Smartphone-based screening for atrial fibrillation (eBRAVE-AF) – A pragmatic siteless digital randomized clinical trial

A Bauer, KD Rizas, L Freyer, N Sappler, L von Stülpnagel, P Spielbichler, A Krasniqi, M Schreinlechner, FN Wenner, F Theurl, A Behroz, E Eiffener, MP Klemm, A Schneidewind, M Zens, T Dolejsi, U Mansmann, S Massberg

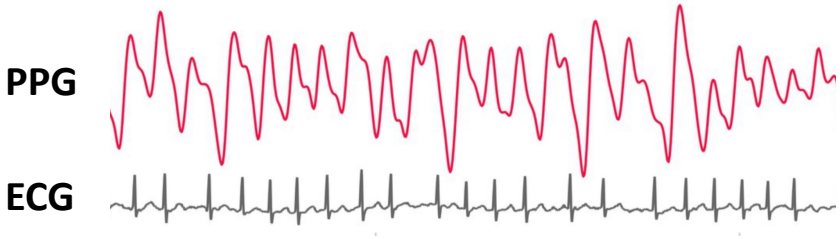
Barcelona, 28th August 2022

LMU KLINIKUM

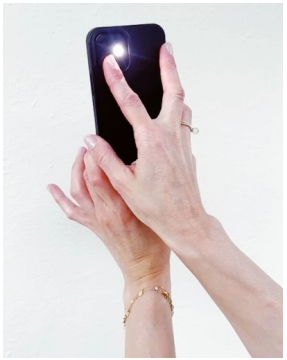
Universitätsklinik
Innere Medizin III
Innsbruck

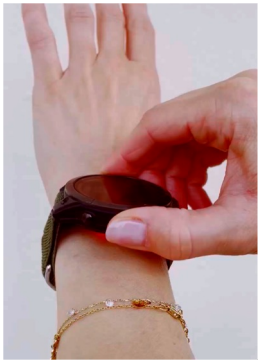
Background

- Photoplethysmographic (PPG) sensors on smart devices can detect irregularities of pulse waves indicative of atrial fibrillation (AF)



Väliaho et al., Front Physiol 2022





*e*BRAVE-AF

Background

- Photoplethysmographic (PPG) sensors on smart devices can detect irregularities of pulse waves indicative of atrial fibrillation (AF)
- Consumer-oriented observational studies, e.g. the Apple[1], Huawei[2] and Fitbit Heart[3] Studies, demonstrated than smart devices can identify individuals with AF
- However, these studies were not randomized, selected participants by ownerships of certain devices and treatment relevance of detected AF was unclear.

[1]Pherez et al., NEJM 2019, [2]Guo et al., JACC 2019, [3]Lubitz et al., Circulation (suppl.) 2021

*e*BRAVE-AF

Objective

- To test the efficacy of a scalable digital screening strategy using ordinary smartphones for detection of treatment-relevant AF in an elderly at-risk population in head-to-head comparison with usual care

