Dr. rer. med. Florian Brandt MSc
Marc Kreiser MSc
Dipl.-Ing. (FH) Christoph Eisert
Univ.-Prof. Dr. med. Axel Bauer MHBA

Smartphonebasiertes Screening auf Vorhofflimmern: Erkenntnisse der eBRAVE-AF-Studie

Summary

Atrial fibrillation (AF) is the most common relevant cardiac arrhythmia and can lead to severe sequelae. For example, unrecognised and untreated VHF leads to a significant increase in the risk of stroke. Such risks can be counteracted by treatment with blood-thinning medication - so-called oral anticoagulation (OAC). Often, however, VCF is not detected in time. Smartphone-based screenings offer a low-threshold and scalable approach to address this problem. In the randomised controlled eBRAVE-AF study, such an approach was investigated among 5,551 at-risk patients. In the first phase of the study, 2,860 participants (intervention group) underwent a screening programme that included a screening app, a connected telemedical centre and - in the case of an abnormal app measurement - a 14-day ECG, while a further 2,691 participants (control group) received regular care. After six months, the group membership changed (cross-over design) and a second, six-month study phase followed. The screening programme more than doubled the detection rate of treatment-emergent VCF in both phases. This study report provides further insight into this and other findings.

Schlüsselwörter

Cardiac arrhythmia, cardiology app, stroke prevention, study report, VHF diagnostics

Crossref/doi

http://doi.org/10.24945/MVF.03.23.1866-0533.2514

Background

With a lifetime risk of about one in four, atrial fibrillation (AF) is one of the most common cardiac arrhythmias (Lloyd-Jones et al.; 2004). In those affected, the heart beats irregularly for a prolonged period of time, which leads to an inadequate blood supply in the body. As a consequence, dangerous blood clots can form. These in turn can trigger a so-called thromboembolism - i.e. a blockage of blood vessels - and lead, among other things, to an ischaemic stroke - the second most common cause of death worldwide (Lozano et al., 2012) (Kirchhof et al., 2016). In Europe alone, more than 430,000 people died in 2013 as a result of this circulatory disorder in the brain, also known as cerebral infarction - of which almost 60,000 were in Germany (Eurostat, 2016). In addition, stroke is a major cause of acquired disability in adulthood (Murray et al., 2012).

Etwa 20–30% aller Schlaganfälle sind mit einem Vorhofflimmern (VHF) assoziiert (Grond et al., 2013; Kishore et al., 2014). Da VHF jedoch oft nur sporadisch und ohne jegliche Symptome auftritt, ist es gegebenenfalls schwer zu erkennen (Jaakkola et al., 2016). Eine rechtzeitige Identifikation von VHF ist jedoch äußerst wichtig, da nur so eine Therapie eingeleitet und das Schlaganfallrisiko reduziert werden kann. In diesem Zusammenhang empfiehlt die einschlägige medizinische Leitlinie – bei positivem Testergebnis im Rahmen der VHF-Diagnostik – eine Abschätzung des individuellen Schlaganfallrisikos mithilfe des sog. CHA2DS2-VASc-Risikoscores, der durch die Vergabe von Punkten für die Erfüllung bestimmter Risikotatbestände (z. B. Erreichen definierter Altersschwellen oder Vorliegen anderer risikoerhöhender Erkrankungen) ermittelt wird (Hindricks et al., 2021). Unter einem Score von 2 kann eine bloße Anpassung des Lebensstils ausreichen, während bei einem Score ≥ 2 regelmäßig eine sog. orale Antikoagulation (OAK), d. h. eine Gabe von Medikamenten zur Hemmung der Blutgerinnung (auch als „Blutverdünner" bezeichnet), indiziert ist. Im Falle einer indizierten OAK kann diese das Schlaganfallrisiko um etwa 70% verringern (Hart et al., 2007; López-López et al., 2017) – in Anbetracht schlaganfallassoziierter direkter Krankheitskosten von durchschnittlich ca. 43.200 Euro auch ökonomisch von Bedeutung (Birkemeyer et al., 2020).

