Digital hypertension management

A cluster-randomised trial in primary care (PIA)

Doctoral thesis

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List of abbreviations

ACEI	Angiotensin-converting enzyme inhibitors
AI	Artificial Intelligence
ANOVA	Analysis of Variance
ARB	Angiotensin Receptor Blockers
BP	Blood Pressure
CCB	Calcium Channel Blockers
CG	Control Group (Usual care group)
cRCT	cluster-Randomised Controlled Trial
DBP	Diastolic Blood Pressure
DDD	Defined Daily Dose
EHR	Electronic Health Record
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GDPR	General Data Protection Regulation
GLMM	Generalised Linear Mixed Models
GP	General Practitioner
ICT	Information Communication Technology
IG	Intervention Group
IQR	Interquartile Range
Max	Maximum

Min	Minimum
mmHg	Millimetre mercury
NNT	Number Needed to Treat
PIA	PC-supported case management of hypertensive patients to implement guideline-based hypertension therapy using a physician-defined and -supervised, patient-specific therapeutic algorithm
PIN	Personal Identification Number
PrA	Practice Assistant
PrMc	Practice Management centre
RCT	Randomised-Controlled Trial
RRR	Relative Risk Reduction
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMS	Short Message Service

1. Introduction

1.1 Hypertension prevalence

According to representative German national data from 2014/2015 from the GEDA and EHIS (German health update and European health interview survey), nearly one in three adults in Germany (30.9 % of women and 32.8 % of men) has known physician-diagnosed hypertension (Robert Koch-Institut 2017). This is similar in other studies: the hypertension prevalence in persons aged 30 to 79 years in 22 German studies between 1989 and 2014 differed slightly between genders: 25.0 % in women and 34.4 % in men (NCD Risk Factor Collaboration 2021).

However, for patients in German general practices, an even higher prevalence of 55 % was reported in a study of 35.869 patients from 1.511 primary practices (Balijepalli et al. 2014). 61 % to 81 % of these had inadequate blood pressure (BP) control despite treatment with market-available antihypertensives (Balijepalli et al. 2014; Sharma et al. 2004). Starting from age 40, the prevalence of essential hypertension rises continuously until old age: 61-70 years: 37.7 %, 71-80 years: 46.0 %, and from the age of 80 even every second patient (49.5 %) (Balijepalli et al. 2014).

1.2 Hypertension-related mortality, morbidity, and health economic costs

Hypertension is a so-called ‘silent killer’ because high blood pressure typically does not cause symptoms and is only detected by blood pressure measurements (Williams et al. 2018). The lack of blood pressure control is a chronic healthcare deficit which leads to increased morbidity, mortality, and subsequent costs for healthcare systems and societies (WHO 2013; Nugent 2015; Ettehad et al. 2016). With increasing blood pressure, the incidences of stroke, myocardial infarction, sudden cardiac death, heart failure, peripheral arterial disease, and chronic renal failure rise continuously (Williams et al. 2018). In 2022, the cost for these morbidities in Germany was enormous: stroke accounted for 1.7 % (€ 7.4 billion), myocardial infarction for 1.8 % (€ 7.9 billion), heart failure for 1.7 % (€ 7.4 billion) and hypertension alone for another 1.5 % (€ 6.6 billion) of the annual healthcare costs (Statistisches Bundesamt 2023). In addition, cardiovascular diseases were responsible for 33 % of mortality in 2020 (Statistisches Bundesamt 2023). The societal

burden was also high due to cardiovascular disease-related early retirement of 13 % in men and 5 % in women in 2021 (Deutsche Rentenversicherung 2022).

1.3 Guidelines recommendations for blood pressure measurements and targets

Several international and national guidelines summarising current evidence are available for hypertension management. For the PIA study, we referred to the ESH/ESC (European Society of Cardiology and European Society of Hypertension) guidelines 2018 which include not only epidemiological and therapeutic information but also advice on valid BP readings (Williams et al. 2018).

According to this guideline, upper arm blood pressure readings with automatic sphygmomanometers are reliable, non-invasive measurements. The method is based on an inflated upper arm cuff to compress the brachial artery. As cuff inflation is decreased slowly, systolic and diastolic blood pressures can be obtained. The systolic value indicates the maximum pressure of the blood on the arterial wall as generated by the contraction of the left ventricle. In contrast, the diastolic pressure indicates the pressure of the blood column on the blood vessel in the heart relaxation phase. A prerequisite for a reliable practice blood pressure reading is a resting phase of five minutes with three subsequent measurements separated by one to two minutes and additional measurements only if the first two readings differ by > 10 mmHg. The blood pressure is calculated as the average of the last two blood pressure measured values. (Williams et al. 2018) According to various international and German national care guidelines, a resting practice BP of less than 140/90 mmHg is considered a target value protecting against disease sequelae (Williams et al. 2018; Nationale Verorgungs Leitlinie Hypertonie 2022). Lower values are recommended for some diseases, such as chronic renal insufficiency and heart failure. For daytime home blood pressure measurement, a value less than 135/85 mmHg is re-commended (Williams et al. 2018).

1.4 Effectiveness of non-pharmacological and pharmacological interventions

Extensive population-based studies show that a systolic blood pressure < 140/90 mmHg is associated with a significantly lower prevalence of cardiovascular events (Williams et al. 2018). Effects can be achieved by lifestyle and/or pharmacological interventions, with lifestyle interventions being recommended first if feasible. A meta-analysis of 47

randomised-controlled trials involving 153,825 patients showed that blood pressure reductions of as little as 10 mmHg systolic and 5 mmHg diastolic resulted in a significant relative risk reduction (RRR):

- for heart failure, the RRR was 43 % (Number needed to treat (NNT) for 5 years: 73),
- for stroke, the RRR was 36 % (NNT for 5 years: 58),
- for cardiovascular-related deaths, the RRR was 18 % (NNT for 5 years: 141), and
- for coronary heart disease, the RRR was 16 % (NNT for 5 years: 58).

This study showed an RRR of 25 % for serious cardiovascular events. (Thomopoulos et al. 2014) Similar results for significant relative risk reduction were shown in another meta-analysis with 123 studies involving data from 613,815 patients. The meta-analysis demonstrated that a reduction of systolic blood pressure by 10 mmHg resulted in the following relative risk reductions: 27 % for stroke, 17 % for coronary heart disease, 20 % for serious cardiovascular events, and 28 % for myocardial infarction. (Ettehad et al. 2016) Significant reductions in disease sequelae were documented at the population level for reductions as low as 2 mmHg (Stamler 1991).

In patients with hypertension, the treatment comprises lifestyle measurements and – if unsuccessful – pharmacological interventions (Williams et al. 2018). Various antihypertensive groups and numerous substances were developed and evaluated not only regarding their blood pressure-lowering potential but also their beneficial effects on morbidity and mortality (Williamson et al. 2016; Wright et al. 2015). Since 2003, the ESH/ESC hypertension guidelines recommend five groups of antihypertensives in adequate dosing as first-line agents: angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers, calcium channel blockers (CCB), and thiazide diuretics (Williams et al. 2018; Mancia et al. 2013). In Germany, one of the leading drug and substance databases lists 2,813 approved drugs in various dosages of single or combined agents for essential hypertension (ICD-I10) (Gelbe Liste 2023). As most medications available were generics, the cost of the medication is no concern and is covered by statutory health insurance and private insurance in Germany. The total consumption of antihypertensive drugs among patients with statutory health insurance in Germany increased from about 5.5 billion defined daily doses (DDD) in 1996 to approximately 16.9 billion DDD in 2021. In 2021, the costs of antihypertensive drugs amounted to €2.8 billion.

(Arzneimittel Atlas 2022) However, despite this increase and an overall improvement in BP control rates in Germany (Neuhauser et al. 2016), BP control in Germany and other nations is still insufficient. For the US population, the so-called ‘hypertension paradox’ was shown. Despite higher detection and treatment rates, the prevalence of uncontrolled BP increased due to an increase in the population’s hypertension, which is mainly attributable to longevity (stiffening of arteries over lifetime) and the obesity pandemic. (Chobanian et al. 2003; Chobanian 2009)

1.5 Barriers to guideline implementation in standard care

The marked discrepancies between guideline recommendations and usual care result from various barriers in implementation on behalf of patients, clinicians, and health systems (Milman et al. 2018; Chowdhury et al. 2013; Lawrence S. Phillips et al. 2001; Phillips et al.; Phillips et al. 2001). For example, the US National Health and Nutrition Examination Survey (NHANES) analysed data from 9,320 US adults with hypertension. The results from 2009/2010 showed that 40 % of people with hypertension who were taking medication did not achieve BP control (Basile and Bloch 2012). Similar results were documented in the EUROASPIRE studies II-IV in 8,456 coronary patients between 1990-2013 in Belgium, the Czech Republic, Finland, France, Germany, Ireland, the Netherlands, Poland, Slovenia, and the United Kingdom (Kotseva et al. 2017). Such deficits in the implementation of guidelines result from barriers in care which require thorough analyses and detailed strategies for overcoming. Several studies addressed and structured such barriers in care, which span from patient to provider to healthcare system barriers. (Milman et al. 2018; Zolnierek and Dimatteo 2009; Cabana et al. 1999; Phillips et al. 2001; Chowdhury et al. 2013)

While issues such as access to care and the financing of medication costs typically do not play a role in Germany given the statutory health insurance, barriers on behalf of patients, practices, and provider teams (general practitioners = GPs; practice assistants = PrA) are relevant. Figure 1 illustrates this. All of these listed barriers from Figure 1 were addressed as part of the PIA study.

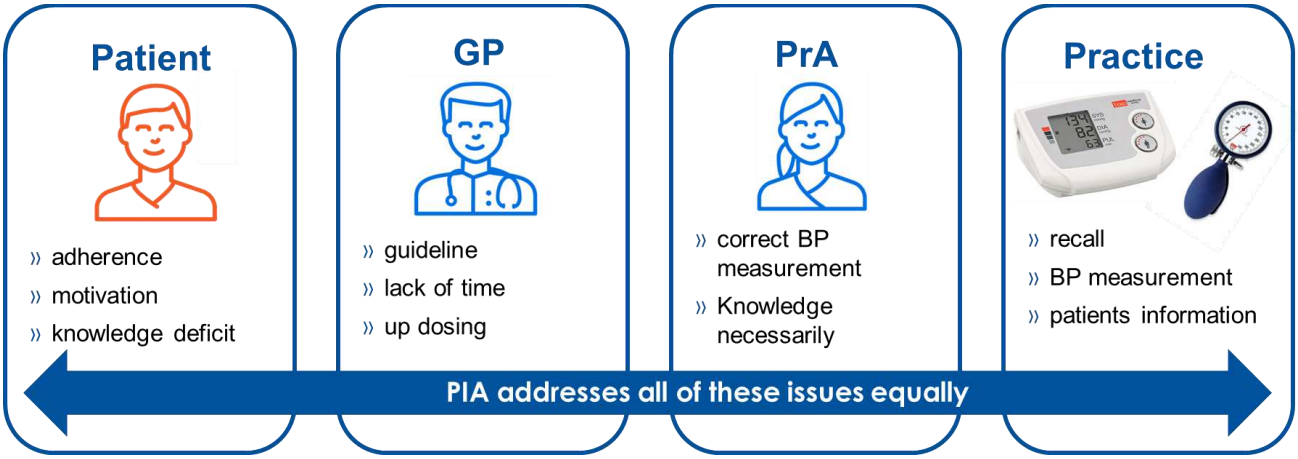


Fig. 1: Barriers to guideline recommendations in standard care

On behalf of patients, the key barriers are a lack of motivation and adherence to lifestyle recommendations (e.g., exercises, weight reduction, low salt nutrition, and low alcohol consumption). In addition, a lack of medication adherence plays a role, given the need to use antihypertensives daily. (Milman et al. 2018; Williams et al. 2018; Cabana et al. 1999) Concerning this matter, the number of tablets plays a crucial role. In a retrospective analysis of 238 hypertensive patients from the UK and 93 from the Czech Republic, Gupta et al. showed 2017 that adherence was strongly influenced by the number of tablets prescribed for hypertension control. Non-adherence was generally < 10 % with a single pill and increased to 20 % with two and 40 % with three tablets. With five or more antihypertensives prescribed, partial or complete non-adherence to the medication was observed. Market-available combination pills can address this problem with up to three antihypertensive agents. (Gupta et al. 2017)

On behalf of physicians, barriers comprise a lack of knowledge about guidelines and appropriate blood pressure targets, high patient volumes and a lack of time to address hypertension given multiple other patient needs (Phillips et al. 2001; Milman et al. 2018; Cabana et al. 1999). In addition, hesitations to initiate or intensify treatment and deficits in the up-titration of medications to reach blood pressure targets are described (so-called treatment inertia) (Wang et al. 2007). Deficits in the up-titration of medications were shown in the German population-based Heinz Nixdorf-Recall Study (HNR) (Brandt et al. 2020). At baseline, the study included 2,289 participants with blood pressure values above

140/90 mmHg or taking at least one antihypertensive drug. The prevalence of participants on antihypertensive medication was 60.3 % at baseline, which increased to 75.1 % at the follow-up. The average number of antihypertensive agents at baseline and follow-up was 2.0 [SD 1.0]. There was no significant improvement in the prevalence of medication-controlled blood pressure over time (baseline: 54.5 %, follow-up: 56.5 %). In contrast to clinical reasoning, the participants with uncontrolled BP received neither more pharmacological agents nor higher dosing despite outcome-relevant hypertension. Figure 2 illustrates that the patients with uncontrolled BP received the same medication dosing rates as those with controlled BP. (Brandt et al. 2020)

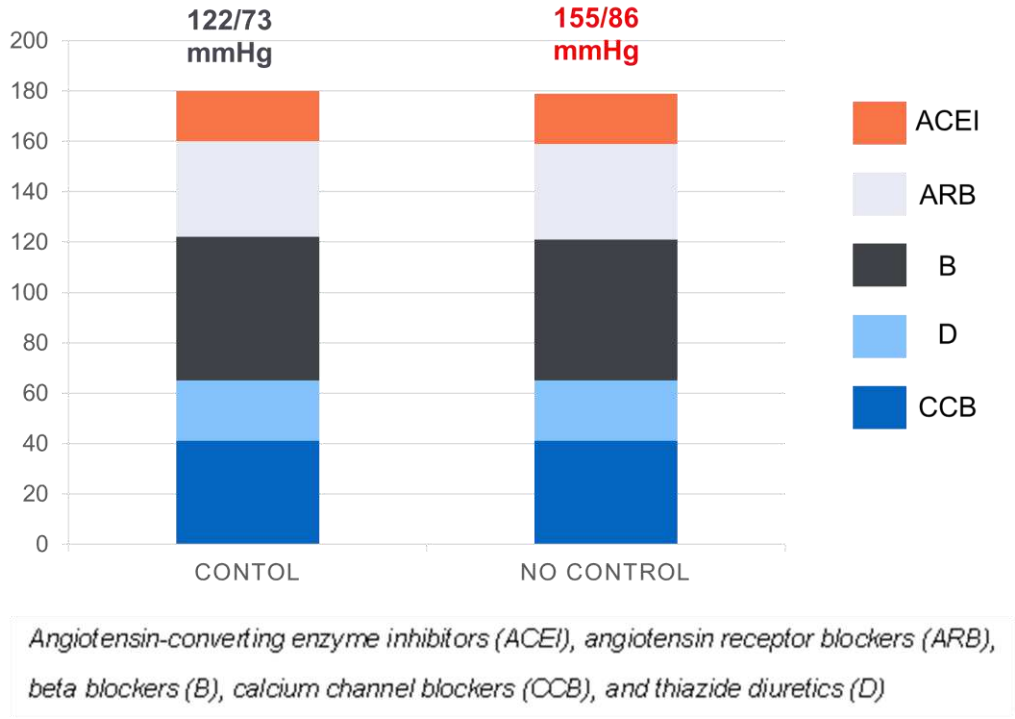


Fig. 2: Medication dosing in hypertensive individuals of the German Heinz Nixdorf Recall Study (N = 2.289): Inadequate up-dosing of antihypertensives in uncontrolled patients (right column) (Brandt et al. 2020)

On behalf of practice assistants (PrA), the need for knowledge or understanding of guidelines, including deficits in guideline-compliant, standardized blood pressure measurements, play a role (Williams et al. 2018; Khatib et al. 2014).