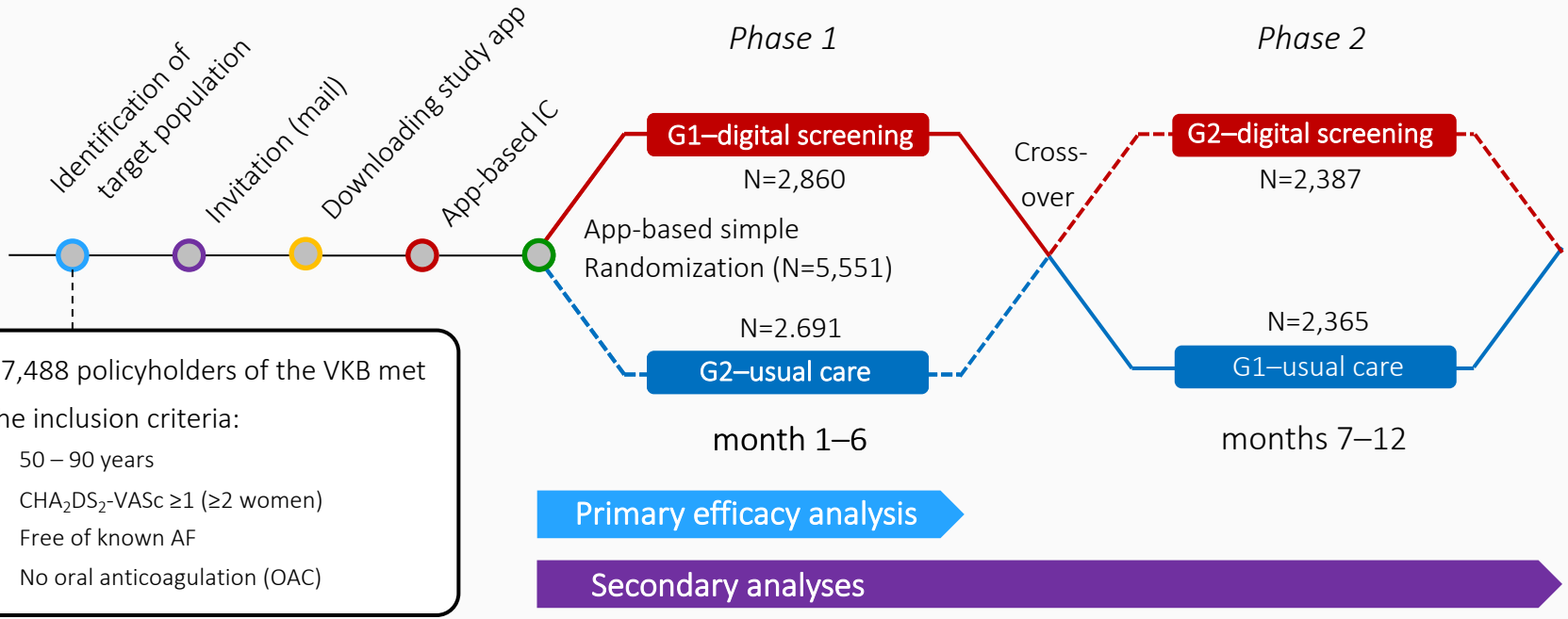
*e*BRAVE-AF

Study oversight

- Investigator-initiated, randomized, siteless, digital trial
- Remote recruitment from the pool of policyholders of the Versicherungskammer Bayern (VKB), a large German health insurance
- Communication through study app, no in-person contact with study participants
- Enrolment from February 4th, 2020, and July 31th, 2020
- Coordination by the Munich University Hospital
- Mainly funded by academic resources, partially funded by Pfizer GmbH, Germany, and Versicherungskammer Bayern (VKB)

*e*BRAVE-AF

Study design & trial overview



Am Heart J 2021 Nov; 241:26-34

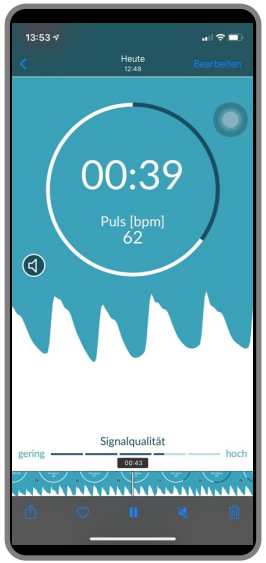
eBRAVE-AF

Digital Screening Usual Care

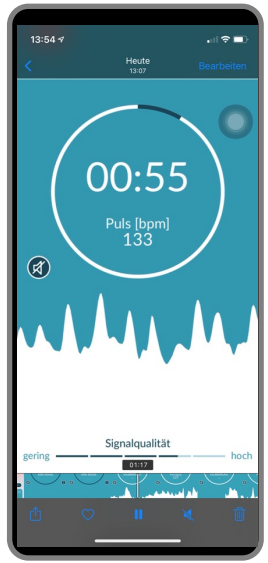
G1–digital screening

G2–usual care

- Installation of the Preventicus Heartbeats app on own smartphone (Android / iOS)
- Repetitive 1-min PPG self-measurements by placing the index finger on the camera
- Twice daily for 14 days, then bi-weekly (scheduled 76 PPGs in 6 months)
- External 14-day ECG loop recorder for evaluation of abnormal PPG measurements
- Treatment decisions by local physicians