Smartphone-based screening vs. regular diagnostics

>> Conventional VHF diagnostics involves measuring the heart's activity with the help of electrodes and displaying it in the form of a curve (so-called electrocardiogram (ECG)). A functioning heart produces a regular image in the ECG, whereas the corresponding image is visibly irregular in an existing cardiac arrhythmia. However, regular ECG measurements have limited sensitivity with regard to VHF, as the irregularities described often do not occur permanently. Even a long-term ECG, where the recording period is usually 24 hours, 1 is in many cases too short to detect a VHF episode. For example, relevant studies have shown that the VHF detection rate only comes close to an optimum when the measurement period is extended to up to 14 days (Turakhia et al., 2013; Quer et al., 2020). Furthermore, current ECG measurement methods are too bulky and costly for large-scale screening and thus not suitable for identifying asymptomatic cases in the field. Instead, more manageable, cost-effective and at the same time reliable screening methods are needed so that the cardiac arrhythmia in such cases does not first become recognisable through a stroke (Jaakkola et al., 2016). One such possibility is the two-stage VHF screening of Preventicus GmbH. The central components are - as shown in Figure 1 - a clinically validated screening app (Preventicus Heartbeats), a connected telemedical centre (Herzklinik Ulm) and a 14-day ECG, which is recorded with an external ECG loop recorder (CardioMem CM 100XT, GETEMED) in the event of an abnormal app measurement.

Preventicus Heartbeats is a certified Class IIa medical device that can distinguish between normal and irregular heart rhythm with a reported sensitivity and specificity of 89.9% and 99.1% (based on a one-minute measurement), respectively (Brasier et al., 2019). For this purpose, the user positions the camera of the smartphone on any fingertip. Using the LED flash and the smartphone camera, Preventicus Heartbeats records the heart rhythm - based on the photoplethysmography (PPG) method, which is also used by commercially available pulse oximeters -analyses it and summarises the results in an ECG-comparable report. All that is needed to use it is a commercially available smartphone. It is not necessary to purchase any

1: In the EBM, a minimum recording duration of 18 hours is defined according to GOP 03322, 04322, 13252 or 27322.

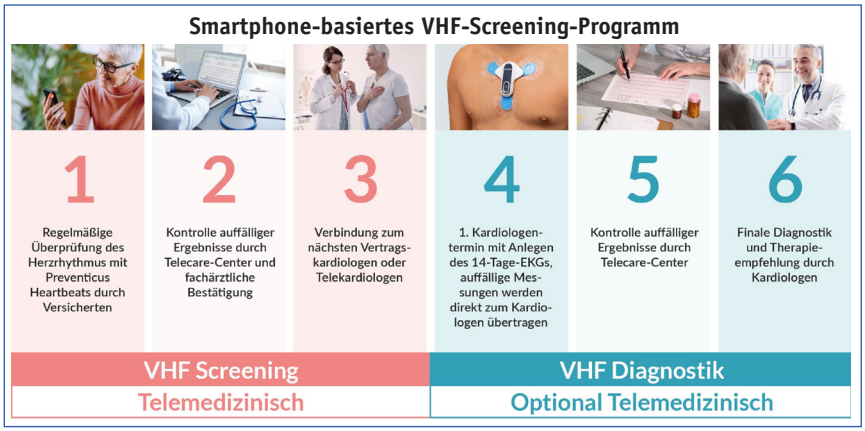


Fig. 1: Smartphone-based VHF screening programme. Source: Preventicus GmbH.

accessories, which increases its suitability for large-scale and regular screenings.

