016.
13. Fitzmaurice DA, Hobbs FD, Jowett S, Mant J, Murray ET, Holder R, et al. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. BMJ. 2007;335(7616):383.
14. Halcox JPJ, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, et al. Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study. Circulation. 2017;136(19):1784-94.
15. Kaasenbrood F, Hollander M, de Bruijn SH, Dolmans CP, Tieleman RG, Hoes AW, et al. Opportunistic screening versus usual care for diagnosing atrial fibrillation in general practice: a cluster randomised controlled trial. Br J Gen Pract. 2020;70(695):e427-e33.

16. Uittenbogaart SB, Verbiest-van Gurp N, Lucassen WAM, Winkens B, Nielen M, Erkens PMG, et al. Opportunistic screening versus usual care for detection of atrial fibrillation in primary care: cluster randomised controlled trial. BMJ. 2020;370:m3208.
17. Lubitz SA, Atlas SJ, Ashburner JM, Lipsanopoulos ATT, Borowsky LH, Guan W, et al. Screening for Atrial Fibrillation in Older Adults at Primary Care Visits: the VITAL-AF Randomized Controlled Trial. medRxiv. 2021:2021.08.13.21261969.
18. Freedman B. AF-SCREEN international collaboration. Eur Heart J. 2016;37(47):3490-1.
19. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, et al. Screening for Atrial Fibrillation: A Report of the AF-SCREEN International Collaboration. Circulation. 2017;135(19):1851-67.
20. Boriani G, Schnabel RB, Healey JS, Lopes RD, Verbiest-van Gurp N, Lobban T, et al. Consumer-led screening for atrial fibrillation using consumer-facing wearables, devices and apps: A survey of health care professionals by AF-SCREEN international collaboration. Eur J Intern Med. 2020;82:97-104.
21. Crofton J. The MRC randomized trial of streptomycin and its legacy: a view from the clinical front line. J R Soc Med. 2006;99(10):531-4.
22. Mlinarić A, Horvat M, Šupak Smolčić V. Dealing with the positive publication bias: Why you should really publish your negative results. Biochem Med. 2017;27(3):030201.
23. Snyder RJ. Lack of Transparency in Publishing Negative Clinical Trial Results. Clin Podiatr Med Surg. 2020;37(2):385-9.
24. Bury G, Swan D, Cullen W, Keane D, Tobin H, Egan M, et al. Screening for atrial fibrillation in general practice: a national, cross-sectional study of an innovative technology. Int J Cardiol. 2015;178:247-52.
25. Chan NY, Choy CC, Chan CK, Siu CW. Effectiveness of a nongovernmental organization-led large-scale community atrial fibrillation screening program using the smartphone electrocardiogram: An observational cohort study. Heart Rhythm. 2018;15(9):1306-11.
26. Steinhubl SR, Waalen J, Edwards AM, Ariniello LM, Mehta RR, Ebner GS, et al. Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation: The mSToPS Randomized Clinical Trial. JAMA. 2018;320(2):146-55.
27. Hald J, Poulsen PB, Qvist I, Holm L, Wedell-Wedellsborg D, Dybro L, et al. Opportunistic screening for atrial fibrillation in a real-life setting in general practice in Denmark-The Atrial Fibrillation Found On Routine Detection (AFFORD) non-interventional study. PLoS One. 2017;12(11):e0188086.
28. Bacchini M, Bonometti S, Del Zotti F, Lechi A, Realdon F, Fava C, et al. Opportunistic Screening for Atrial Fibrillation in the Pharmacies: A Population-Based Cross-Sectional Study. High Blood Press Cardiovasc Prev. 2019;26(4):339-44.
29. Berge T, Brynildsen J, Larssen HKN, Onarheim S, Jenssen GR, Ihle-Hansen H, et al. Systematic screening for atrial fibrillation in a 65-year-old population with risk factors for stroke: data from the Akershus Cardiac Examination 1950 study. Europace. 2018;20(Fi_3):f299-f305.
30. 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(8):930-7.
31. Gwynne K, Flaskas Y, O'Brien C, Jeffries TL, McCowen D, Finlayson H, et al. Opportunistic screening to detect atrial fibrillation in Aboriginal adults in Australia. BMJ open. 2016;6(11):e013576.
32. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893-962.

33. Jonas DE, Kahwati LC, Yun JDY, Middleton JC, Coker-Schwimmer M, Asher GN. Screening for Atrial Fibrillation With Electrocardiography: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2018;320(5):485-98.
34. Lowres N, Olivier J, Chao TF, Chen SA, Chen Y, Diederichsen A, et al. Estimated stroke risk, yield, and number needed to screen for atrial fibrillation detected through single time screening: a multicountry patient-level meta-analysis of 141,220 screened individuals. PLoS Med. 2019;16(9):e1002903.