On behalf of practices, barriers include a lack of time or resources to provide patients with comprehensive education and care, a need for systems to identify and follow up on patients with poorly controlled blood pressure. In addition to such structural deficits, a lack

of coordination and communication within practice teams is of relevance. (Khatib et al. 2014; Zolnierek and Dimatteo 2009)

1.6 Structured hypertension management including digital approaches

The medical literature reports several studies and reviews which improved hypertension control by single or bundled strategies. Overall, the more barriers of the complex process to hypertension care were addressed by these interventions, the more effective they are. In a Cochrane review comprising 72 randomised-controlled trials (RCTs) that integrated various hypertension management interventions. Some interventions were able to reduce SBP/DBP as follows: An organised system of regular review allied to vigorous antihypertensive drug therapy (-8.0/-4.3 mmHg); BP self-monitoring (-2.5/-1.8 mmHg); Health professional led care (-2.5/-1.5 mmHg); Appointment reminder (-4.6/-0.5 mmHg). Studies of educational interventions directed at patients or health professionals were heterogeneous and did not appear to result in significant net reductions in BP on their own. This review was conducted to summarise that an organised system of registration, reminders, and regular monitoring, combined with an intensive stepped treatment approach to antihypertensive medications, is most likely to improve the control of hypertension. (Glynn et al. 2010)

A meta-analysis of 33 studies of hypertension management delegated to non-physician staff (nurses) without digital components found significantly higher blood pressure reductions than usual care (-8.2 mmHg systolic). Interventions involving medication adjustments and nurse prescribing achieved effects of -8.9/-4.0 mmHg (Clark et al. 2010). Physician-directed, nurse-led hypertension management, including patient self-measurements and medication algorithms showed similar results (-8.5/-3.1 mmHg). Hypertension therapy was improved as medication changes were 4-fold more frequent in the intervention group compared to the control group with usual care (p-value < 0.01). (Rudd et al. 2004). A meta-analysis of 21 trials of digitally-supported and nurse-led hypertension management showed significant blood pressure reductions of -6.49 mmHg systolic and -3.3 mmHg diastolic compared with usual care (p-value < 0.05). These studies investigated different digital technologies, including telephone, mobile applications, chat communication, telehealth devices, text messages and email. Some trials in this meta-analysis showed improvements in hypertension self-management (three

studies), medication adherence (six studies) and dietary adherence (two studies). (Hwang and Chang 2023)

More recent studies from the US (Margolis et al. 2013), England (McManus et al. 2018; McManus et al. 2021), and Scotland (McKinstry et al. 2013; Hammersley et al. 2020) analysed the effectiveness of comprehensive digital hypertension management systems. Some of these studies integrated delegation models to non-physician staff (nurses or clinician pharmacists) using medication algorithms and systematic recall. In these five trials with ICT (information and communication technology)-supported hypertension management, BP was reduced significantly by −6.0 to −21.4 mmHg systolic and −4.0 to −9.4 mmHg diastolic after 6 to 12 months. These randomised-controlled trials and a cohort study are described here in more detail:

- In the cluster-randomised controlled trial (cRCT) by Margolis et al. (2013) 12 months of intervention and 450 patients (Intervention group 228; usual care group 222) with uncontrolled hypertension from 16 primary care clinics were enrolled. The intervention group implemented a home blood pressure telemonitoring and a delegation to a clinical pharmacist for hypertension management. Patients in the intervention group reported blood pressure data via an automatic blood pressure monitor to a secured web-space. They were then evaluated by clinician pharmacists, who adjusted antihypertensive therapy accordingly. At 12 months, BP was controlled in 71.2 % (95 % CI, 62.0 % - 78.9 %) of telemonitoring Intervention patients and 52.8 % (95 % CI, 45.4 % - 60.2 %) of usual care patients (p-value 0.005). (Margolis et al. 2013)
- In the TASMINH4 study, a randomised-controlled trial, 1,182 hypertensive patients (telemonitoring group 393; self-monitoring group 395; usual care group 394) from 142 GP practices were studied. The self-monitoring group noted their blood pressure values and sent them weekly by mail to their practice for review. In contrast, the telemonitoring group sent their values via SMS and a web-based platform. The treating GPs could access the web-based via the web-based platform. At 12 months, systolic blood pressure values were lower in both intervention groups than in the usual care group (self-monitoring: 137.0 [SD 16.7] mmHg, telemonitoring: 136.0 [SD 16.1] mmHg, usual care: 140.4 [SD 16.5] mmHg). There was no significant difference between the groups that self-monitored and those that used telemonitoring. (McManus et al. 2018)

- The randomised-controlled trial by McManus et al. (2021) included 622 (intervention group 305; usual care group 317) hypertensive patients from 76 GP practices. Patients in the intervention group transmitted their blood pressure measurements to a secure online platform that patients and their treating physicians could view. This platform offered a feedback system for blood pressure readings, optional lifestyle counselling and motivational support. After 12 months, mean blood pressure fell from 151.7/86.4 mmHg to 138.4/80.2 mmHg in the intervention group and from 151.6/85.3 mmHg to 141.8/79.8 mmHg in the standard care group, yielding a mean difference in systolic blood pressure of -3.4 mmHg. In McManus et al. (2021) and (2018), patients received paper-based algorithms for medication self-titration if the electronic platform told them to do so, with physician contact at the latest after two adjustments. (McManus et al. 2021)
- The 2013 randomised-controlled trial by McKinstry et al. included 401 patients (intervention group 200; usual care group 201) with uncontrolled BP from 20 GP practices. Patients in the intervention group received a six-month intervention in which they automatically transmitted measured blood pressure values via a BP monitor to a secure website via short message service (SMS). The treating GPs reviewed this. After six months, it was shown that the intervention led to significant improvements in systolic (4.3 mmHg; 95 % CI, 2.0 to 6.5; p-value 0.0002) and diastolic (2.3 mmHg; 95 % CI, 0.9 to 3.6; p-value 0.001) blood pressure compared with usual care. (McKinstry et al. 2013)
- In the Hammersley et al. (2022) implementation study, the telemonitoring system from McKinstry et al. 2013 was subsequently implemented and evaluated in routine care in a large Scottish Area with 3,200 patients in 72 primary care practices. This study integrated a telemonitoring system for hypertension management (transmission of blood pressure values via SMS to the practice) into routine primary care. In an evaluation of the subgroup of 8 practices with 905 patients, mean SBP decreased by -6.5 mmHg [SD 15.17] and mean DBP decreased by -4.2 mmHg [SD 8.68] within 6 - 12 months. The study found that telemonitoring for hypertension can be widely implemented in routine primary care without impacting practice workload. Integrating telemonitoring readings into existing electronic health record (EHR) systems was essential for successful implementation. (Hammersley et al. 2020)

These studies will be compared to the PIA study results later in this text.

1.7 Participatory and agile development of digital care

In managing chronic diseases such as hypertension, the long-term use of technologies is essential for clinical effectiveness (Margolis et al. 2018; Bashi et al. 2020; Chiauzzi et al. 2015). It is of primary importance that these technologies have a high level of user acceptance to ensure consistent and long-term use (Davis 1989; Schoeppe et al. 2016; Bashi et al. 2020). It is widely recognized that the participatory development of information technology is central to the success of a system, especially in terms of acceptance and system use (Ayat et al. 2021; He and King 2008; Boyd et al. 2012). Participatory development is a process in which end users and other relevant stakeholders' collaborate with researchers on all aspects of intervention development, from an in-depth understanding end user needs to content development and pilot testing (Boyd et al. 2012; Talevski et al. 2023; Ekstedt et al. 2021). Participatory development of healthcare interventions has increased in many disciplines in recent years (Ekstedt et al. 2021), because of such participatory development of interventions as this promotes acceptance and long-term use of digital interventions (Talevski et al. 2023; Ekstedt et al. 2021; Jahnel and Schüz 2020; Greenhalgh et al. 2004). This was also confirmed in a scoping review of 24 studies in which participatory development of interventions for the secondary prevention of cardiovascular disease occurred (Talevski et al. 2023). Bradbury et al. (2018) used a systematic method based on Yardley's framework (Yardley et al. 2015) that can be used to evaluate and optimize the development of a digital intervention for patients with hypertension (Bradbury et al. 2018). Yardley et al. 2015 recommend four core principles for person-based evaluation in intervention development: 1. sensitivity to context; 2. engagement and rigour; 3. transparency and coherence; 4. impact and meaning (Yardley et al. 2015). Bradbury et al. (2018) highlight using think-aloud interviews and hands-on testing with stakeholders to optimize the digital hypertension management intervention in their study. Scientifically, user orientation is facilitated by the iterative use of qualitative research in the various development steps (Bradbury et al. 2018). On a technological site, such participatory development is supported using agile and not the classical software development methods (Sindhwani et al. 2019; Ivanova and Kadurin 2021). Agile development is an iterative and incremental approach and emphasizes active stakeholder involvement, end-user involvement, responsiveness to change, and evolutionary/iterative product delivery throughout the development processes (Kokol

2022; Highsmith and Cockburn 2001). The goals of using agile software development in the healthcare sector follow the objectives: Improving clinical outcomes, quality of healthcare, health management, and patient (Sindhwani et al. 2019; Ivanova and Kadurin 2021). Agile software development is also increasingly used in the development of telemedicine applications in the wake of the recent digital transformation of healthcare (Kokol et al. 2022). Agile software development strengthens software development in healthcare through closer collaborations between healthcare practitioners and software developers (Ekstedt et al. 2021). In summary, participatory and agile development should ensure high user acceptance and adoption of intervention and enable continuous improvement and adjustment in the healthcare development context. The development of the PIA-Intervention is illustrated later in the text about the knowledge from these studies.

1.8 Research context and research question

Given the described deficit in hypertension control in German primary care despite an array of non-pharmacological and pharmacological therapeutic options, the PIA study aimed to develop digital hypertension management for the German primary care setting. The effectiveness of this digital care management was evaluated in the PIA study, which stands for **P**C-supported case management of hypertensive patients to **i**mplement guideline-based hypertension therapy using a physician-defined and -supervised patient-specific therapeutic **a**lgorithm (Leupold et al. 2023). The target group were patients aged 40 to 79 years with essential hypertension. Digital hypertension management comprises an app for patients with a secure connection to general practices. It realized a physician-supervised delegation model to PrAs trained for this hypertension management. The PIA-Intervention's effectiveness including the PIA digital solution and eLearning for practice personnel, was evaluated in a cluster-randomized controlled study with 60 practices. The primary outcome was the blood pressure control rate, defined as the percent of patients reaching the blood pressure target according to guidelines (> 140/90 mmHg).

2. Material and methods

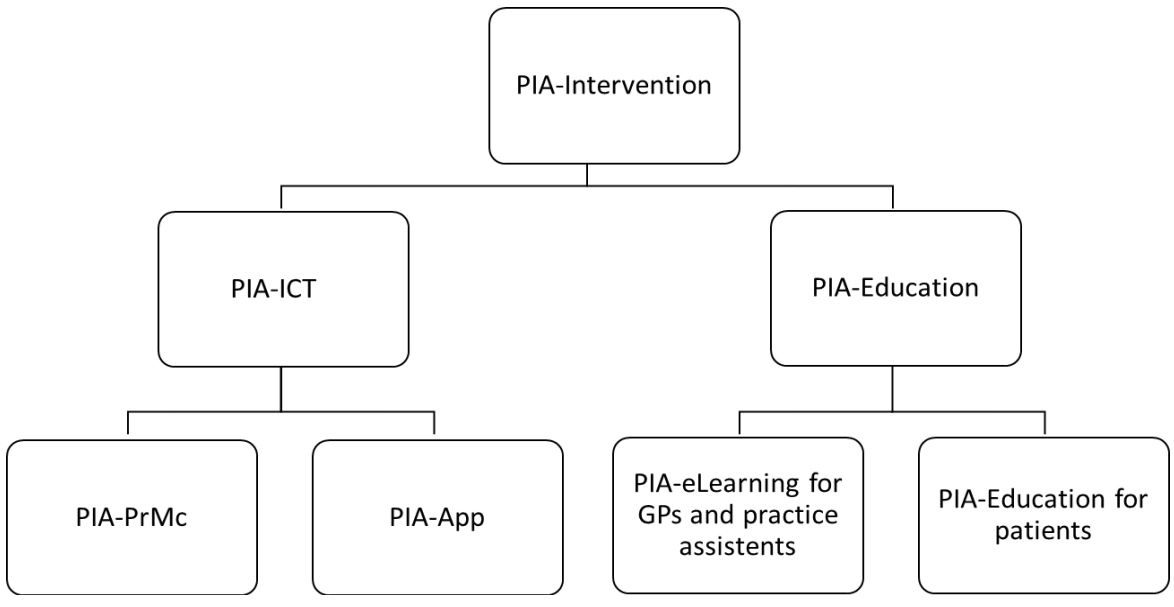
2.1 Overview of the PIA-Intervention

Conceptually, the PIA-Intervention applied four principles to address barriers in care and improve hypertension care:

1. introduction of accelerated, low-barrier communication between patients and GP practices with reduced efforts for all parties involved;
2. standardization of care through the systematic application of guideline-supported, individualized therapy algorithms;
3. implementation of an adherence-promoting, patient-activating form of care for a chronic disease that is relevant to reduce morbidity and mortality;
4. implementation of an IT-supported delegation approach in which qualified practice assistants (non-physician practice staff) to better support primary care physicians.

The developed and evaluated PIA-Intervention (see Figure 3) consists of 2 components:

- the digital solution with the PIA-App for patients and the PIA practice management centre for practices. The latter implemented the digital delegation model (see Figure 4), and
- an eLearning for GPs, practice assistants and patients.



(PIA-ICT: PIA Information and Communication Technology; PIA-PrMc: PIA Practice Management Centre)

Fig. 3: PIA-Intervention (Karimzadeh et al. 2021)

The PIA information and communication technology (PIA-ICT) with PIA practice management centre (PIA-PrMc) and PIA-App allows for digital communication between practice and patients which is compliant with European data protection laws (GDPR = General Data Protection Regulation). The data protection officer of the University Hospital Bonn approved the digital solution.