Conspicuous results are automatically transmitted to the connected telemedical centre for confirmation. If the abnormalities are confirmed, a 14-day long-term ECG is recorded to confirm the diagnosis, which in this respect goes far beyond the usual 24-hour recording in standard care. The external ECG loop recorder used for this purpose can automatically recognise, record and save various cardiac arrhythmias. This so-called event triggering is a necessary condition for a 14-day ECG, as the automated preselection of potentially relevant measurement phases is what makes it possible in the first place to analyse such a long measurement period - despite scarce time resources in cardiological care.

In the statutory health insurance (SHI), the programme is offered within the framework of the RhythmusLeben contract according to § 140a SGB V (Brandt et al., 2021). Here, after the smartphone-based screening, the external ECG loop recorder is used in a telemedical variant. This means that all events are transmitted to a telemedical centre for technical pre-assessment. Participating cardiologists can access all data via a special web application and use it to make a diagnosis.

The eBRAVE-AF study

In the eBRAVE-AF study (eHealth-based Bavarian Alternative Detection of Atrial Fibrillation), the effectiveness of the described smartphone-based VCF screening programme was scientifically investigated for the first time in comparison to regular care (Freyer et al., 2021; Rizas et al., 2022). The following study report provides information on the central key points and findings of this randomised controlled trial (RCT).

Design and implementation

The primary interest of the study was to find out whether the screening programme shown in figure 1 could detect a significantly higher number of ‚hidden' cases of VCF than in standard care. The focus was on patients at risk who are eligible for subsequent OAK due to an elevated CHA2DS2-VASc score.

This resulted in the following inclusion criteria:

- Age between 50 and 90 years ,
- CHA2DS2-VASc score ≥ 1 (men) or ≥ 2 (women),
- no existing VHF and
- no ongoing OAK .

The study participants were recruited throughout Germany in 2020 among insured persons of the cooperating Versicherungskammer Bayern. The number of persons in the target group who were invited, participated and dropped out during the course of the study is shown in the flow chart in Figure 2. A total of 67,488 insured persons fulfilled H.

- based on the case data of the Versicherungskammer Bayern - fulfilled the inclusion criteria and were invited to participate in the study. Of these, 5,587 (8.3%) downloaded the specially developed study coordination app, completed the initial questionnaire stored there and electronically declared their consent to study participation. The majority (5,551 people) continued to fulfil the defined inclusion criteria - also taking into account the information provided in the initial questionnaire - and were included in the study. Finally, 4,453 participants completed the study, while 100 participants were diagnosed with VCF with indicated OAC during the course of the study, i.e. the primary endpoint was reached, and 633 participants dropped out for other reasons (e.g. withdrawal of informed consent or death).

The study design provided for a parallel group comparison (intervention group = smartphone-based screening (Preventicus) vs. control group = standard care), whereby standard care wassimulated in that control group patients - virtually on their own - did not receive any diagnostic services within the study. Group allocation was randomised and unblinded, as the nature of the intervention was not amenable to blinding. After six months each in the control and