normal

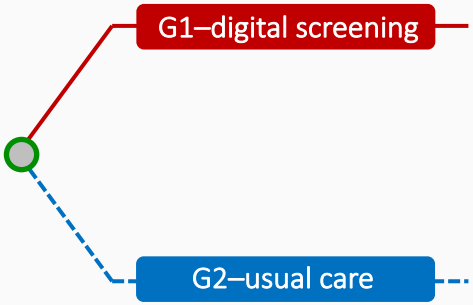


abnormal

Am Heart J 2021 Nov; 241:26-34

*e*BRAVE-AF

Usual care



- No study-related diagnostic interventions

Am Heart J 2021 Nov; 241:26-34

*e*BRAVE-AF

Endpoints and statistical analyses

- **Primary endpoint (phase 1)[1]**
  - Newly diagnosed AF[2] leading to initiation of oral anticoagulation by an independent physician not involved in the study
- **Secondary endpoints (phase 1 & 2)**
  - Newly diagnosed AF[2]
  - Newly prescribed oral anticoagulation
  - Stroke & thromboembolic events
  - Major bleedings (BARC ≥2)
- **All analyses done on an intention-to-treat principle**

[1] verified by independent endpoint adjucation committee

[2] ≥30 sec AF on ECG loop recorder *or* clinical diagnosis by treating physician

Am Heart J 2021 Nov; 241:26-34

Follow-up

- Follow-up information from following sources

1. Questionnaires through the study app
2. Telephone calls (if final questionnaires after phase 1 and 2 were not answered)

available for 98.2% participants

3. Insurance claims data (ICD-10 and ATC codes)

100% participants

4. Medical reports for all potentially endpoint-relevant events

all but one primary endpoints*

* Primary endpoints solely based on claims data considered to be valid

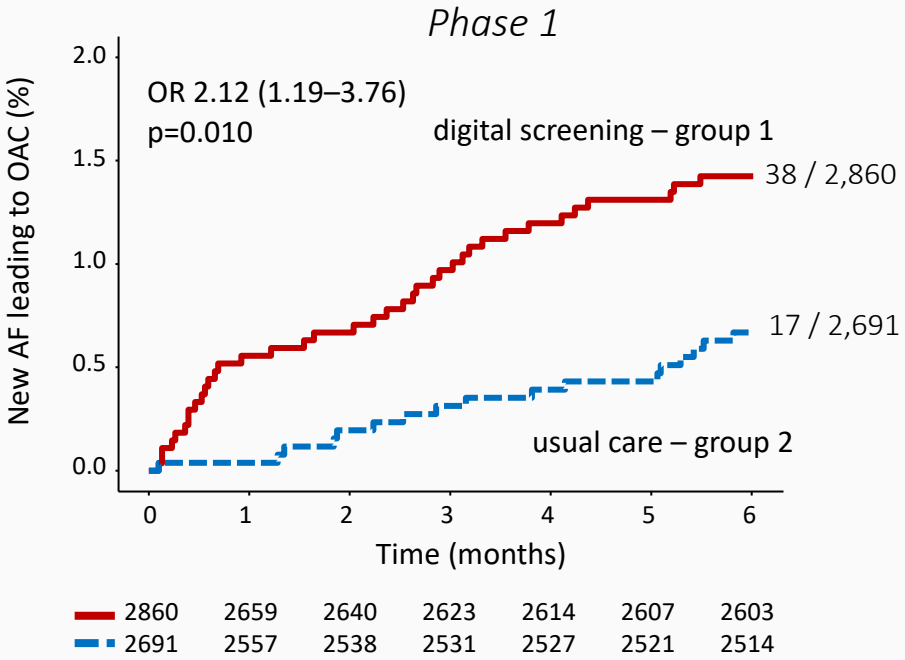
*e*BRAVE-AF

Characteristics of study participants

	Group 1 (N=2,860)	Group 2 (N=2,691)
Age (years)	65 (60 - 71)	66 (60 - 71)
Females (%)	31%	31%
CHA_2DS_2-VASc	3 (2 - 3)	3 (2 - 3)
Coronary heart disease	15%	14%
Heart failure	4%	4%
History of stroke	6%	6%
Diabetes mellitus	14%	12%
ACE inhibitor or ARB	13%	13%
Beta-blocker	3%	3%
Aspirin	1%	1%
Statins	2%	2%