Technically, the PIA-PrMc is a Windows application used by primary care physicians and PrAs to manage their patients' hypertension therapy. The practice centre has several features:

- review of the patient’s blood pressure data,
- adjustment of medication regimens according to guidelines,
- transmission of medication plans in the unified federal format to patients, and
- implementation of a patient-specific, physician-supervised delegation model to PrAs.

The PIA-App is a patient-centred application for smartphones or tablets with Android operating systems. Features include:

- Recording and transmission of blood pressure values from the patient to the GP practice,
- graphic display of blood pressure readings over time,
- current medication regimes,
- prescription ordering,
- chat function with the practice,
- access to the learning video on home blood pressure measurement, and
- links to evidence-based information on the topic of hypertension.

2.1.1 PIA digital care solution with PIA-App for patients

The digitally supported PIA care was conducted as follows: The patient entered his or her blood pressure measurements into the PIA-App, which were then automatically transmitted to the PIA practice management centre in practice. The PIA-practice assistants checked the incoming blood pressure values and, if the target blood pressure value was not reached, suggested a change in medication according to the GP's pre-settings for a patient. The GP-supervised this, adjusted the medication if needed, and signed the

new medication plan with his physician personal identification number (PIN). Using the physicians PIN triggered the transfer of the new medication plan from the PIA practice management centre to the patient's PIA-App. The digital communication allowed for an additional function, namely exchanging text messages between the practice and the patient (chat function). The flow of the digital PIA-Communication is outlined in Figure 4.

The PIA care aims to improve blood pressure control (practice blood pressure < 140/90 mmHg). However, patient-specific targets can be implemented if deemed appropriate by the physician in charge.

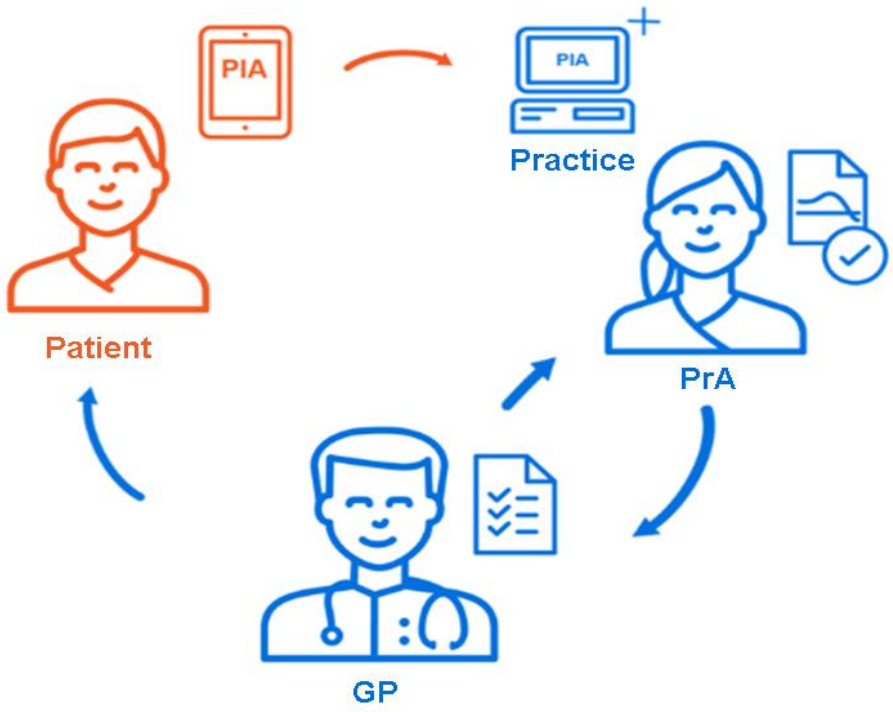


Fig. 4: PIA-Communication

2.1.2 PIA eLearning and on-site learning for physicians, practice assistants and patients

All participants of the digital care model were qualified as follows:

- Physician and practice assistants participated in eLearning (learning video and slides): This informed on hypertension and its sequelae, standardized BP measurements, hypertension management with delegation model, and using the PIA-PrMc.
- Online or on-site training was optionally available at the request of the practice.

- Practice assistants took an exam and received the PIA certificate if they passed. They were then certified for the delegation model as so-called PIA-practice assistants (PIA-PrA).

All patients were trained on-site and via the PIA-App:

- The patients were trained in the practice by the PIA-PrAs. The contents were: correct home blood pressure measurements, the functions of the PIA-App and how to use them.
- In addition, the app included a learning video on state-of-the-art home blood pressure measurements and provided links with additional information.

The process of developing the PIA-Intervention: The PIA-Intervention was developed using Yardley's framework (Yardley et al. 2015) for a participatory and agile process: First, during the planning phase, hypertension management was observed in one family practice. Experiences from the existing literature (Margolis et al. 2013; McKinstry et al. 2013; McManus et al. 2018; McManus et al. 2021; Weltermann et al. 2016) were also included in the planning of the intervention. Second, virtual scenarios and standardized workflows were defined and discussed with all stakeholders. From this, the concept was developed. Third, a team of scientists, GPs and PrAs defined the requirements for the PIA-ICT. Another new aspect was that the teams were in close exchange (Daily+ Sprints) several times daily. This resulted in the requirements specification sheet. The development of PIA-ICT proceeded in each iteration cycle as follows: tasks for the developers were defined from the requirements specification. The requirements specification was readapted to the resulting requirements after each test. The developers were in a close exchange (Daily+ Sprints). The products developed in each iteration were shared with the research team. The research team tested and discussed the results with the developers several times daily. This resulted in new requirements and therefore new tasks. The finished prototypes were tested with the target users and new tasks emerged. The new were again discussed in the team with the developers and flowed into the requirements specification. These iterations were repeated until a finished product was ready for use in the intervention group. For more details, see Figure 5. Fourth, when all components of the PIA-Intervention and the questionnaires were developed, they were

tested in detail using the think-aloud method (Fonteyn et al. 1993; van Someren et al. 1994): Patients, GPs, and PrAs used the PIA-ICT, the training sessions, and completed the questionnaires under the observation of two researchers, saying aloud what they thought. Subsequently, patients, GPs, and PrAs used the PIA-App and PIA-PrMc for six weeks and were interviewed about their experiences with the intervention. During this phase, users were asked about usability and acceptance. The results from the interviews were incorporated into the development process.

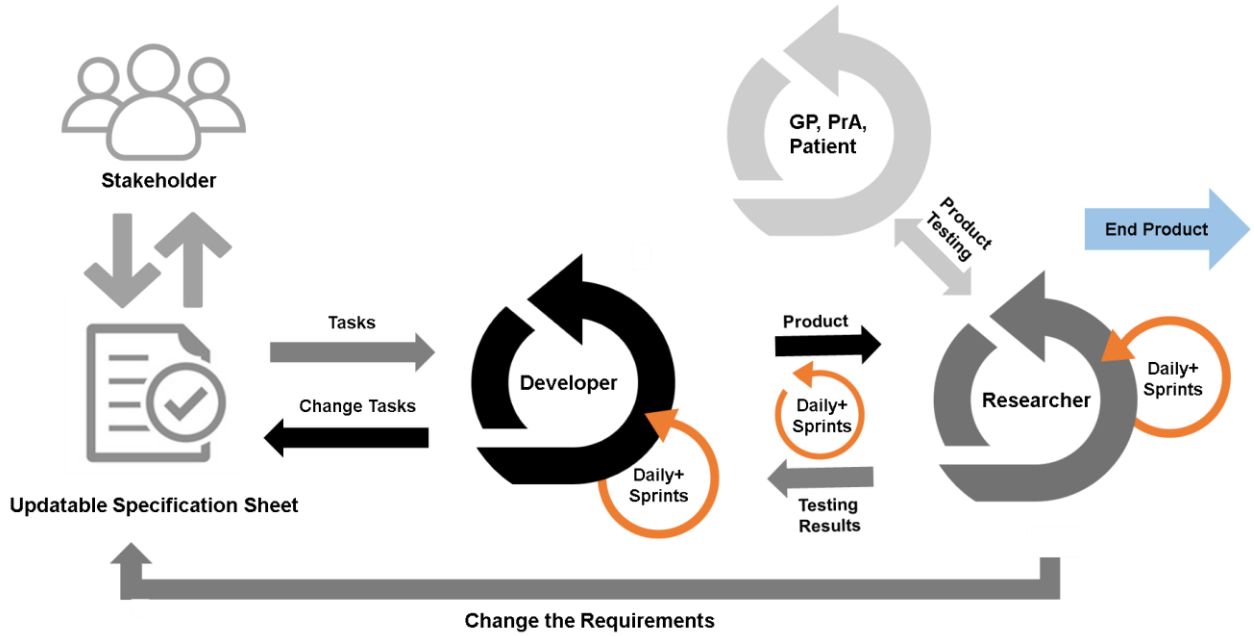


Fig. 5: The Iteration Cycle in the agile development of PIA-ICT

2.2 Design and conduct of the PIA study

2.2.1 Cluster-randomised controlled design

The PIA-Intervention was evaluated in a cluster-randomised controlled trial (cRCT), which considered the gold standard for practice intervention studies (Campbell et al. 2000). Randomisation took place at the practice level, not at the patient level, to avoid contamination of the control group: blood pressure treatment was provided by using the digital hyper-tension management with its delegation model (PIA-Intervention) or by usual care (control). Patients in the control group did not receive the PIA-App during the study, and there were no specifications for hypertension therapy in the control group to reflect

usual care. This implied that it was up to the individual physician’s discretion whether and how hypertension treatment was provided. The control group received the digital care solution after the follow-up survey, which occurred 6 to 12 months after the baseline (waiting list control design) (Karimzadeh et al. 2021). For more details see Figure 6.

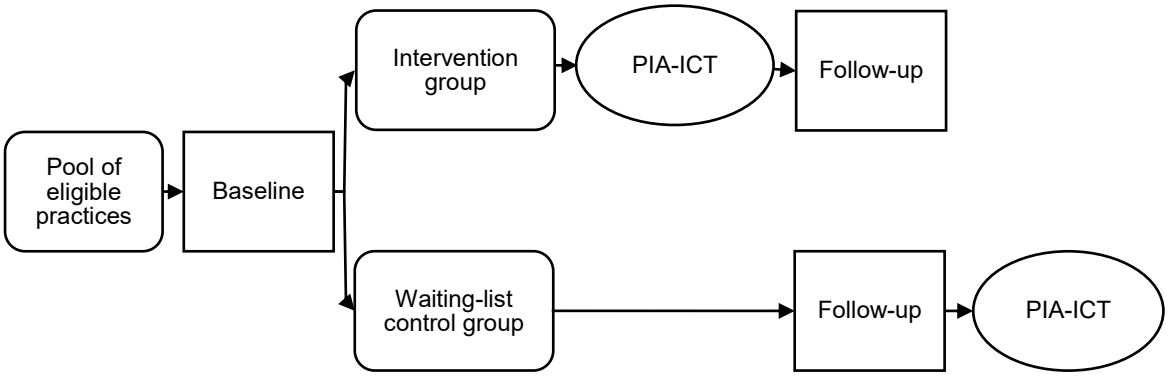


Fig. 6: Study design: cluster randomized trial with waiting-list control arm (Karimzadeh et al. 2021)

The PIA study targeted patients with essential arterial hypertension (ICD I10), i.e., no secondary hypertension is known. At the study inclusion, the patients' blood pressure needed to be ≥ 140/90 mmHg (practice blood pressure measurement). Patients aged between 40 and 79 years who were insured in the statutory health insurance could be included. In addition, at least one antihypertensive medication was already given or needed.

Regarding technical requirements, a smart device (smartphone or tablet) with an Android operating system in version 6 or higher and the ability to use the smart device at least three times per week were required to participate in the PIA study.

2.2.2 Participants and recruitment

Inclusion and exclusion criteria were predefined for both participant groups, namely general practices (GP practices) and patients.

Inclusion and exclusion criteria for GP practices: GP practices with physicians licensed for statutory health insurance and a PC with internet access in their practice were eligible to participate in the study. Practices with a GP who is a certified hypertensiologist and all practices that had participated in developing the intervention or our previous cluster-randomised trial on hypertension management were excluded (Weltermann et al. 2016). In each practice, at least one PrA was designated and recruited by the practice owner to qualify as a PIA-PrA (intervention arm) a contact person during the study (control arm). In Germany, PrAs have a vocational education of three years and are certified by the regional Medical Council.

Practice owners were asked to recruit PrAs who work in practice every day. Preferably, PrAs with higher responsibility (so-called lead PrAs) should be engaged. In addition, a deputy was designated. All PrAs and deputies underwent eLearning for the PIA study and completed the PIA exam. A re-test was offered for those who still needed to pass the PIA exam.

Inclusion and exclusion criteria for patients: The new digitally supported care format addressed patients with uncontrolled arterial hypertension in the participating primary care practices.

The inclusion criteria for patients were as follows:

- Covered by the statutory health insurance,
- Diagnosis of essential arterial hypertension (ICD I10),
- Age ≥ 40 years and < 80 years: this age group was chosen for two reasons: for younger patients, the guidelines recommend different diagnostic standards with obligatory work-up for secondary hypertension; for patients ≥ 80 years, higher blood pressure target values are recommended to prevent falls (Williams et al. 2018),
- Inadequate blood pressure control after 6 months of non-pharmacological therapy with the need to prescribe ≥ 1 antihypertensive,
- Practice blood pressure ≥ 140/90 mmHg (second measurement of 2 successive practice blood pressure measurements in sitting, resting position),
- Sufficient German language skills to understand the study documents,
- Smart device (tablet or smartphone) with Android and internet access, and

- Sufficient computer literacy (self-reported computer/tablet/smartphone use at least 3 times; ability to install the app via a link/QR code and submit messages by communication apps).

The following exclusion criteria applied for patients:

- White coat hypertension,
- Critical health condition at the time of inclusion (e.g., hypertensive crisis, BP-related symptoms such as dizziness or headache),
- Requiring dialysis, and
- Pregnancy.

The same inclusion and exclusion criteria were applied to control patients (usual care).

Recruitment of GP practices and patients:

The study was conducted starting from 9/2019 through 9/2021. The study implementation included recruitment, data collection and data management.

The details for the recruitment are as follows:

- Recruitment of primary care physicians from 9/2019 to 12/2020,
- Recruitment of patients by primary care practices from 04/2020 to 03/2021,
- End of follow-up period: 9/30/2021.

Starting in 2/2020, study implementation was delayed by a total of 3 lockdowns due to the SARS-CoV-2 pandemic (see Figure 7).