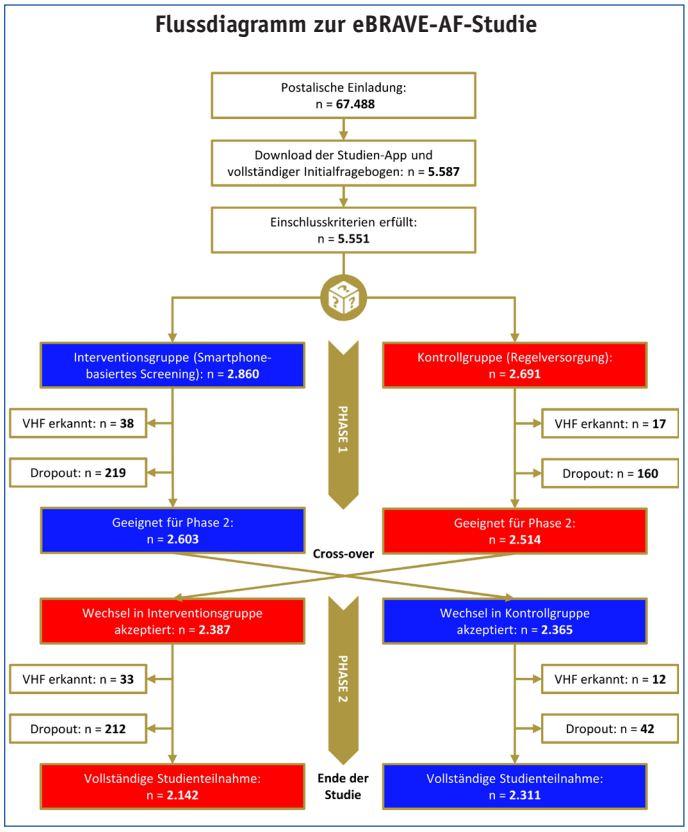


Fig 2: Flow chart of the eBRAVE-AF study. Source: own representation based on Rizas et al., 2022.