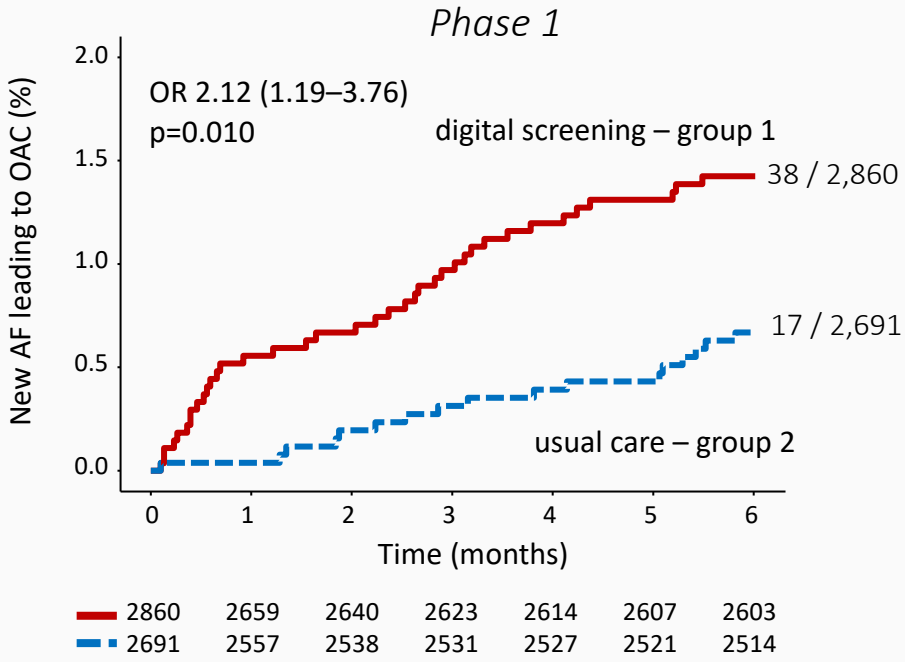
*e*BRAVE-AF

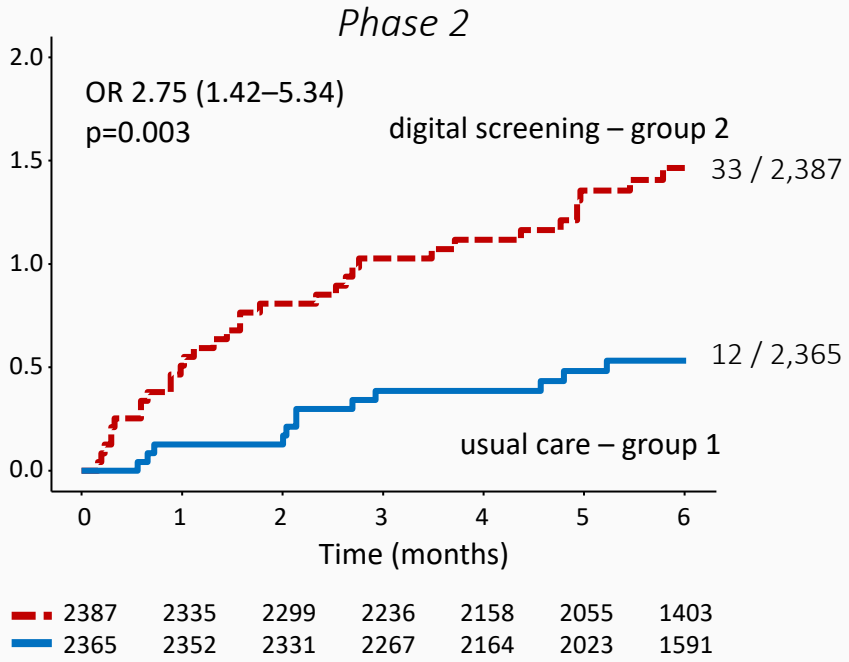
Primary efficacy analysis



*e*BRAVE-AF

Cross-over phase





eBRAVE-AF

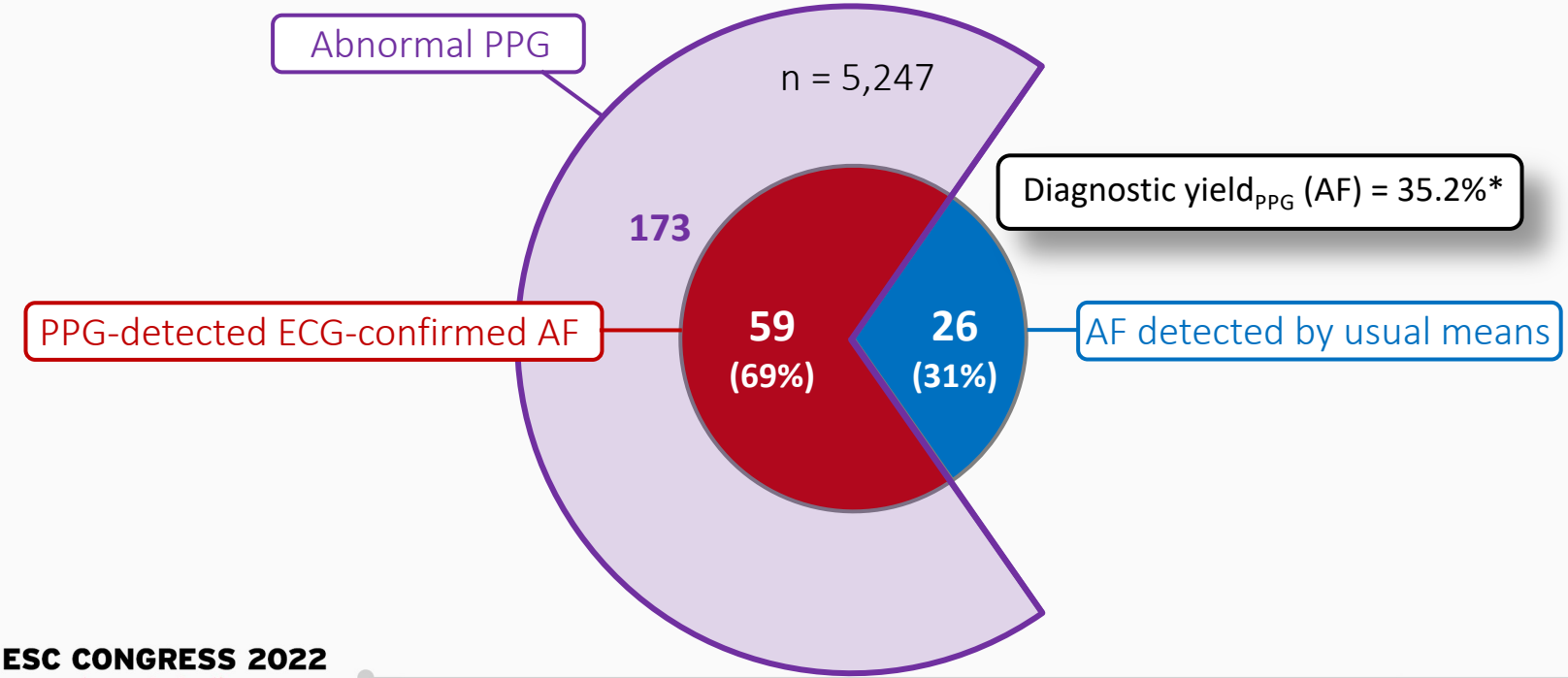
Secondary endpoints

	Phase 1				Phase 2			
	Group 1 (N=2,860) (digital)	**Group 2 (N=2,691) (usual)**	**OR (95% CI) (digital vs usal)**	**P-value**	**Group 1 (N=2,365) (usual)**	**Group 2 (N=2,387) (digital)**	**OR (95% CI) (digital vs usual)**	**P-value**
New AF	**48 (1.7%)**	24 (0.9%)	1.9 (1.16–3.11)	0.011	16 (0.7%)	**37 (1.6%)**	2.3 (1.3–4.2)	0.005
New OAC	49 (1.7%)	23 (0.9%)	2.0 (1.23 - 3.33)	0.006	23 (1.0%)	45 (1.9%)	2.0 (1.2-3.2)	0.010
Stroke	12 (0.4%)	11 (0.4%)	1.0 (0.5 – 2.35)	0.950	11 (0.5%)	7 (0.3%)	0.6 (0.3-1.7)	0.348
Thromboembolic events	11 (0.4%)	5 (0.2%)	2.1 (0.7–6.0)	0.177	9 (0.4%)	11 (0.5%)	1.2 (0.5-3.0)	0.661
Major bleeding	15 (0.5%)	14 (0.5%)	1.0 (0.5–2.1)	0.983	6 (0.3%)	12 (0.5%)	2.0 (0.8-5.3)	0.166