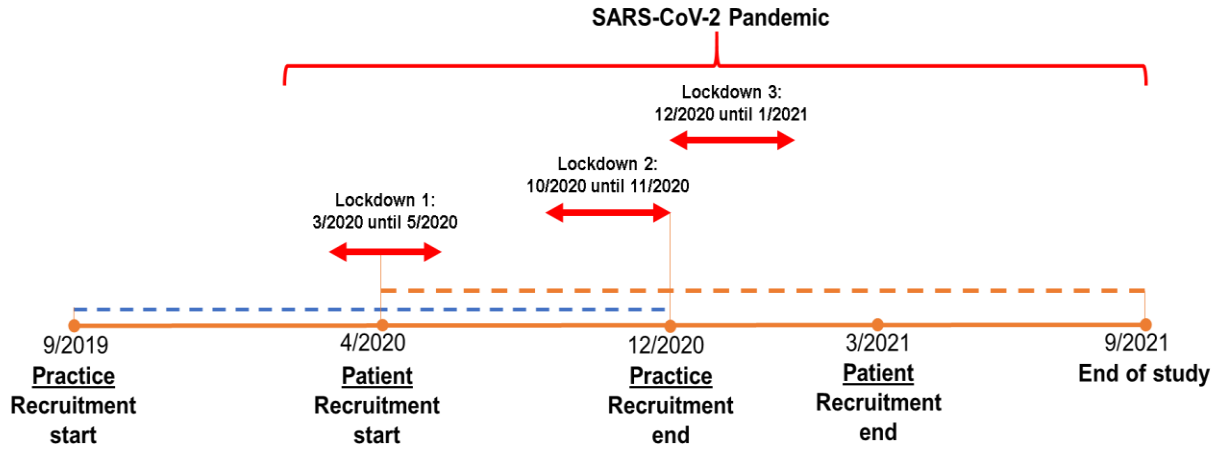


Fig. 7: Timing of practice and patient recruitment: delays due to recurrent lockdown phases in the SARS-CoV-2 pandemic

A multi-stage process was used to recruit practices:

- GP practices received invitation letters through different contact modes (by letter, fax, and email).
- Subsequently, the recruitment team contacted these GP practices by telephone with study nurses, PhD students and physicians in training.
- After successful recruitment, the independent study centre performed 1:1 randomisation at the practice level into either intervention or control practices. This means that each practice and all patients were assigned to either the intervention group (IG) or the control group (CG).
- Randomization was based on computer-generated random numbers.

After group allocation, the participating practices were visited by the study team, which informed about the study and explained the study materials.

All participating practices received a study folder containing the survey forms for patients, GPs, and practice PrAs. The practice visits took place at the study's beginning and end. All practices received training on practice recruitment and study procedures at the first practice visit. This included an educational video on standardized practice blood pressure measurements. Participating practices then recruited patients using the study flyers and study posters for the waiting room.

All participating GPs, PrAs, and patients completed a questionnaire at baseline and the end of the study. Each participating patient received a standardized BP measurement at the beginning and end of the study: after resting for five minutes, the practice BP was measured twice by the PrAs at a one-minute interval. Measurements were taken with calibrated upper arm sphygmomanometers. A 24/7 available video informed GPs and practice personnel on such standard practice blood pressure readings according to guidelines.

All intervention practices received access to the PIA-PrMc and the PIA eLearning. The PrAs of the intervention practices were qualified as PIA-PrAs using eLearning. After passing the PIA examination, they received the certificate as a 'PIA-PrA'. This short examination with 10 questions addressed issues of blood pressure targets, validated blood pressure readings, the role of the PIA-PrA, and the digitally supported delegation

model to support the up-dosing of antihypertensives. The PIA-PrAs were trained to educate patients on how to use the PIA-App and the calibrated, automated upper arm blood pressure monitor handed out to patients.

2.2.3 Primary and secondary outcomes

The **primary endpoint of the study** was the blood pressure (BP) control rate. This was defined as the percentage of patients with a practice blood pressure value of less than 140 mmHg systolic and 90 mmHg diastolic, i.e., a simultaneous undershooting of the second threshold value. (Practice measurement: two successive measurements at intervals of 1 min each in a seated position).

The primary research question for evaluating the PIA care model was: which proportion of hypertensive patients reaches blood pressure control (BP < 140/90 mmHg) with the digital care PIA compared to those with usual care?

The selected primary outcome blood pressure control is internationally recognized as a surrogate parameter for preventing secondary diseases (EMA/238/1995/Rev. 3 2010).

Our hypothesis was that blood pressure control rates at 12 months would be at least 15 % higher in patients with the new digital care compared to patients without this new care (assumptions: 65 % versus 50 %). These assumptions were based on the effectiveness of digital hypertension management published by Margolis et al. 2013 (Margolis et al. 2013).

The **secondary outcomes** addressed the effects of the PIA study on all participating parties (patients, GPs, PrAs, and primary care practices) using suitable evaluation strategies. Key secondary outcomes were:

- changes of SBP and DBP practice measurements between baseline and follow-up,
- patients' satisfaction with hypertension management,
- frequency of home BP measurement,
- reminder for home BP measurements,
- medication changes.

In the intervention group only, the following parameters were obtained:

- satisfaction with the PIA-Intervention by patients, GPs, and practice PrAs,
- number of home BP measurements,
- number of contacts between the practice team and patients via PIA-ICT.

In addition, patient, practice, GP, and PrA characteristics, including socio-demographic and medical parameters, were obtained.

The subsequent table (Table 1) presents all endpoints with the respective survey instruments, times, and evaluation components. Further information on the survey instruments used can be found in the published study protocol (Karimzadeh et al. 2021).

Tab. 1: Overview of study time table (enrolment, intervention, assessments), and commitment for trial participants including evaluation parameters (Karimzadeh et al. 2021)

	En-roll-ment	Allo-ca-tion	Base-line	Treat-ment (IG only)	Implement-ation (IG only) 2 to 4 quar-ters (Q) = 6 to 12 months[1]	Fol-low-up	Waiting-list CG = 1 to 3 months (m)
			Study periods				
TIME POINTS	$-t_3$	$-t_2$	$-t_1$	0	Q_1 to Q_4	t_1	m_1 to m_3
ENROLLMENT							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
TRAINING							
Training of GPs				X			X
Training of PrA				X			X
Training of patients[2]				X			X
ASSESSMENTS							
Patients							
<u>Primary outcomes:</u>							
BP measurements			X			X	

	En-roll-ment	Allo-ca-tion	Base-line	Treat-ment (IG only)	Implement-ation (IG only) 2 to 4 quar-ters (Q) = 6 to 12 months[1]	Fol-low-up	Waiting-list CG = 1 to 3 months (m)
			Study periods				
TIME POINTS	$-t_3$	$-t_2$	$-t_1$	0	Q_1 to Q_4	t_1	m_1 to m_3
<u>Secondary Outcomes:</u>							
Time to BP control: Serial BP measure-ments					◆——◆	X	
Changes of SBP and DBP						X	
Medical history / comorbidities			X			X	
Number of medica-tion adjustments (Medication plans)			X		◆——◆	X	
Satisfaction regard-ing hypertension therapy by GP prac-tice			X			X	
Socio-demographic data			X			X	
Frequency of home BP measurement			X			X	
Reminder for home BP readings			X			X	
Satisfaction with PIA intervention						X	
GPs							
Satisfaction with PIA-Intervention[3]						X	
Socio-demographic data			X				
Professional qualifi-cation			X				
Practice assistants							
Satisfaction with PIA-Intervention[3]						X	

	En-roll-ment	Allo-ca-tion	Base-line	Treat-ment (IG only)	Implement-ation (IG only) 2 to 4 quar-ters (Q) = 6 to 12 months[1]	Fol-low-up	Waiting-list CG = 1 to 3 months (m)
			Study periods				
TIME POINTS	$-t_3$	$-t_2$	$-t_1$	0	Q_1 to Q_4	t_1	m_1 to m_3
Socio-demographic data			X				
Professional qualifi-cation			X				
Patients in Intervention group only							
Transmitted BP measurements via PIA-App to PIA-PrMc					◆——◆		
Number of contacts between practice and patient via PIA-ICT					◆——◆		
Frequency of use of the different func-tions in PIA-ICT					◆——◆		

[1] Required Due to the SARS-CoV-2 pandemic: changed to at least 6 months, [2] Patients received up to four training sessions as, [3]Intervention group only This Table is modified from the study protocol (Karimzadeh et al. 2021).CG = Control group; IG = Intervention group.

2.3 Statistical analysis

The sample size was calculated based on the primary outcome. In an RCT, Margolis et al. (2013) investigated the effect of clinical pharmacist-guided case management of hypertension patients compared to usual care: patients performed blood pressure self-measurements. They transmitted the values to the case manager, who adjusted medications. After 1 year, blood pressure control rates of 71 % (intervention arm) and 53 % (control arm) were documented (Margolis et al. 2013). Following this effectiveness, we assumed a conservative blood pressure control rate of 65 % in the intervention arm and 50 % in the control arm after at least 6 months for our practice assistant-supported, physician-supervised delegation model.

Sample size calculations were performed in PASS V14 using an unpooled 2-sided Z-test to compare two proportions in a cluster-randomised design. Under the assumption that both study arms included the same number of clusters (practices), the intra-cluster correlation coefficient was set at 0.055 (Singh et al. 2015), and the mean cluster size was 15 patients. This resulted 2 x 300 = 600 patients (20 clusters per study arm = in total 40 GP practices), which were required to detect a group difference of 15 % (65 % vs. 50 %) with a power of 80 %. Although the sample size calculation was based on a 2-sided Z-test with unpooled variance in a cluster-randomised setting, there was sufficient power to calculate a generalised linear mixed model (GLMM) with additional covariates.

Primary endpoint: The confirmatory analysis for the primary endpoint was based on a generalised linear mixed model (GLMM) with a significance level of 95 % (2-sided). A GLMM was used because the primary endpoint was an outcome on the patient level and embedded in the cluster design (practices). The model included relevant patient covariates (four age groups, sex, and coronary disease/myocardial infarction history). The recruitment period was included as a covariate because the COVID-19 pandemic delayed patient recruitment. To account for the data's cluster structure, the patients' affiliation to practice was entered into the model as a random effect. The null hypothesis (no difference in blood pressure control rate) was rejected if the p-value < 0.05. In addition, the adjusted odds ratio (OR) and associated 95 % confidence interval were reported. Robustness analyses with imputation procedures for missing values were performed. Statistical software used R 3.6 (GLMM model: lme4 [1.1-26]).

Secondary Endpoints: The secondary outcomes addressing BP measurements (changes in SBP and DBP) were evaluated using GLMM with random effects to account. For the SBP and DBP differences and associations Z statistics were used. All other secondary analyses were performed in exploratory using adequate standard statistical procedures. To test for differences and associations, the t-Tests or Mann-Whitney U-tests statistics were used for metric variables, while the Chi-square test was applied for categorical variables. Statistical software used IBM SPSS 27 on Windows and R 3.6 (GLMM model: lme4 [1.1-26]). A significance level of 95 % was assumed for all statistical analyses.

2.4 Ethics and data protection

The Ethics Committee of the Medical Faculty of the University of Bonn raised no legal or ethical objections against the study (Ethics No. 156/18, initial vote 2018/08/02, additional vote from 2021/09/24). Subsequent ethical votes were provided by the ethics committees of the North-Rhine Medical Association (Ethics No. 2018400, ethics votes from 2019/03/07, 2021/10/28, and 2021/10/26), the Medical Association of Westphalia-Lippe (ethics No. 2020-514-bS, votes from 2020/07/20 and 2021/10/26), the Medical Association of Rhineland-Palatinate (ethics No. 2020-15178_5, ethics votes from 2020/09/02 and 2021/11/15) and the Medical Association of Baden-Württemberg (ethics No. B-F-2020-097, ethics votes from 2020/09/04 and 2021/11/18). The data protection officer of the University Hospital Bonn reviewed the data protection concept of the PIA study and approved the approach on 2019/10/14 and 2020/03/09.

The Advisory Board included three international experts from primary care, digital hypertension management, and telemedicine. In addition, the Advisory Board included a specialist in general medicine who is a recognized national expert from the Expert Commission for Medical Malpractice of the North-Rhine Medical Association. He was responsible for independently assessing patient-relevant outcomes in case such events occurred.

3. Results

3.1 Characteristics of participating practices and patients

In total, 64 practices and 848 patients were recruited. The recruitment process was markedly impaired due to the pandemic and yielded an overall participation rate of practices was 3.6 %. This aligns with the usual recruitment rates from the literature (Güthlin et al. 2012). The details are shown in the CONSORT flowchart (Figure 8).

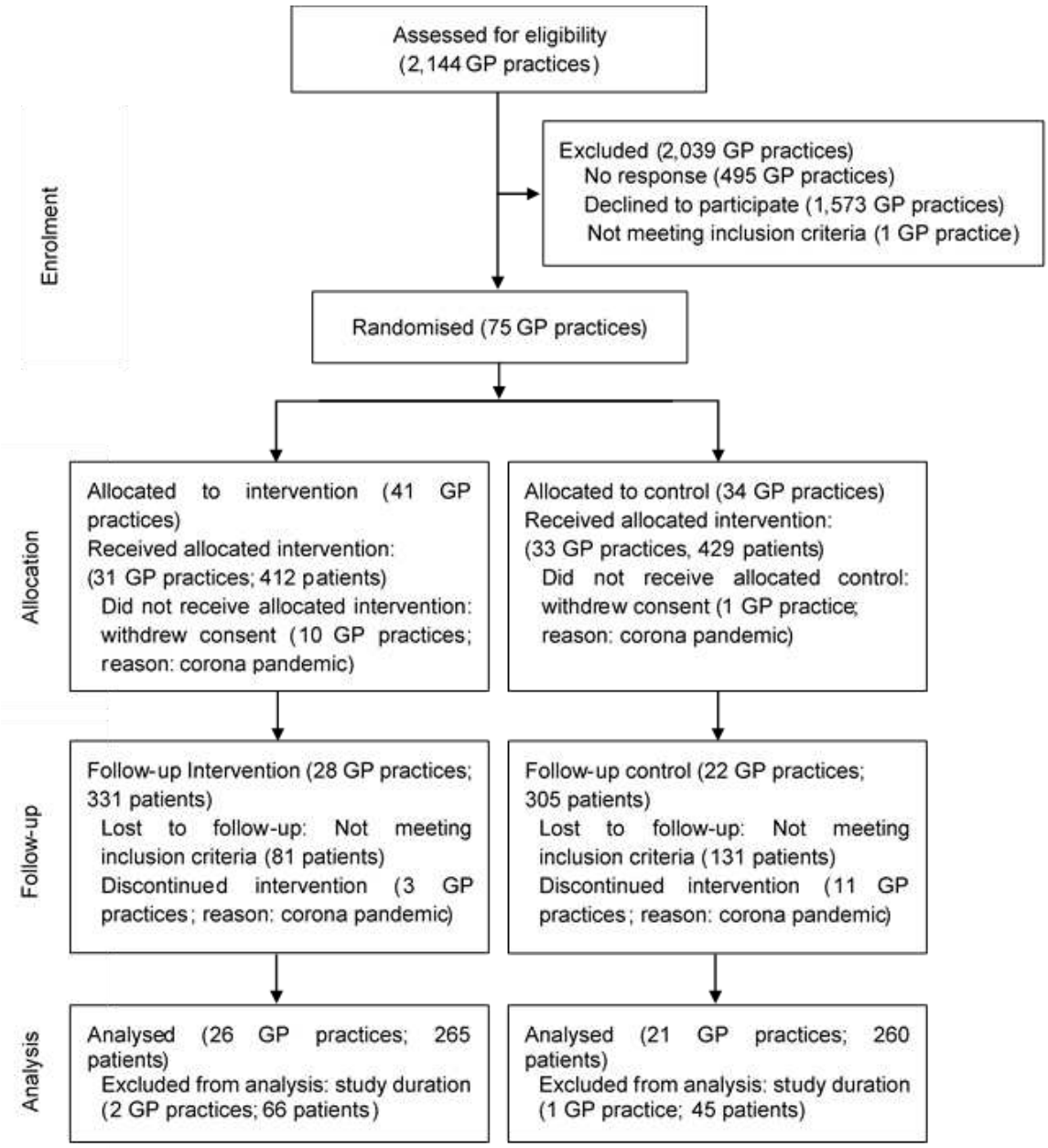


Fig. 8: CONSORT flow diagram (Leupold et al. 2023)

The reasons for not including practices and patients in the final study population were as follows: due to a pandemic-related burden (25 practices), failure to meet the pre-defined inclusion criteria (212 patients) and due to too short duration of participation (3 practices; 111 patients). The final study set for analysis included: 47 practices; 525 patients; 51 GPs; 61 practice assistants.