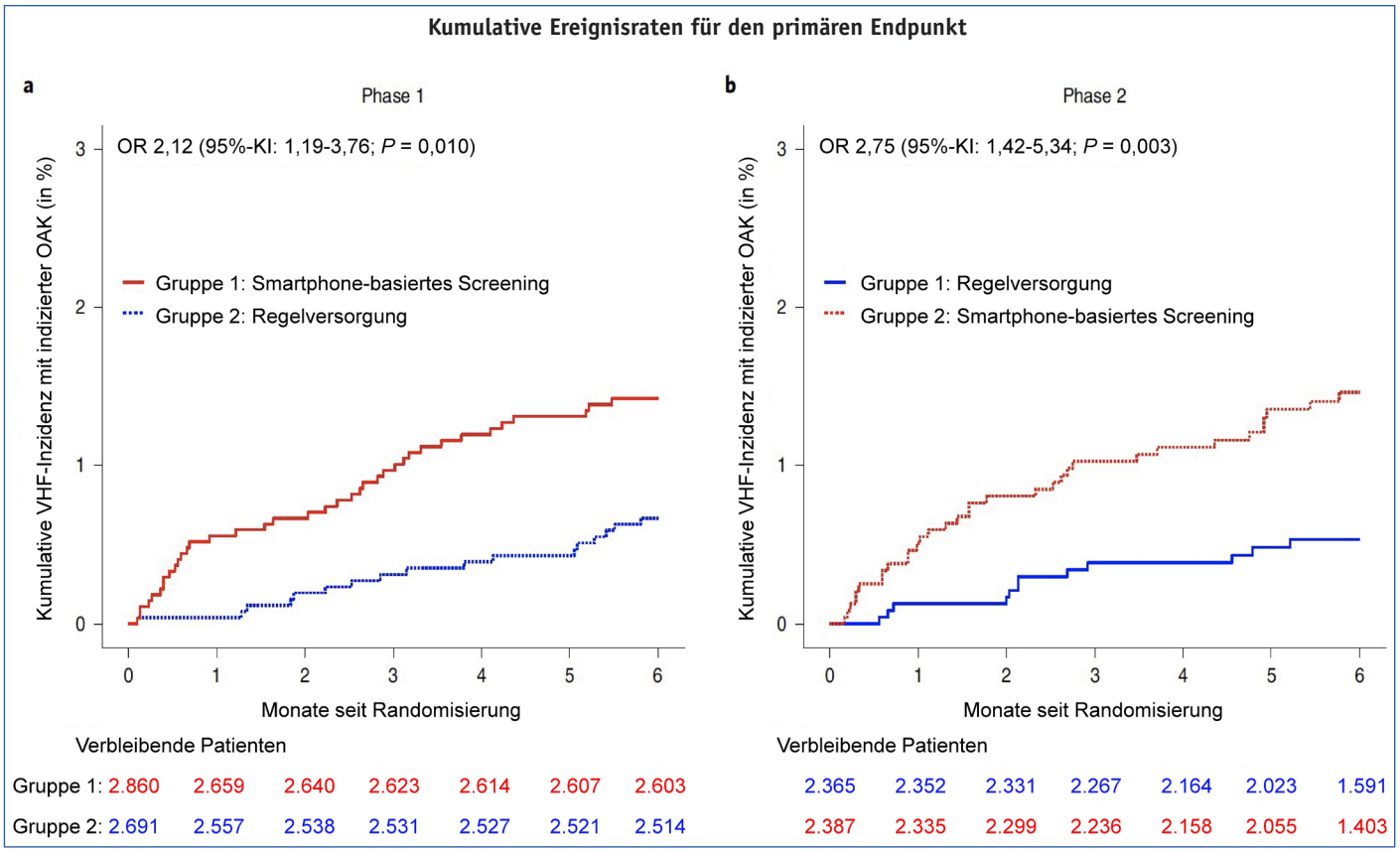


Fig 3: Cumulative event rates for the primary endpoint (detection of VCF with indicated OAC). Abbreviations: CI = confidence interval; OR = odds ratio. Source: Illustration modified from Rizas et al., 2022.

intervention group, a six-month cross-over phase followed, i.e. the group allocation was swapped. In this way, none of the study participants had to be deprived of the innovative screening programme. In addition, the cross-over design enabled both inter- and intra-group comparisons, which - in addition to randomisation - safeguarded the study results against possible biases resulting from structural differences between the comparison groups. If VCF was detected during the course of the study, participants were referred to their local doctor. The respective physicians were not involved in the study and made all subsequent treatment decisions, e.g. the initiation of OAK, at their own discretion. The research data were collected during the study through app-based questionnaires and telephone calls and supplemented at the end of the study with case data from the Versicherungskammer Bayern (diagnoses made according to ICD-10-CM and medicines dispensed according to ATC).

The effect of screening on the primary endpoint was investigated using a logistic regression analysis to estimate the effect of an independent variable (here: type of VCF screening) on the time to a dependent event (here: detection of VCF with indicated OAC). The effect of smartphone-based screening on the primary endpoint was quantified using the odds ratio (OR). The OR represents the calculated odds of the event ‚detection of VCF with indicated OAC' in the ratio of the intervention group to the control group. It can assume values between 0 and ∞, with values > 1 representing a greater chance of detection in the intervention group.

The effect of smartphone-based screening on the primary endpoint was quantified using the odds ratio (OR). The OR represents the calculated odds of the event ‚detection of VCF with indicated OAC' in the ratio of the intervention group to the control group. It can assume values between 0 and ∞, with values > 1 representing a greater chance of detection in the intervention group.

Secondary endpoints were the effects of screening on VCF diagnoses in general (i.e. also those without indicated OACs), OAC prescriptions, strokes, thromboembolism and major bleeding. The analyses were performed separately for both study phases and according to the intention-to-treat principle, whereby patients with known VCF or ongoing OAC were excluded. In all analyses, differences were considered statistically significant if the two-sided P-value was less than 0.05.

Results and interpretation

The numbers of participants reached are shown in the flow chart in figure 2. Of the 5,551 people included, 31% were female. The median age was 65 years and the median CHA2DS2-VASc score was 3. Acceptance of the smartphone-based screening programme was high, as reflected in comparatively good adherence and a low dropout rate:

- More than 50% of the participants in the intervention group performed at least one smartphone measurement per week over the entire six months in phase 1 .

- 618 participants (11.1%) dropped out of the study prematurely, of which only 421 (7.6%) did so while in the intervention group .