AF atrial fibrillation; OAC oral anticoagulation

*e*BRAVE-AF

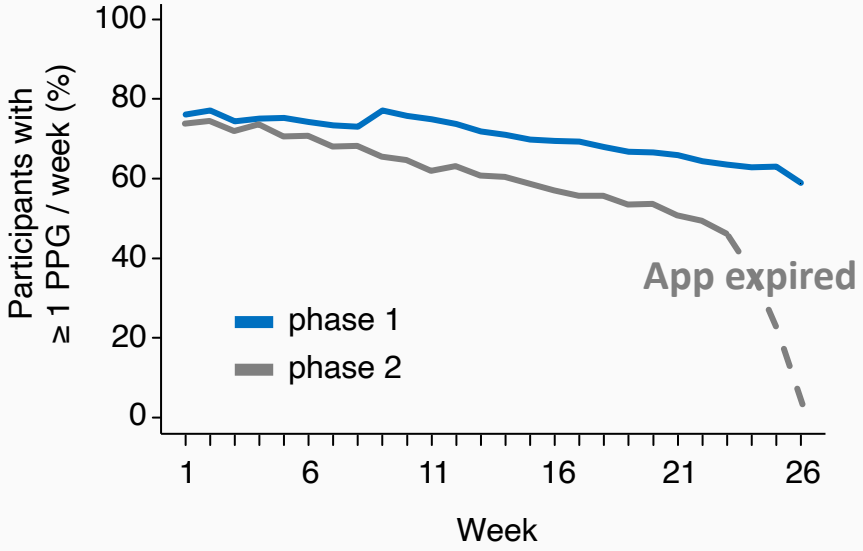
Modes of AF detection during ***digital*** screening (pooled analysis)

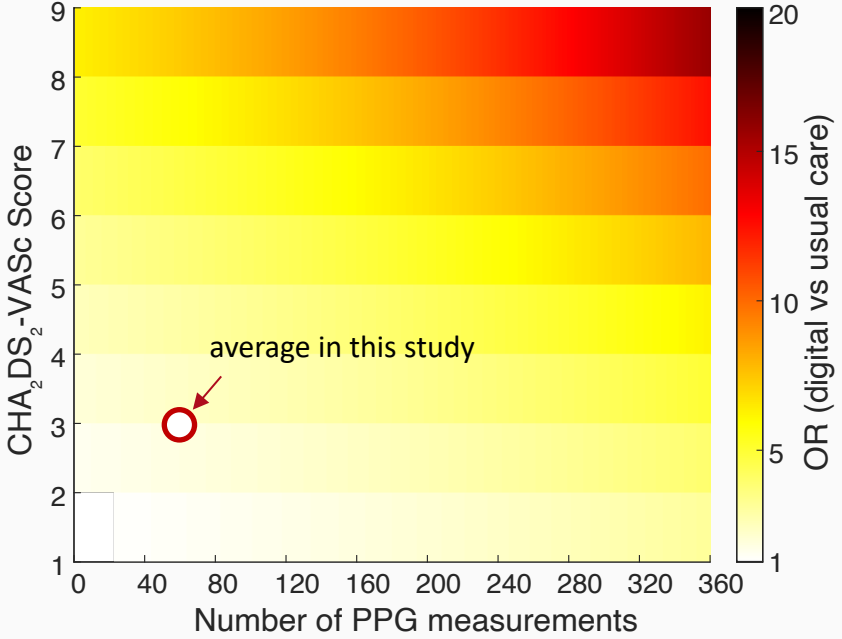


* included two participants with abnormal PPGs during digital screening, but AF diagnosed after cross-over