Patient characteristics: At baseline, 636 patients who met the inclusion criteria had complete data to evaluate the primary outcome (see section 2). These patients belonged to a total of 50 practices (intervention: 28; control: 22), which means that an average of 12.7 patients per practice were recruited (intervention: 11.8 patients [SD 9.9]; control: 13.9 [SD 11.2]). For more details, see Table 2.

Complete follow-up data were available for 525 (82.5 %) of these patients from a total of 47 practices (intervention: 26; control: 21). These patients and practices comprised the final dataset for analysis. Each practice contributed 11.2 patients [SD10.3] to the final data set. For more details see Table 3.

To detect potential selection biases, the characteristics of these patients were compared. There were no significant differences between the study participants with complete data at baseline and those with complete data at both time points.

Tab. 2: Patient characteristics at baseline (n = 636) (Leupold et al. 2023)

	All (N = 636)	**Intervention group (n = 331)**	**Usual care group (n = 305)**
Social demographic characteristics			
Sex, n (%)			
Women	301 (47.3 %)	150 (45.3 %)	151 (49.5 %)
Man	335 (52.7 %)	181 (54.7 %)	154 (50.5 %)
Age, mean [SD]	58.0 [9.2]	56.9 [8.7]	59.2 [9.7]
Marital status, n (%)			
Married or cohabiting	411 (64.7 %)	213 (64.4 %)	198 (64.9 %)
Divorced or separated living	84 (13.2 %)	43 (13.0 %)	41 (13.4 %)
Widowed	38 (6.0 %)	17 (5.1 %)	21 (6.9 %)
Single	69 (10.8 %)	38 (11.5 %)	31 (10.2 %)

	All (N = 636)	Intervention group (n = 331)	Usual care group (n = 305)
Missing data	34 (5.3 %)	20 (6.0 %)	14 (4.6 %)
School graduation, n (%)			
No school graduation	26 (4.1 %)	13 (3.9 %)	13 (4.3 %)
Finished 9th grade	206 (32.3 %)	98 (29.5 %)	108 (35.5 %)
Finished 10th grade	178 (28.0 %)	103 (31.0 %)	75 (24.7 %)
Finished 12th grade	50 (7.9 %)	25 (7.6 %)	25 (8.2 %)
High school diploma	126 (19.8 %)	63 (19.0 %)	63 (20.7 %)
Graduated from other schools	14 (2.2 %)	8 (2.4 %)	6 (2.0 %)
Missing data	36 (5.7 %)	25 (7.6 %)	11 (3.6 %)
Occupation, n (%)			
Working	347 (54.6 %)	196 (59.2 %)	151 (49.5 %)
Retired	171 (26.9 %)	75 (22.7 %)	96 (31.5 %)
In early retirement	12 (1.9 %)	7 (2.1 %)	5 (1.6 %)
Searching for work	20 (3.1 %)	12 (3.6 %)	8 (2.6 %)
Housewife or househusband	27 (4.2 %)	12 (3.6 %)	15 (4.9 %)
Not working	23 (3.6 %)	9 (2.7 %)	14 (4.6 %)
Missing data	36 (5.7 %)	20 (6.0 %)	16 (5.2 %)
General health status, n (%)			
Excellent	6 (0.9 %)	2 (0.9 %)	4 (1.3 %)
Very good	53 (8.3 %)	25 (8.3 %)	27 (8.9 %)
Good	347 (54.4 %)	175 (54.8 %)	172 (56.5 %)
Less good	155 (24.3 %)	91 (24.4 %)	64 (21.0 %)
Bad	25 (3.9 %)	12 (3.6 %)	13 (4.3 %)
Missing data	50 (8.2 %)	26 (7.9 %)	24 (7.9 %)
Blood pressure, mean [SD]			
SBP (mmHg), M1	156.9 [14.8]	157.8 [16.2]	155.9 [13.1]
DBP (mmHg), M1	93.7 [9.6]	94.8 [9.8]	92.5 [9.3]
SBP (mmHg), M2	154.1 [14.1]	154.7 [15.7]	153.5 [12.1]
DBP (mmHg), M2	93.1 [9.6]	94.6 [9.8]	91.5 [9.1]

	All (N = 636)	Intervention group (n = 331)	Usual care group (n = 305)
Coronary heart disease and/or myocardial infarction, n (%)			
Without coronary heart disease or myocardial infarction	529 (83.2 %)	280 (84.5 %)	249 (81.6 %)
With coronary heart disease and/or myocardial infarction	107 (16.8 %)	51 (18.4 %)	56 (18.4 %)
Current smoker, n (%)	160 (25.2 %)	86 (26.0 %)	74 (24.3 %)

BP M1 = first measurement after five minutes rest, BP M 2 = second measurement after one minute; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.

Tab. 3: Patient characteristics at baseline with complete follow-up data (n = 525) (Leupold et al. 2023)

	All (N = 525)	Intervention group (n = 265)	Usual care group (n = 260)
Social demographic characteristics			
Sex, n (%)			
Women	248 (47.2 %)	119 (44.9 %)	129 (49.6 %)
Man	277 (52.8 %)	146 (55.1 %)	131 (50.4 %)
Age, mean [SD]	59.4 [9.7]	57.7 [8.7]	58.6 [9.2]
Marital status, n (%)			
Married or cohabiting	347 (66.1 %)	178 (67.2 %)	169 (65.0 %)
Divorced or separated living	72 (13.7 %)	32 (12.1 %)	40 (15.4 %)
Widowed	35 (6.7 %)	17 (6.4 %)	18 (6.9 %)
Single	50 (9.5 %)	26 (9.8 %)	24 (9.2 %)
Missing data	21 (4.0 %)	12 (4.5 %)	9 (3.5 %)
School graduation, n (%)			
No school graduation	23 (4.4 %)	11 (4.2 %)	12 (4.6 %)
Finished 9th grade	185 (35.2 %)	89 (33.6 %)	96 (36.9 %)
Finished 10th grade	147 (28.0 %)	81 (30.6 %)	66 (25.4 %)
Finished 12th grade	38 (7.2 %)	21 (7.9 %)	17 (6.5 %)
High school diploma	103 (19.6 %)	48 (18.1 %)	55 (21.2 %)
Graduated from other schools	6 (1.1 %)	2 (0.8 %)	4 (1.5 %)
Missing data	23 (4.4 %)	13 (4.9 %)	10 (3.8 %)

	All (N = 525)	Intervention group (n = 265)	Usual care group (n = 260)
Occupation, n (%)			
Working	280 (53.3 %)	153 (57.7)	127 (48.8)
Retired	155 (29.5 %)	71 (26.8 %)	84 (32.3 %)
In early retirement	11 (2.1 %)	6 (2.3 %)	5 (1.9 %)
Searching for work	16 (3.0 %)	8 (3.0 %)	8 (3.1 %)
Housewife or househusband	21 (4.0 %)	8 (3.0 %)	13 (5.0 %)
Not working	19 (3.6 %)	7 (2.6 %)	12 (4.6 %)
Missing data	23 (4.4 %)	12 (4.5 %)	11 (4.2 %)
General health status, n (%)			
Excellent	5 (1.0 %)	1 (0.4 %)	4 (1.5 %)
Very good	45 (8.6 %)	21 (7.9 %)	24 (9.2 %)
Good	290 (55.2 %)	142 (53.6 %)	148 (56.9 %)
Less good	129 (24.6 %)	74 (27.9 %)	55 (21.2 %)
Bad	22 (4.2 %)	10 (3.8 %)	12 (4.6 %)
Missing data	34 (6.5 %)	17 (6.4 %)	17 (6.5 %)
Blood pressure, mean [SD]			
SBP (mmHg), M1	156.9 [14.5]	158.5 [16.4]	155.2 [12.2]
DBP (mmHg), M1	93.6 [9.7]	94.5 [10.1]	92.6 [9.3]
SBP (mmHg), M2	154.4 [13.8]	155.4 [15.7]	153.3 [11.6]
DBP (mmHg), M2	93.0 [9.8]	94.4 [10.2]	91.6 [9.1]
Coronary heart disease and/or myocardial infarction, n (%)			
Without coronary heart disease or myocardial infarction	429 (81.7 %)	217 (81.9 %)	212 (81.5 %)
With coronary heart disease and/or myocardial infarction	96 (18.3 %)	48 (18.1 %)	48 (18.5 %)
Current smoker, n (%)	131(25.0 %)	68 (25.7 %)	63 (24.2 %)

BP M1 = first measurement after five minutes rest, BP M 2 = second measurement after one minute; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.

The intervention and the usual care group were compared in both samples to detect any inhomogeneity. These between-group comparisons showed that patients in the control group were slightly older by a mean of 2.3 years (all study participants) and 1.7 years

(study participants with complete data at both time points). The final model controlled for this difference.

The population shown in Table 3 constituted the final study population for the clinical effectiveness analysis. In short, slightly more patients were male than female (52.8 % vs. 47.2 %), and their average age was 59. The majority lived with a spouse or partner (66.1 %), had a school degree (95.6 %), and were currently working (53.3 %). The majority had self-assessed their health as good or better (64.8 %), while 28.8 % had rated their health as not good or bad. A fourth of the population were current smokers, and 18.3 % had a known coronary disease or history of myocardial infarction.

Characteristics of practices, GPs, and practice assistants: The characteristics of the participating GPs and practice assistants are shown in Tables 4 and 5. There were no significant differences between the study arms.

The mean age of the participating GPs was 47 years, and they were licensed on average for 20 years. Most were self-employed (70.5 %) and working full-time (95.1 %). The vast majority was Board-certified as specialist in general medicine and/or internal medicine (77.0 %). There were no differences between study arms. For details, see Table 4.

Tab. 4: GP characteristics at baseline

	All (N = 61)	**Intervention group (n = 32)**	**Usual care group (n = 29)**
Sex, n (%)			
Man	30 (49.9 %)	17 (53.1 %)	13 (44.8 %)
Women	31 (50.8 %)	15 (46.9 %)	16 (55.2 %)
Age, mean [SD]	47.52 [10.7]	47.25 [11.04]	47.83 [10.6]
Medical license in years, mean [SD]	20.30 [10.3]	19.30 [9.0]	21.34 [11.5]
Employment, n (%)			
Employed	18 (29.5 %)	11 (34.4 %)	7 (24.1 %)
Self-employed	43 (70.5 %)	21 (65.6 %)	22 (75.9 %)
Working time, n (%)			
Part-time, n (%)	3 (4.9 %)	2 (6.3 %)	1 (3.4 %)

	All (N = 61)	Intervention group (n = 32)	Usual care group (n = 29)
Full-time, n (%)	58 (95.1 %)	30 (93.7 %)	28 (96.6 %)
GPs with board-certified, n (%)			
GP without Board-certified	3 (4.9 %)	0 (0.0 %)	3 (10.3 %)
Board-certified in general medicine	25 (41.0 %)	14 (43.8 %)	11 (37.9 %)
Board-certified in internal medicine	15 (24.6 %)	9 (28.1 %)	6 (20.7 %)
Board-certified in internal and general medicine	7 (11.5 %)	2 (6.3 %)	5 (17.2 %)
Board-certified in other qualifications	11 (18.0 %)	7 (11.5 %)	4 (6.6 %)

Most of the 82 practice assistants had completed vocational training (91.5 %) and were female (97.6 %). On average, they were 36 years old and worked in the respective practice for 9 years. Slightly more practice assistants worked full-time (57.3 %) than part-time (41.5 %). The practice assistants did not differ between study groups (see Table 5).

Tab. 5: Practice assistants´ characteristics at baseline

	All (N = 82)	Intervention group (n = 46)	Usual care group (n = 36)
Sex, n (%)			
Man	2 (2.4 %)	2 (4.3 %)	0 (0.0 %)
Women	80 (97.6 %)	44 (95.7 %)	36 (100.0 %)
Age, mean [SD]	36.3 [11.4]	35.2 [0.2]	37.7 [11.7]
Years in this practice, mean [SD]	8.9 [8.2]	7.8 [7.2]	10.2 [9.4]
Qualification, n (%)			
Physician assistant	25 (30.5 %)	13 (28.3 %)	12 (33.3 %)
Practice assistant	50 (61.0 %)	28 (60.8 %)	22 (61.1 %)
Physician assistance (without completed professional training)	1 (1.2 %)	0 (0.0 %)	1 (2.8 %)
Others, n (%)	6 (7.3 %)	5 (10.9 %)	1 (2.8 %)

	All (N = 82)	Intervention group (n = 46)	Usual care group (n = 36)
Working time, n (%)			
Full-time	47 (57.3 %)	24 (52.2 %)	23 (63.9 %)
Part-time	34 (41.5 %)	21 (45.6 %)	13 (36.1 %)
Not specified	1 (1.2 %)	1 (2.2 %)	0 (0.0 %)

The different practice categories did not differ significantly between the two study arms, and most participating practices were single practices (54.0 %). For details, see Table 6.

Tab. 6: Practice characteristics at baseline

	All (N = 50)	Intervention group (n = 28)	Usual care group (n = 22)
Practice category, n (%)			
Single practice	27 (54.0 %)	15 (53.6 %)	12 (54.5 %)
Group Practice	13 (26.0 %)	7 (25.0 %)	6 (27.3 %)
Joint practice	8 (16.0 %)	5 (17.9 %)	3 (13.6 %)
Medical Service Centres	2 (4.0 %)	1 (3.6 %)	1 (4.5 %)

3.2 Primary outcome: Blood pressure control rate

The first and second blood pressure readings were recorded for each patient at baseline and follow-up. These unadjusted blood pressure values and the systolic and diastolic BP changes are displayed in Table 7. Only the second readings were used for the final analysis.

In the total study population, the unadjusted mean systolic BP at baseline was 154.4 mmHg, which improved to 136.0 mmHg. This decrease of more than 15 mmHg is outcome-relevant for patients in both study arms. Furthermore, the unadjusted systolic BP improved significantly more in the intervention than in the control group (134.3 mmHg versus 137.8 mmHg). Similarly, the systolic BP control rate improved to 72.5 % in the intervention, which was significantly higher than in the control group (50.4 %) (p-value < 0.001). Also, the unadjusted data for the primary endpoint (% of patients with BP < 140/90 mmHg) showed a significant difference between the study arms: intervention group 62.6 % with controlled BP; control arm: 44.6 % (p-value < 0.001).