For a digital study without direct contact with test persons, these are pleasing values. In this context, it should be emphasised that the tested health care innovation was also well accepted by the older

participants, whereby the age group 65-71 even tended to carry out the most PPG measurements (P < 0.05). There were also no differences between older and younger participants with regard to the quality of the measurements or their correct performance. There were no significant differences between the groups with regard to the characteristics ‚age', ‚gender', ‚BMI' and with regard to various existing diseases and therapy references. A distorting influence on the results of the analysis by the potential confounding factors mentioned could therefore be largely excluded. The cumulative event rates for the primary endpoint are shown in figure 3.

Within the first 6 months (phase 1), the primary endpoint was reached by 38 participants (1.33% of 2,860) who were assigned to smartphone-based screening, while only 17 participants (0.63% of 2,691) in the regular control group reached the primary endpoint. The corresponding OR for the primary endpoint was 2.12 (95% CI: 1.19-3.76) and was significant (P = 0.010) (see Figure 3a). Of the remaining participants from phase 1, 4,752 accepted the invitation to participate in the subsequent six-month phase 2, which was associated with a change in group membership (cross-over). Here, too, the smartphone-based screening showed its superiority over standard care. 33 participants in the intervention group (1.38% of 2,387) were diagnosed with treatment-relevant VCF, while standard care only led to 12 corresponding diagnoses (0.51% of 2,365). The OR in the second phase was 2.75 (95% CI: 1.42-5.34) and was also significant (P = 0.003) (cf. fig. 3b).

In this context, it should be noted that the ORs between the phases are not comparable. The phase 2 participants differ in one significant characteristic in that they are already characterised by a negative screening result from phase 1. Overall, the chance of detecting a treatment-seeking but previously hidden VCF was more than twice as high in both study phases when participating in the smartphone-based screening programme.

With regard to the secondary endpoints, there were no significant differences between the groups in terms of clinical endpoints such as the occurrence of strokes or relevant bleeding. However, in both phases of digital screening , VCF was diagnosed more frequently and oral blood thinners were prescribed more often (significant in each case, i.e. P < 0.05).

Although there are related studies on digital screening for HF using smartwatches or comparable tracking devices worn on the wrist - e.g. the Apple, Fitbit or Huawei Heart Study (Guo et al., 2019; Perez

Literature

Birkemeyer, R./Müller, A./Wahler, S./von der Schulenburg, J. (2020): A cost-effectiveness analysis model of Preventicus atrial fibrillation screening from the point of view of statutory health insurance in Germany. In: Health Economics Review, 10 (1): 16

Brandt, F./Kreiser, M./Harks, O. (2021): Vorhofflimmern frühzeitig erkennen, Schlaganfälle vermeiden. In: Welt der Krankenversicherung, 10 (12): 306–309

Brasier, N./Raichle, C./Dörr, M. et al. (2019): Detection of atrial fibrillation with a smartphone camera: first prospective, international, two-center, clinical validation study (DETECT AF PRO). In: Europace, 21 (1): 41–47

Eurostat (2016): Pressemitteilung: Todesursachen im Jahr 2013 – Über 1 Million Personen starben in der EU an einem Herzinfarkt oder Schlaganfall. In: https://ec.europa.eu/eurostat/de/web/products-euro-indicators/-/3-04052016-bp (abgerufen am 10.10.2022)

Freyer, L./von Stülpnagel, L./Spielbichler, P./[...]/Bauer, A. (2021): Rationale and design of a digital trial using smartphones to detect subclinical atrial fbrillation in a population at risk: the eHealth-based Bavarian Alternative Detection of Atrial Fibrillation (eBRAVE-AF) trial. In: American Heart Journal, 241: 26–34

Grond, M./Jauss, M./Hamann, G. et al. (2013): Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke: a prospective multicentre cohort study. In: Stroke, 44 (12): 3357–3364

Guo, Y./Wang, H./Zhang, H. et al. (2019): Mobile photoplethysmographic technology to detect atrial fibrillation. Journal of the American College of Cardiology, 74 (19): 2365–2375