*e*BRAVE-AF

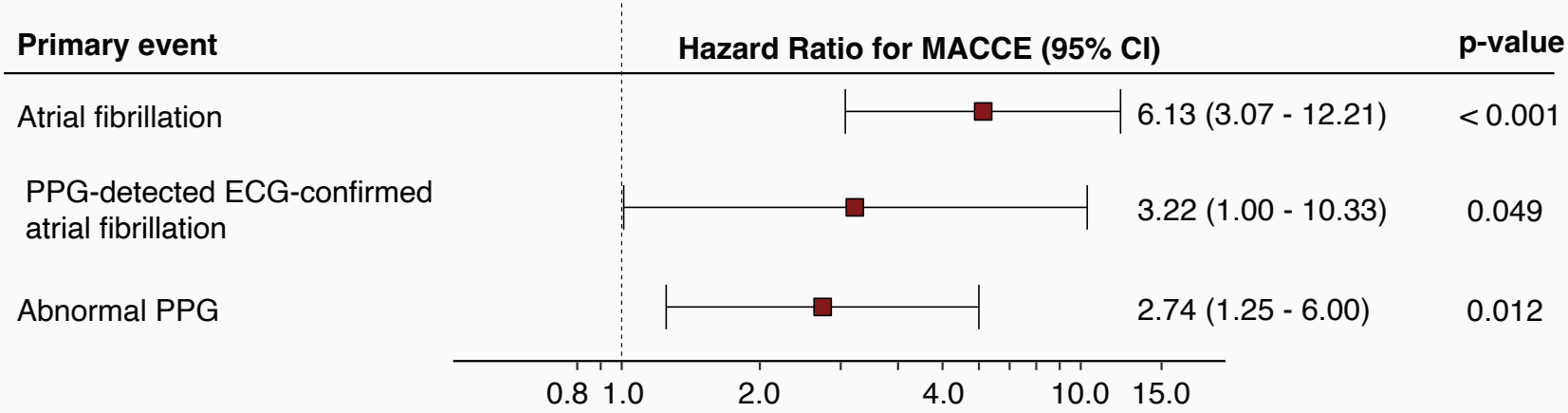
Compliance with and efficacy of digital screening





*e*BRAVE-AF

Association with MACCE*



126 MACCE* during 391 days (IQR 62)

*Cardiovascular mortality, hospitalizations due to heart failure or myocardial infarction, thrombosis, pulmonary embolism, stroke and thromboembolic events

Limitations

- Findings of our study might not be representative for other healthcare systems
- Enrolment of participants could be subject to selection bias
- Continuous passive screening with wrist-worn devices likely provides a better sensitivity for AF detection
- Increased awareness of AF due to study participation may have favoured usual care

Conclusions

- A scalable digital screening strategy using ordinary smartphones provides a substantial benefit to usual care in detecting treatment-relevant AF
- The findings of our study are most likely generalizable to other smart device-based PPG technologies
- Digitally detected ECG-confirmed AF as well as abnormal PPG measurements *per se* represent prognostically relevant digital biomarkers
- Future studies are needed to test whether improved AF diagnostics through digital technologies translate into better treatment outcomes

eBRAVE-AF

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01979-w

Smartphone-based screening for atrial fibrillation: a pragmatic randomized clinical trial

Konstantinos D. Rizas[1,2,6], Luisa Freyer[1,2,6], Nikolay Sappler[3,6], Lukas von Stülpnagel[1,2,3], Peter Spielbichler[1,2], Aresa Krasniqi[1,2], Michael Schreinlechner[3], Felix N. Wenner[1,2], Fabian Theurl[3], Amira Behroz[1,2], Elodie Eiffener[1,2], Mathias P. Klemm[1,2], Annika Schneidewind[1,2], Martin Zens[4], Theresa Dolejsi[3], Ulrich Mansmann[5], Steffen Massberg[1,2] ✉ and Axel Bauer[1,2,3] ✉

KD Rizas

L. Freyer

N Sappler

L v Stuelpnagel

Thanks to all eBRAVE-AF investigators, the Versicherungskammer Bayern (VKB) and Preventicus GmbH