Tab. 7: Blood pressure measurements at baseline and follow-up (unadjusted) (n=525): two measurements each for systolic and diastolic values (Leupold et al. 2023)

	All (N = 525)	Intervention group (n = 265)	Usual care group (n = 260)	p-value*
Baseline blood pressure, mean [SD]				
SBP (mmHg), M1	156.9 [14.5]	158.5 [16.4]	155.2 [12.2]	0.01
DBP (mmHg), M1	93.6 [9.7]	94.5 [10.1]	92.6 [9.3]	0.03
SBP (mmHg), M2	154.4 [13.8]	155.4 [15.7]	153.3 [11.6]	0.08
DBP (mmHg), M2	93.0 [9.8]	94.4 [10.2]	91.6 [9.1]	0.001
Follow-up blood pressure, mean [SD]				
SBP (mmHg), M1, Mean [SD]	138.6 [17.3]	136.0 [16.4]	141.3 [17.8]	< 0.001
DBP (mmHg), M1, Mean [SD]	84.5 [11.0]	84.1 [10.9]	84.9 [11.1]	0.40
SBP (mmHg), M2, Mean [SD]	136.0 [15.1]	134.3 [14.5]	137.8 [15.5]	0.01
DBP (mmHg), M2, Mean [SD]	83.3 [10.1]	83.1 [9.7]	83.4 [10.6]	0.73
BP, M1, n (%)	242 (46.1 %)	149 (56.2 %)	93 (35.8 %)	< 0.001
BP control rates at follow-up, n (%)				
Controlled SBP, M1, n (%)	282 (53.7 %)	173 (65.3 %)	109 (41.9 %)	< 0.001
Controlled DBP, M1, n (%)	361 (68.8 %)	194 (73.2 %)	167 (64.2 %)	0.03
Controlled SPB, M2, n (%)	323 (61.5 %)	192 (72.5 %)	131 (50.4 %)	< 0.001
Controlled DBP, M2, n (%)	387 (73.7 %)	206 (77.7 %)	181 (69.6 %)	0.04
Primary endpoint: BP control M2, n (%)	282 (53.7 %)	166 (62.6 %)	116 (44.6 %)	< 0.001

**= Z-test; BP M1 = first measurement after five minutes rest. BP M 2 = second measurement after one minute; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.*

The statistical analysis of the primary endpoint, i.e., the simultaneous undershoot of BP readings of systolic 140 mmHg and diastolic 90 mmHg at the study end, was performed using a generalised mixed linear model (GLMM). Due to the dichotomous nature of the endpoint (controlled BP: yes/no), a logit link function was used. Practice ID entered the model equation as a random effect (random intercept) to account for the clustered structure of the data. Other influencing variables (age, gender, concomitant diseases, and recruitment period) were included in the model as described above.

The patient characteristics, gender and age (at baseline) potentially influence variables in outcome model calculations. To capture non-linear age dependencies, 10-year age groups were formed and subsequently included in the model calculations as dummy variables.

In the medical literature, coronary artery disease and a history of acute coronary syndrome are relevant variables in interventions aiming at blood pressure control (Margolis et al. 2013; McManus et al. 2018). Information on these two potentially relevant influencing variables was obtained from the medical sheets completed by the GPs at baseline. Therefore, coronary heart disease and myocardial infarction were included in model calculations as a dichotomous variable (yes/no) so that the presence of either or both conditions was combined into one response category (yes). Since the blood pressure measurements differed between the study arms at baseline (the values of the intervention group were consistently higher), the raw blood pressure values of the second measurement were also included in the GLMM model.

Because the onset of the Corona pandemic strongly influenced the originally planned recruitment start in March 2020 was by, assignments of patients to two recruitment phases (quarter 1 (Q1) to quarter 4 (Q4) 2020 versus Q1 2021) were included in the model as a potential influencing variable (dichotomous).
The population-adjusted proportion of patients with controlled blood pressure at the end of the study was 59.8 % (95 % CI: 47.4 - 71.0 %) in the intervention group and 36.7 % (24.9 - 50.3 %) in the control group. This resulted in a difference of 23.1 % points (95 %-CI: 5.4 - 40.8 % points) which is higher for the PIA-Intervention digital care than the estimated difference of 15 % used a priori for the sample size calculations.

In the statistical model, the covariates of age, sex, and the presence of coronary heart disease and/or myocardial infarction had no significant influence. The recruitment period, which was divided into two recruitment phases (1st quarter, 2021 compared to 1st to 4th quarter, 2020), indicated with an odds ratio of 1.67 (95 % CI: 0.97 - 2.88) that patients who were recruited later had a greater chance of achieving a controlled blood pressure. However, this result missed the 5 % probability of error (p-value 0.07). The model with the estimates for the various variables is shown in Table 8.

Tab. 8: GLMM model of primary endpoint (Leupold et al. 2023)

	Odds Ratio	**95 %-CI**	**p-value***
(Intercept)	0.38	0.17 — 0.81	0.01
Study arm			
Usual care arm (Reference)			
Intervention arm	2.57	1.23 — 5.37	0.01
Age			
40 – 49 years (Reference)			
50 – 59 years	1.16	0.66 — 2.03	0.61
60 – 69 years	1.09	0.59 — 2.03	0.73
70 – 79 years	1.38	0.69 — 2.97	0.34
Sex			
Women (Reference)			
Man	1.07	0.67 — 1.84	0.78
Comorbidities			
Without coronary heart disease and/or myocardial infarction (Reference)			
With coronary heart disease and/or myocardial infarction	0.78	0.45 — 1.34	0.36
Recruiting duration			
Recruiting (first quarter to fourth quarter in 2020) (Reference)			
Recruiting (first quarter in 2021)	1.67	0.97 — 2.88	0.07

	Odds Ratio	95 %-CI	p-value*
Blood pressure (Baseline. M2)			
SBP, mmHg	0.98	0.96 — 0.99	0.00
DBP, mmHg	0.99	0.97 — 1.02	0.57

**= Z-test; Blood pressure M 2 = second measurement after one minute; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; Statistical measures: Variance of random effects (practice ID) τ00 = 0.86 [SD 0.88]. Intra-cluster correlation coefficient ICC = 0.21*

We performed a sensitivity analysis using the mean value of both BP measurements instead of the results of the second blood pressure measurement only. This model yielded an odds ratio for the study arm of 2.59 (95 % CI: 1.35 - 4.96. p-value 0.004). This result showed again that the null hypothesis (the intervention does not effect on achieving controlled BP) could be rejected with a 5 % probability of error (2-sided test). The results of this model are shown in Table 9.

Tab. 9: Sensitivity analysis: GLMM model of the primary endpoint using the mean of the first and second blood pressure readings (Leupold et al. 2023)

	Odds Ratio	95 %-CI	p-value*
(Intercept)	0.40	0.2 — 0.81	0.01
Study arm			
Usual care arm (Reference)			
Intervention arm	2.59	1.35 — 4.96	0.00
Age			
40 – 49 years (Reference)			
50 – 59 years	1.12	0.66 — 1.91	0.67
60 – 69 years	1.01	0.56 — 1.81	0.98
70 – 79 years	1.1	0.55 — 2.19	0.78
Sex			
Women (Reference)			
Man	1.09	0.74 — 1.6	0.66
Comorbidities			
Without coronary heart disease and/or myocardial infarction (Reference)			
With coronary heart disease and/or myocardial infarction	0.89	0.53 — 1.49	0.66

	Odds Ratio	95 %-CI	p-value*
Recruiting duration			
Recruiting (first quarter to fourth quarter in 2020) (Reference)			
Recruiting (first quarter in 2021)	1.58	0.95 — 2.62	0.08
Blood pressure (Baseline), mean M1/M2			
SBP, mmHg	0.98	0.96 — 0.99	0.00
DBP, mmHg	0.99	0.97 — 1.01	0.48

**= Z-test; Blood pressure M1 = first measurement and M 2 = second measurement after one minute; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; Statistical measures: Variance of random effects (practice ID) τ00 = 0.66 [SD 0.8]. Intra-cluster correlation coefficient ICC = 0.17*

For the intervention group, the validity of the practice readings was confirmed by comparison of the office BP measurement with the home BP recordings. It should be noted that the international target values for practice measurements is a blood pressure below 140/90 mmHg, whereas this is 5 mmHg lower for home measurements (below 135/85 mmHg) (Williams et al. 2018). This difference of 5 mmHg from international guidelines corresponds well with the difference of 4.95 mmHg measured for SBP in our study. For details, see Table 10.

Tab. 10: Home blood pressure measurement compared to office measurement (follow-up)

	Home BP measurement (n = 265)	**office BP measurement (follow-up)** (n = 265)	**difference**	**p-value***
SBP, M2, mmHg, mean [SD]	129.45 [12.27]	134.30 [14.50]	4.95	< 0.001
DBP, M2, mmHg, mean [SD]	82.76 [9.26]	83.10 [9.70]	0.34	0.57

** Statistical tests for metric variables t-test or Mann-Whitney U-test; for categorical variables chi-square.*

3.3 Secondary outcomes

3.3.1 Acceptance by patients and practice personnel

Patients in the intervention group were significantly more satisfied with their BP treatment than patients in the control group. In the intervention group, 91.5 % of patients rated their blood pressure treatment as good to excellent, compared with 82.6 % in the control group, which was significantly (p-value 0.02) lower, for more details, show Table 11.

Tab. 11: Patient satisfaction with hypertension care received from their general practice.

	All (N = 525)	**Intervention group (n = 265)**	**Usual care group (n = 260)**	**p-value***
Blood pressure treatment assessment, n (%)				0.02
Excellent	43 (8.3 %)	23 (8.7 %)	20 (7.7 %)	
Very good	152 (29.0 %)	88 (33.2 %)	64 (24.6 %)	
Good	232 (44.4 %)	116 (43.7 %)	116 (44.6 %)	
Sufficient	52 (9.9 %)	16 (6.0 %)	36 (13.8 %)	
Poor	11 (2.2 %)	5 (1.9 %)	6 (2.3 %)	
I do not know	17 (3.2 %)	4 (1.5 %)	13 (5.0 %)	

** Statistical tests for metric variables t-test or Mann-Whitney U-test; for categorical variables chi-square.*

Patients rated the PIA-App and its features from 1 (very good) to 5 (poor), which are the German school grades. On average, patients rated the app with an overall grade of 1.7 [SD 0.9]. The app's feature were also rated as "very good" (average 1.5 to 1.9). See Table 12 for more details.

Tab. 12: Patients' evaluation of the PIA-App and its features (according to school grades: 1 = very good to 5 = poor)

	Intervention group (n = 265)
Overall rating of the PIA-App, mean [SD]	1.7 [0.9]
Features of the PIA-App, mean [SD]	
Entry of blood pressure values	1.5 [0.8]
Blood pressure trend graphics	1.7 [0.9]
Medication overview	1.6 [0.9]
Prescription ordering	1.8 [1.1]

	Intervention group (n = 265)
Chat communication	1.8 [1.1]
eLearning for blood pressure measurement	1.8 [1.1]
Information links on hypertension and treatment (lifestyle, diet and medication)	1.9 [1.1]

The PIA-PrMc received “very good” ratings from both GPs and PrAs, with overall scores of 1.8 [SD 0.5] and 1.9 [SD 0.7], respectively. These scores are shown in Table 13.

The different features were rated on a scale of 1.5 to 2.6 by GPs and 1.5 to 2.4 by PrAs. The more straightforward features, such as the patient list, add a patient, blood pressure trend graphics and chat communication, received better ratings from both GPs and PrAs than complex features (e.g., up-dosing of medications). However, the features for general and individual settings and sending a new medication plan to patients were not enabled for practice assistants and could only be activated by the physician PIN.

Tab. 13: GP and practice assistant evaluation of the PIA-Practice management centre and its features (according to school grades: 1 = very good – 5 = poor)

	Intervention group	
	GP (n = 26)	**PrA (n = 30)**
Overall rating of the PIA-App, mean [SD]	1.8 [0.5]	1.9 [0.7]
Features, mean [SD]		
Patient list	1.6 [0.6]	1.7 [0.7]
Add patient	1.6 [0.9]	1.6 [0.7]
General settings	2.1 [1.0]	1.9 [0.8]
Individual settings	2.3 [1.1]	1.9 [1.0]
Blood pressure trend overview	1.6 [0.7]	1.5 [0.7]
Medication and dosing algorithm	2.6 [0.9]	2.4 [1.2]
Transmitting the medication plan from EHR to PIA-PrMc	2.0 [1.8]	2.3 [1.2]
Sending the medication plan to patients	1.8 [1.3]	2.0 [1.1]
Chat communication with patients	1.7 [0.8]	1.9 [0.8]
Practice internal chat communication	1.5 [1.2]	2.0 [1.1]

	Intervention group	
	GP (n = 26)	**PrA (n = 30)**
Ordering of prescriptions	1.5 [0.8]	2.2 [1.4]
Structure of workflows	2.2 [0.7]	2.2 [1.0]
Clarity of workflows	2.1 [0.7]	2.0 [0.8]
Process in the PIA-PrMc	2.1 [0.9]	2.2 [0.9]

EHR = Electronic health record; PIA-PrMc = PIA practice management centre; PrA = Practice assistant;

3.3.2 Home blood pressure measurements

At baseline, significantly more patients in the control group (187; 71.9 %) measured their blood pressure “at least once a month”, “at least once a week” or “every day” compared to patients in the intervention group (159; 60.0 %; p-value 0.03). In contrast, at follow-up after 6 - 12 months of intervention, significantly (p-value < 0.001) more patients in the intervention group (233; 87.9 %) measured their blood pressure at “at least once a month”, “at least once a week” or “every day” compared to patients in the control group (182; 70.0 %). All patients in the intervention group received a blood pressure monitor as part of the study. Of the 10 (3.8 %) patients in the control group who did not have a blood pressure monitor at baseline, only 2 (0.8 %) patients still did not have a blood pressure monitor at follow-up. For more details, see Table 14.

Tab. 14: Follow-up and baseline survey: Frequency of blood pressure measurement in the last three months among patients.