Hart, R./Pearce, L./Aguilar, M. (2007): Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. In: Annals of Internal Medicine, 146 (12): 857–867

Hindricks, G./Potpara, T./Dagres, N. et al. (2021): 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and 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. In: European Heart Journal, 42 (5): 373–498

Jaakkola, J./Mustonen, P./Kiviniemi, T. et al. (2016): Stroke as the first manifestation of atrial fibrillation. In: PLoS One, 11 (12): e0168010

Kirchhof, P./Benussi, S./Kotecha, D. et al. (2016): 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. In: European Heart Journal, 37 (38): 2893–2962

Kishore, A./Vail, A./Majid, A. et al. (2014): Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. In: Stroke, 45 (2): 520–526

Lloyd-Jones, D./Wang, T./Leip, E. et al. (2004): Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. In: Circulation, 110 (9): 1042–1046

López-López, J./Sterne, J./Thom, H. et al. (2017): Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. In: BMJ, 359: j5058

Lozano, R./Naghavi, M./Foreman, K. et al. (2012): Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. In: Lancet, 380 (9859): 2095–2128

Lubitz, S./Faranesh, A./Selvaggi, C. et al. (2022): Detection of Atrial Fibrillation in a Large Population Using Wearable Devices: The Fitbit Heart Study. In: Circulation, online ahead of print

Murray, C./Vos, T./Lozano, R. et al. (2012): Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. In: Lancet, 380 (9859): 2197–2223

Perez, M./Mahaffey, K./Hedlin, H. et al. (2019): Large-scale assessment of a smartwatch to identify atrial fibrillation. New England Journal of Medicine, 381 (20): 1909–1917

Rizas, K./Freyer, L./Sappler, N./[...]/Bauer, A. (2022): Smartphone-based screening for atrial fibrillation: a pragmatic randomized clinical trial. In: Nature Medicine, 28 (9): 1823–1830

Quer, G./Freedman, B./Steinhubl, S. (2020): Screening for atrial fibrillation: predicted sensitivity of short, intermittent electrocardiogram recordings in an asymptomatic at-risk population. In: Europace, 22 (12): 1.781–1.787

Turakhia, M./Hoang, D./Zimetbaum, P. et al. (2013): Diagnostic utility of a novel leadless arrhythmia monitoring device. In: American Journal of Cardiology, 112 (4): 520–524

et al., 2019; Lubitz et al., 2021). However, the eBRAVE-AF study is the first of its kind in which the screening programme studied was initially purely smartphone-based, i.e. it did not require any special hardware, and in which the effectiveness of the screening programme was systematically compared with standard care. Thus, for the first time in an RCT, which is considered the gold standard of clinical trial designs, it was demonstrated that the detection rate of VCF requiring treatment can be increased two- to threefold by applying such a low-threshold screening strategy. Similar to previous digital screening studies, recruitment followed a ‚direct-to-participant' approach. However, instead of recruiting participants from a pool of smartwatch owners, policyholders of a private health insurance company were selected based on specific risk criteria. As a result, the relevant risk group was addressed much more specifically in the eBRAVE-AF study. As a result, not only a diagnostic but also a therapeutic efficacy was shown, since the VHF detection demonstrably led to OAK prescriptions. This in turn suggests a positive effect on stroke prevention, as the risk of stroke in risk groups can be significantly reduced by OACs (Hart et al., 2007; López-López et al., 2017). In addition, VCF is associated with a number of other diseases, the development or progression of which may be prevented by early VCF detection.

Finally, some limitations - both with regard to the conduct of the study and with regard to the screening programme investigated - should be reported. The fact that the study was conducted exclusively among people with private health insurance limits its representativeness, because in Germany almost 90% are covered by SHI (selection bias). Due to the structure of SHI as a social insurance system based on the principle of solidarity, the structure of the insured differs from that of private health insurance, which provides for an individual risk assessment at the beginning of the insurance. Furthermore, the participation in the study - also in the control group - could have awakened the attention for the topic in the first place. Consequently, it cannot be ruled out that the participation in the study as such had a distorting influence on the utilisation of VHF-associated diagnostic services in standard care. It is possible that the study conditions would have relativised the effect shown here by artificially intensifying the diagnostic process in the control group and that the screening would have been even more effective under real conditions.

As with most screenings, there is also the risk of unnecessary tests and costs resulting from false-positive measurements. Due to the vast majority of ‚healthy' people, false-positive measurements simply carry more weight. In the eBRAVE-AF study, two out of three participants with abnormal PPG measurements did not subsequently have confirmed VCF. Some of the unconfirmed cases could be explained by the fact that arrhythmias other than VHF led to the abnormal PPG measurement or that the patient did not subsequently make use of any ECG diagnostics or that VHF did not occur while wearing the ECG device. On the other hand, due to the preventive character, there are various avoidable medical costs. A differentiated health economic model calculation already came to the conclusion that smartphone-based VCF screening is also advantageous from an economic point of view - especially because avoidable stroke costs more than compensate for the costs of screening (Birkemeyer et al., 2020)

Conclusion

The results of the eBRAVE-AF study show that, with the help of a screening strategy based on common smartphones, the detection rate of VCF requiring treatment in the 50+ age group can be more than doubled compared to standard care. The high prevalence of smartphones in the population makes corresponding screenings easily accessible and scalable in the target group. In this context, the study results also indicate a high acceptance of the procedure among older users (65+). As a consequence, treatment with blood-thinning medication can be initiated in many of the VHF cases detected in this way, in order to avoid potential secondary diseases - especially strokes. Future studies are needed, however, to investigate the effects of digital VCF screening on clinical endpoints - such as stroke prevention. <<

Author's statement

Dr Florian Brandt is an employee of the IKK Südwest in Saarbrücken. Marc Kreiser and Christoph Eisert are employees of Preventicus GmbH in Jena. Prof. Dr. Axel Bauer is Director of the University Clinic for Internal Medicine III at the Medical University of Innsbruck and head of the eBRAVE-AF study. The work was carried out solely by the authors named and without financial support from third parties.

Zitationshinweis

Brandt et al.: ‚Smartphone-based screening for atrial fibrillation: Findings from the eBRAVE-AF study', in: „Monitor Versorgungsforschung" (03/23), PP. 49–54. http://doi.org/10.24945/MVF.03.23.1866-0533.2514

Dr. rer. med. Florian Brandt MSc ORCID: 0000-0003-4947-1770
works as Health Innovation Manager at IKK Südwest, where he is involved in the development, implementation and evaluation of novel approaches to improve health care. In addition to his professional activities, he researches and publishes on current health science topics. Previously, he completed a degree in economics and a PhD in theoretical medicine at Saarland University. Contact: Florian.Brandt@ikk-sw.de



Marc Kreiser, MSc ORCID: 0000-0003-3201-5461
studied medical technology and is responsible for the further development and commercialisation of the digital care concepts offered at Preventicus GmbH with the Marketing and Product Management departments. Contact: Marc.Kreiser@preventicus.com.



Dipl.-Ing. (FH) Christoph Eisert ORCID: 0000-0002-1964-5154
studied biomedical engineering and has more than 20 years of experience in the medical technology industry in the field of cardiovascular diseases, especially cardiac arrhythmias. At Preventicus GmbH he is responsible for the new and further development of digital managed care concepts. Contact: Christoph.Eisert@preventicus.com



Prof. Dr. med. Axel Bauer MHBA ORCID: 0000-0001-9201-8555
is an internist, cardiologist, intensive care physician and Clinic Director of the University Clinic for Internal Medicine III, Cardiology and Angiology, at the Medical University of Innsbruck. His long-standing research interests are digital medicine, biosignal analysis and sudden cardiac death. Contact: Axel.Bauer@i-med.ac.at