	All (N = 525)	**Intervention group (n = 265)**	**Usual care group (n = 260)**	**p-value***
How often have you measured your blood pressure in the last three months? n (%)				
Baseline				0.03
Every day	124 (23.6 %)	55 (20.8 %)	69 (26.5 %)	
At least once a week	143 (27.2 %)	67 (25.3 %)	76 (29.2 %)	
At least once a month	79 (15.0 %)	37 (14.0 %)	42 (16.2 %)	
At least once in the last three months	34 (6.5 %)	16 (6.0 %)	18 (6.9 %)	
Very rarely	60 (11.4 %)	34 (12.8 %)	26 (10.0 %)	
Never	48 (9.1 %)	31 (11.7 %)	17 (6.5 5 %)	
I do not have a device	21 (4.0 %)	11 (4.2 %)	10 (3.8 %)	
Missing data	16 (3.0 %)	14 (5.3 %)	2 (0.8 %)	

	All (N = 525)	Intervention group (n = 265)	Usual care group (n = 260)	p-value*
How often have you measured your blood pressure in the last three months? n (%)				
Follow-up				< 0.001
Every day	160 (30.5 %)	114 (43.0 %)	46 (17.7 %)	
At least once a week	203 (38.7 %)	108 (40.8 %)	95 (36.5 %)	
At least once a month	52 (9.9 %)	11 (4.2 %)	41 (15.8 %)	
At least once in the last three months	19 (3.6 %)	0 (0.0 %)	19 (7.3 %)	
Very rarely	51 (9.7 %)	17 (6.4 %)	34 (13.1 %)	
Never	18 (3.4 %)	1 (0.4 %)	17 (6.5 %)	
I do not have a device	2 (0.4 %)	0 (0.0 %)	2 (0.8 %)	
Missing data	20 (3.8 %)	14 (5.3 %)	6 (2.3 %)	

** Statistical tests for metric variables t-test or Mann-Whitney U-test; for categorical variables chi-square.*

For the follow-up, it was surveyed how the patients were reminded to measure their BP. The analysis showed that the majority 62.3 % (IG: 66.4 %; CG: 58.1 %) of patients did not use a reminder to measure their BP, and only 23.6 % (IG: 26.0 %; CG: 21.2 %) of patients were reminded to measure their BP. There was no significant difference between the two study arms. About 8.8 % of patients were reminded by meals, 6.3 % by another person, 5.0 % by their mobile phone, 1.5 % by an alarm clock, 0.6 % by a computer, and 3.4 % by other resources. This is distributed relatively similarly between the two study arms except, that 7.2 % of patients in the intervention group and only 2.7 % in the control group were reminded to measure blood pressure by mobile phone.

In this survey, patients were asked whether they did not measure their blood pressure regularly or not. Significantly (p-value < 0.001), fewer patients in the control group (3.4 %) answered that they did not measure their blood pressure or did not measure it regularly compared to patients in the control group (23.8 %). For more details, see Table 15.

Tab. 15: Follow-up survey: blood pressure measurement reminder

	All (N = 525)	Intervention group (n = 265)	Usual care group (n = 260)	p-value*
Reminder for BP measurement				0.73
With reminder	124 (23.6 %)	69 (26.0 %)	55 (21.2 %)	
Without reminder	327 (62.3 %)	176 (66.4 %)	151 (58.1 %)	

	All (N = 525)	Intervention group (n = 265)	Usual care group (n = 260)	p-value*
Missing data	74 (14.1 %)	20 (7.5 %)	54 (20.8 %)	
I do not measure blood pressure regularly	71 (13.5 %)	9 (3.4 %)	62 (23.8 %)	< 0.001
I am reminded of the blood pressure measurement by (Multi-choice):				
Meal	46 (8.8 %)	26 (9.8 %)	20 (7.7 %)	
Person	33 (6.3 %)	16 (6.0 %)	17 (6.5 %)	
Mobile phone	26 (5.0 %)	19 (7.2 %)	7 (2.7 %)	
Clock	8 (1.5 %)	4 (1.5 %)	4 (1.5 %)	
Computer	3 (0.6 %)	2 (0.8 %)	1 (0.4 %)	
Others	18 (3.4 %)	8 (3.0 %)	10 (3.8 %)	
Nothing	337 (64.2 %)	180 (67.9 %)	157 (60.4 %)	

** Statistical tests for metric variables t-test or Mann-Whitney U-test; for categorical variables chi-square.*

Use of the PIA-ICT: The PIA-ICT was frequently used by both patients and practices. On average, 10.6 medication plans were transferred to patients (SD 11.3; median 8.0; min - max 0 - 48). A mean of 249.8 blood pressure readings were transmitted from patients to practices (SD 228.9; median 164.0; min - max 0 - 1138). On average, 3.7 chats were sent from patients to practices (SD 8.0; median 1.0; min - max 0 - 91), while practices sent 6.9 messages (SD 8.9; median 3.0; min - max 0 - 49). These messages included automated ones indicating a new medication plan. For details, see Table 16.

Tab. 16: Frequency of use of the PIA-ICT by patients and practices (Leupold et al. 2023)

	Intervention group (n = 265)		
Frequency of use of the PIA-ICT by patients and practices	Mean [SD]	Median [IQR]	min - max
Number of medication plans sent to the patient	10.6 [11.3]	8.0 [1.0; 16.0]	0 - 48
Number of transmitted blood pressure values	249.8 [228.9]	164.0 [86.0; 353.0]	0 - 1138
Number of messages from patient to practice	3.7 [8.0]	1.0 [0.0; 4.5]	0 - 91
Number of messages from practice to patient	6.9 [8.9]	3.0 [1.0; 9.0]	0 - 49

PIA-ICT = PIA information communication technology; SD = standard deviation; IQR = interquartile range

3.3.3 Medication changes

On average, patients received 2.1 [SD 1.1] antihypertensives at baseline and 2.3 [SD 1.2] at follow-up. The number of drugs and drug categories did not differ significantly between the intervention and control groups at baseline. However, at follow-up, patients in the intervention group received significantly more antihypertensives than patients in the control group (p-value 0.05). Similarly, while the number of prescribed antihypertensive classes did not differ significantly between the two study arms at baseline, patients in the intervention group were prescribed significantly more antihypertensive classes on average than patients in the control group at follow-up. At baseline, none of the patients in the two study arms received antihypertensive drugs from five drug groups, but at follow-up, a total of 3.2 % patients received drugs from five drug groups. The number of patients with a thiazide diuretics antihypertensive was significantly higher in the intervention than in the control group at follow-up (37.7 % vs. 24.1%; p-value 0.001). For details, see Tables 17 and 18.

Tab. 17: Medications at baseline: all patients and by study arms

	All (n = 492)	**Intervention group (n = 248)**	**Usual care group (n = 244)**	**p-value***
Number of antihyperten-sives, mean [SD]	2.1 [1.1]	2.1 [1.1]	2.0 [1.2]	0.37
Number of prescribed drug classes, mean [SD]	1.7 [0.9]	1.8 [0.9]	1.7 [0.9]	0.34
Without antihypertensives, n (%)	28 (5.7 %)	13 (5.3 %)	15 (6.1 %)	
One drug class, n (%)	199 (40.4 %)	98 (39.5 %)	101 (41.4 %)	
Two drug classes, n (%)	174 (35.4 %)	87 (35.1 %)	87 (35.7 %)	
Three drug classes, n (%)	75 (15.2 %)	39 (15.7 %)	36 (14.8 %)	
Four drug classes, n (%)	16 (3.3 %)	11 (4.4 %)	5 (2.0 %)	
Five drug classes, n (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
Drug classes, n (%)				
ACEI and ARB	430 (87.4 %)	222 (89.5 %)	208 (85.2 %)	0.15
Beta-blockers	223 (45.3 %)	116 (46.8 %)	107 (43.9 %)	0.52
Calcium channel blockers	198 (40.2 %)	104 (41.9 %)	94 (38.5 %)	0.44

	All (n = 492)	Intervention group (n = 248)	Usual care group (n = 244)	p-value*
Thiazide diuretics	128 (26.0 %)	71 (28.6 %)	57 (22.0 %)	0.18
Others	80 (16.3 %)	36 (14.5 %)	44 (18.0 %)	0.29

** Statistical tests for metric variables t-test or Mann-Whitney U-test; for categorical variables chi-square. ACEI = Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers = ARB.*

Tab. 18: Medications at follow-up: all patients and by study arms

	All (n = 501)	Intervention group (n = 244)	Usual care group (n = 257)	p-value*
Number of antihyper-tensives, mean [SD]	2.3 [1.2]	2.4 [1.7]	2.2 [1.2]	0.05
Number of prescribed drug classes, mean [SD]	2.3 [1.1]	2.4 [1.1]	2.2 [1.1]	0.04
Without antihypertensives, n (%)	7 (1.4 %)	3 (1.2 %)	4 (1.6 %)	
One drug class, n (%)	132 (26.3 %)	54 (22.1 %)	78 (30.4 %)	
Two drug classes, n (%)	152 (30.3 %)	79 (32.4 %)	73 (28.4 %)	
Three drug classes, n (%)	136 (27.1 %)	64 (26.2 %)	72 (28.0 %)	
Four drug classes, n (%)	58 (11.6 %)	34 (13.9 %)	24 (9.3 %)	
Five drug classes, n (%)	16 (3.2 %)	10 (4.1 %)	6 (2.3 %)	
Drug classes, n (%)				
ACEI and ARB	441 (88.0 %)	220 (90.2 %)	221 (86.0 %)	0.15
Beta-blockers	225 (44.9 %)	109 (44.7 %)	116 (45.1 %)	0.92
Calcium channel blocker	240 (47.9 %)	123 (50.4 %)	117 (45.5 %)	0.27
Thiazide diuretics	154 (30.7 %)	92 (37.7 %)	62 (24.1 %)	0.001
Others	96 (19.2 %)	46 (18.9 %)	50 (19.5 %)	0.86

** Statistical tests for metric variables t-test or Mann-Whitney U-test, for categorical variables chi-square. ACEI = Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers = ARB.*

4. Discussion

4.1 Clinical effectiveness of the PIA-Intervention

This cluster-randomised controlled trial of the PIA-Intervention for hypertension management with 525 patients and 47 GP practices showed a significant improvement in BP control rates after 6 to 12 months (adjusted improvement of control rate: +23.1 %).

4.2 Comparison of the PIA's effectiveness with international studies

The results of this complex intervention for digital hypertension management are comparable to other international studies which performed similar interventions (Margolis et al. 2013; McKinstry et al. 2013; McManus et al. 2018; McManus et al. 2021; Hammersley et al. 2020). In all these studies, as in PIA, patients in the intervention group measured blood pressure at home and transmitted it via SMS or secured web-space automatically or manually to the GP practice or clinical pharmacists. All interventions were applied for 6 to 12 months. In the intervention arm of the PIA study, digital hypertension management led to a significantly decreased SBP by 21.1 mmHg. This is within the range of SBP improvements of 6 mmHg to 22.5 mmHg in the prior mentioned studies. The intervention between the PIA study arms resulted in an average SBP difference of -5.6 mmHg. This difference is consistent with the studies from McKinstry et al. 2013, McManus et al. 2018, McManus et al. 2021, and Margolis et al. 2013 which showed improvements in SBP of -3.4 mmHg to -10.7 mmHg (McKinstry et al. 2013; McManus et al. 2018; McManus et al. 2021; Margolis et al. 2013). The details are presented in Table 19.

Similar results were documented in various older studies which used non-digital, complex interventions. Two meta-analyses of complex interventions with medication management and lifestyle counselling for hypertensive patients delegated to non-physician personnel (clinical pharmacists or nurses) demonstrated a significant reduction of -6.1 mmHg and -8.2 mmHg, respectively, in SBP levels (Clark et al. 2010; Cheema et al. 2014).

Tab. 19: Comparison of effectiveness to international studies on digital hypertension management

Author (year)	Design	Participants	Intervention	SBP decreased by	Follow-up
McKinstry et al. (2013)	Randomised-controlled trial (1:1)	401 patients 20 GP practices	Automatic BP transmission via SMS to practice	-4.3 mmHg	6 months
Margolis et al. (2013)	Cluster-randomised controlled trial (1:1)	450 patients 16 clinics	Automatic BP transmit via modem to a clinical-pharmacist	-10.7 mmHg	12 months
McManus et al. (2018)	Randomised-controlled trial (1:1:1)	1182 patients 142 GP practices	BP transmit via a Web-based data entry to practice	-4.7 mmHg	12 months
McManus et al. (2021)	Randomised-controlled trial (1:1)	622 patients 76 GP practices	BP transmit via a Web-based data entry to practice	-3.4 mmHg	12 months
Leupold et al. (2022) (PIA)	Cluster randomised-controlled trial (1:1)	525 patients 47 GP practices	BP transmit via the PIA-App to PIA-PrMc in the practice	-5.6 mmHg	6 to 12 months

Some international studies mentioned detailed changes in consultation frequencies and home measurements due to the intervention (McKinstry et al. 2013). McKinstry et al. (2013) reported that the intervention was associated with a mean increase of physician consultations in the surgery by 3.6 [SD 2.7] and with a mean increase of practice nurse consultations in the surgery by 1.9 [SD 2.5] and by phone by 0.6 [SD 1.17]. This was similar in the PIA study, with a mean of 6.9 [SD 8.8] chats from GPs and PrA during the intervention period. Regarding the BP measurements, the median number of BP values entered in the PIA-App was 164 [IQR 86, 353], which did not differ by age. In contrast, Persell et al. (2020) reported higher BP readings among patients above the age of 59 years compared to younger ones (seniors ≥ 60 years: median130.0; IQR 73.5, 220.5; young patients < 60 years: median 71.0; IQR 24.0, 117.0) (Persell et al. 2020).

In the PIA study, the proportion of patients who measured their blood pressure at home at least once in the last three months increased from 60 % to 88 % in the intervention arm and decreased from 79 % to 77 % in the usual care group at follow-up. These results were similar to the study by Margolis et al. (IG: 51% to 94%). In the usual care group, the proportion remained unchanged between baseline and follow-up. (Margolis et al. 2013)

4.3 Comparison of the PIA features with international approaches

The electronic transmission of BP home measurements is the key feature in the PIA study and all other digital hypertension managements described prior. However, the studies regarding all other aspects. An overview is provided in Table 20.

Tab. 20: Comparison of features of digital hypertension management systems

Features	McKinstry (2013); Hammerslay (2020)	Margolis (2013)	McManus (2018)	McManus (2021)	Leupold (2022) (PIA)
Transmit BP values to the practice	✓	✓	✓	✓	✓
BP history trends	✓	✓	✓	✓	✓
Guideline-based BP target values stored in the system	✓	✓	✓	✓	✓
Automated BP transmission to a server (e.g., via Bluetooth)	✓	✓	X	X	X
Secure chat communication between the patient and the practice	X	X	X	✓	✓
Integrated delegation model for non-physician staff	X	X	X	X	✓
Transfer of medication plans from the EHR to the practice	X	X	X	X	✓
Electronic transmission of medication plan to patients	X	X	X	X	✓
Guideline-supported algorithms in the digital system for drug therapy adjustment	X	X	X	✓	✓
GDPR (General Data Protection Regulation) compliant	X	X	X	X	✓

Features	McKinstry (2013); Ham-merslay (2020)	Margolis (2013)	McManus (2018)	McManus (2021)	Leupold (2022) (PIA)
Patient-individual settings for medication therapy	X	X	X	X	✓
Patient-individual settings for the displayed blood pressure target values	X	X	X	X	✓
Electronic prescription order	X	X	X	X	✓
Delegation model	X	X	X	X	✓

EHR = Electronic health record; BP = Blood pressure

From the patients' perspective, only the PIA-Intervention realised an app for patients, while the other studies used either SMS (McKinstry et al. 2013; Hammersley et al. 2020), SMS in web-space (McManus et al. 2018; McManus et al. 2021) or transmission from the BP device to a central server (Margolis et al. 2018). We chose not to use automatic blood pressure transmission from the blood pressure monitor to the electronic platform (e.g. via Bluetooth), as used in the studies by Margolis et al. and McKinstry et al., because such blood pressure monitors are more expensive and are not financed by the statutory health insurance in standard care (Margolis et al. 2018; McKinstry et al. 2013; Hammersley et al. 2020). Although such automated data transmission from the device is convenient for patients, these data are not linked with patients' information on well-being and context as in the PIA-App. All systems allow for an overview of blood pressure measurements over time: such graphic and tabled information is included in the PIA-App, while the other systems ask patients to log in a platform (McKinstry et al. 2013; Hammersley et al. 2020; McManus et al. 2021; McManus et al. 2018; Margolis et al. 2013). We set up a secure chat communication system between the practice and the patient in the PIA-ICT for better and secure communication. A similar approach with an in-platform chat was only integrated into the McManus et al. (2021) system (McManus et al. 2021).

From the practices' perspective, the PIA-ICT implemented a secure and General Data Protection Regulation-compliant communication between the patient's PIA-App and the PIA-PrMc. This approach was chosen to avoid additional logins on separate platforms

during busy practice days. Hammerslay et al. 2020 partially solved this problem by implementing an automatic import of blood pressure results from a third-party website into the electronic patient record. Nevertheless, the system is not transferable to Germany as such, a transfer of data via SMS is not data protection compliant. (Hammersley et al. 2020)

Our system was designed to provide a guideline-based pathway to ensure guideline-compliant hypertension management. At the same time, it was possible to customise hypertension management for patients with special needs. These individual adaptations were possible, for example, for the blood pressure targets, the medications used and the up-titration steps. In contrast to the McManus studies, which involved paper-based self-titration of blood pressure medication with a contact by the GP after two changes, we used continuous, GP-initiated up-titration via the PIA-ICT (McManus et al. 2021; McManus et al. 2018).

Our ICT has successfully implemented a delegation model for PrAs. Margolis et al. (2013) integrated a delegation to clinical pharmacists in the intervention, but this was not integrated into the digital system (Margolis et al. 2013). Also, this is the only implemented such digital integration and task definitions.

The PIA-ICT enabled the electronic transfer of medication plans from any practice management system in Germany into the PIA-ICT. Medication plans were sent to patients directly after physician approval. This is an essential step towards the secure digitalisation of care processes. This was not used in previous studies and is an essential feature as about 126 electronic health records (Kassenärztliche Bundesvereinigung 2022) are used in Germany. In addition, prescription orders can be sent directly to the practice via the PIA-App.

4.4 Comparison of the PIA medication adjustments with international results

In the PIA study and all other comparable studies, changes in the antihypertensive medications were a key goal realized in the study. The changes observed were related to the number of drug classes and the average number of antihypertensive drugs.

At follow-up, the mean number of antihypertensive medications for patients in the intervention group was significantly higher than those in the control group. This finding is

consistent with the results reported by McManus et al. (2018) and McKinstry et al. (2013). (McManus et al. 2018; McKinstry et al. 2013) In detail, patients in the PIA study received an average of 2.1 [SD 1.1] antihypertensives at baseline, compared to 1.3 [SD 0.8] at the McManus et al. (2018) study. At follow-up, the mean number of antihypertensive medications in the PIA-Intervention group increased to 2.4 [SD 1.3], compared to 1.7 [SD 0.9] in McManus et al. (2018). (McManus et al. 2018)

The number of antihypertensive classes prescribed in PIA also increased compared to baseline. At follow-up, patients in the intervention group took significantly more antihypertensive classes compared to the control group. Similar results were obtained by Margolis et al. (2013) at 6 months and 12 months (Margolis et al. 2013). In the 2013 study by McKinstry et al. at follow-up, more participants were taking two or three antihypertensive classes than at baseline (McKinstry et al. 2013). This was even higher in the PIA study: more patients were took three or four antihypertensive classes at follow-up. At the same time, the number of patients taking only one or two antihypertensive classes decreased.

Guidelines adherence to medication regimes is a central goal of all hypertension management systems and was evaluated in the studies by McKinstry et al. (2013), McManus et al. (2018) and the PIA study. McKinstry et al. (2013) observed that 74% of the patients received an ACEI or ARB, which was even higher in the PIA study (90 %) and the survey by McManus et al. (2018). (McKinstry et al. 2013; McManus et al. 2018) At follow-up, the McKinstry et al. (2013) study showed that a more significant number of patients in the telemonitoring group received drugs from the ACEI or ARB, calcium channel blockers and thiazide diuretics drug classes compared to the control group (McKinstry et al. 2013). The PIA study also showed that patients in the intervention group received thiazide diuretics significantly more often than patients in the control group. Overall, medication regimes followed guidelines with second class medications used only if blood pressures were not controlled with first-line agents.

4.5 Agile and participatory development of digital care systems

State-of-the-art software development requires the integration of the users to address their needs which is called participatory development (Kokol 2022; Kokol et al. 2022; Boyd et al. 2012; Highsmith and Cockburn 2001). This requires the close cooperation of the

software developers, the future users and – in science – the researchers. These processes are highly iterative regarding concept development, programming, and prototype testing for all stakeholders. Such a process is called agile development. (Wilson et al. 2018; Kokol 2022)

The PIA-ICT aimed at digitalizing every possible aspect of care processes. Therefore, researchers performed in-depth studies of hypertension care processes in general practices. This information was used to define the concept, which was refined by the subsequent involvement of end-users (patients, GPs and PrAs). This practice orientation at each step of the development was a key element in ensuring the applicability and acceptability of the PIA-Intervention. Continuous incorporation of user experience and feedback into product development ensures that the technology or intervention is both effective and user-friendly (Talevski et al. 2023; Ekstedt et al. 2021; Wilson et al. 2018; Kokol 2022; Kokol et al. 2022). Agile software development in a health software development improves interprofessional communication, maintainability, and functionality (Rehman et al. 2018; Tang et al. 2019). In a scoping review, Kokol 2020 concluded that more frequent use of such approaches is needed in healthcare: this could lead to a more prosperous digital transformation of healthcare and consequently to more equitable access to expert-level healthcare, even on a global scale. (Kokol 2022)

In the studies of Margolis et al. (2013), McManus et al. (2018) and McKinstry et al. (2013), no participatory development of the intervention was identified (McKinstry et al. 2013; McManus et al. 2018; Margolis et al. 2013). In the 2021 study, the intervention by McManus et al. (2021) was developed using the Yardleys Framework (Yardley et al. 2015) with patients involved in the development process (McManus et al. 2021). Person-centred development in their system involved three qualitative interview studies (Bradbury et al. 2018): In the first study, patients conducted 'think-aloud' interviews in which they looked at the system with a researcher. In the second study, patients used the system alone for three weeks and were then interviewed about their experience with the intervention. In an additional study, three targeted participants who did not want to use the system to explore their perceptions in semi-structured telephone interviews. (Bradbury et al. 2018)

The agile and participatory intervention of the PIA-ICT is reflected in a high uptake of the system, as shown by the high frequency of use and positive ratings from all users.

4.6 Public health and health economic impact of hypertension management systems

The positive effect of blood pressure-reducing interventions on the prevalence of cardiovascular disease and its consequences has been widely reported in the literature. The meta-analysis and literature review by Ettehad et al. 2016 integrated 123 BP reduction trials and cardiovascular disease prevention and compared data from 613,815 patients. The results show that a 10.0 mmHg reduction in systolic blood pressure leads to a significant risk reduction of 17 % in coronary heart disease, 27 % in stroke, and 28 % in myocardial infarction. (Ettehad et al. 2016) Based on the results of this meta-analysis, the morbidity and mortality risks can be calculated for the PIA population. PIA-Intervention was shown to reduce blood pressure by 5.6 mmHg. This results in a risk reduction of 10 % for coronary heart disease, 15 % for stroke, and 16 % for myocardial infarction.

Based on the assumption that PIA would be introduced nationwide in the statutory health insurance system and that systolic blood pressures could be reduced by 5.6 mmHg across the population, 0.76 billion euros in medical costs for coronary heart disease, 1.13 billion euros for strokes, and 1.16 billion euros for heart attacks could be avoided according to the current medical costs obtained from the German Federal Statistical Office in 2020. Thus, a nationwide introduction of PIA would result in a total of about 3.05 billion euros in avoided costs, by reducing in coronary heart disease, strokes, and heart attacks alone. (Statistisches Bundesamt 2023)

4.7 Strengths and limitations

This cluster-randomised controlled trial was successfully conducted during the pandemic. However, the follow-up and the support of practices and patients required additional time and effort from the study team. The planned sample size of 600 patients (300 per study arm) for the analyses could not be achieved due to the pandemic for several reasons: The recruitment period overlapped with Corona pandemic breakout, which led to considerable uncertainty and an increased workload for GPs. In addition, patients' anxiety and public recommendations to avoid unnecessary contact led to decreased routine visits to GP practices. Although the desired sample size was not fully achieved due to the

pandemic, the improvement in blood pressure can be attributed to the intervention rather than chance, as shown by a supplementary bootstrap analysis. (Leupold et al. 2023)

The primary outcome was initially based on the average of the practices' second and third standardised blood pressure measurements. Due to the pandemic and the need to reduce contact times, we were forced to use the second measurement only. To address this, an analysis of the NHANES data showed that the discrepancy between the second and third measurements is about 0 to 1 mmHg (Handler et al. 2012). Since this systematic bias affects the intervention and control groups, it does not affect the study results. Furthermore, our sensitivity analyses with averages of the first and second BP measurements showed reliable results. Although patients' self-documentation of BP in the app has potential sources of error, the difference between the first and second readings did not indicate any problem.

The PIA-App was developed for Android operating systems, as an additional development for the iOS system would have required even greater resources, which were not available in this study. The decision to focus on Android operating systems was driven by the fact that 68 % of smart devices in Germany run Android and only 34 % iOS (KANTAR Group 2023).

The PIA-Intervention, designed to be person-centred and includes several innovative features, significantly improved blood pressure control rates and received positive feedback from GPs, PrAs and patients. The various functions of PIA-ICT were frequently used. The positive feedback and frequent use show that the users well accepted the system.

The PIA-Intervention resulted in a 5.6 mmHg reduction in systolic blood pressure, which needs to be interpreted in the context of results from large cohort studies, where even a 3 mmHg reduction in systolic blood pressure was associated with lower morbidity and mortality (Stamler 1991; He and MacGregor 2003). However, the long-term success of the PIA-ICT on morbidity and mortality has yet to be evaluated.

4.8 Conclusions and perspectives

PIA is effective and needed in the German healthcare system for routine care. Further developments towards even better IT support of hypertension care processes are needed, e.g., artificial intelligence (AI)-supported management, including substituting delegation models by AI-supported processes, blockchain technologies for large-scale data protection, and full integration of data and processes in EHRs. Given the magnitude of the care problem presented by uncontrolled hypertension, systems need to be as simple and reliable as possible to address the populations needing better care.

5. Abstract

Introduction: Arterial hypertension is a significant risk factor for cardiovascular diseases and the leading cause of mortality and morbidity worldwide. Despite the widespread availability of effective treatment, control of hypertension in Germany still needs to be improved. The main reasons are barriers to guideline implementation in the clinical setting, poor adherence, and organisational failure. International studies showed that blood pressure (BP) control could be optimised through a digital-based hypertension management and delegation model to non-physician staff. In the PIA study we developed and evaluated such an intervention (PIA-Intervention). The PIA-Intervention includes a data protection-compliant system (PIA information communication technology: PIA-ICT) as well as eLearning for GP practices and patients. The PIA-ICT enables the communication between patients and practices, transmission and monitoring of BP values, customisation and transmission of medication plans, and prescription ordering.

Methods: The effectiveness of the PIA-Intervention was evaluated in a cluster-randomised controlled trial. GP practices were randomly assigned (1:1) to the intervention or control group (usual care). The primary outcome was a BP control rate (BP < 140/90 mmHg) after 6 - 12 months. Secondary outcomes were BP changes, PIA-ICT satisfaction, PIA-ICT use frequency, and blood pressure self-measurement and medication changes.

Results: The effectiveness of the PIA-Intervention was evaluated in 47 GP practices and 525 patients (Intervention 265; Control 260). There was a significant increase in BP control rates in the intervention group compared to the control group (59.9 % versus 36.7 %), which corresponds to an improvement of 23.1 % points (adjusted). Patients, GPs and practice assistants were very satisfied with the PIA-ICT and used the system frequently. The PIA-Intervention also led to a significant increase in the frequency of self-measurements and the average number of antihypertensives prescribed.

Discussion: Given the high effectiveness and acceptance among patients and health professionals, implementing the PIA-Intervention in usual care is reasonable. Calculated for nationwide implementation of the PIA-Intervention and assuming a population-wide reduction of systolic BP by 5.6 mmHg, 3.05 billion euros could be saved in statutory healthcare costs.

6. List of figures

7. List of tables

8. References

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9. Appendix

9.1 Publication 1

Optimizing blood pressure control by an Information Communication Technology-supported case management (PIA study): study protocol for a cluster-randomized controlled trial of a delegation model for general practices

Trials (2021) - 22:738

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STUDY PROTOCOL

Open Access

Optimizing blood pressure control by an Information Communication Technology-supported case management (PIA study): study protocol for a cluster-randomized controlled trial of a delegation model for general practices

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Abstract

Background: Longitudinal hypertension control prevents heart attacks, strokes, and other cardiovascular diseases. However, 49% of patients in German family medicine practices do not reach blood pressure (BP) targets (< 140/90 mmHg). Drawing on successful international approaches, the PIA study introduces the PIA information and communication technology system (PIA-ICT) for hypertension management in primary care. The PIA-ICT comprises the PIA-App for patients and the PIA practice management center for practices. Case management includes electronic communication with patients, recall, and stepwise medication adjustments following guidelines. The system supports a physician-supervised delegation model to practice assistants. General practitioners are qualified by eLearning. Patients learn how to obtain reliable BP readings, which they communicate to the practice using the PIA-App.

Methods: The effectiveness of the PIA-Intervention is evaluated in a cluster-randomized study with 60 practices, 120 practice assistants, and 1020 patients. Patients in the intervention group receive the PIA-Intervention; the control group receives usual care. The primary outcome is the BP control rate (BP < 140/90 mmHg) after 12 months. Using a mixed methods approach, secondary outcomes address the acceptance on behalf of physicians, practice assistants, and patients. This includes an evaluation of the delegation model.

Discussion: It is hypothesized that the PIA-Intervention will improve the quality of BP care. Perspectively, it may constitute an important health service model for primary care in Germany.

Trial registration: German Clinical Trials Register DRKS00012680. Registered on May 10, 2019

Keywords: Hypertension, Blood pressure, Telemedicine, Family medicine, General practice, Home blood pressure monitoring, Delegation, mHealth, Information technology, Mobile application

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Administrative information

Title {1}	Optimizing blood pressure control by an ICT supported case management (PIA study): study protocol for a cluster-randomized controlled trial of a delegation model for general practices
Trial registration {2a and 2b}.	German Clinical Trials Register, DRKS00012680. Registered May 10th 2019, https://www.drks.de/drks_web/setLocale_EN.do.
Protocol version {3}	Protocol Version 1.0, 22.03.2021
Funding {4}	German Innovation Fund, located at the Federal Joint Committee (Innovationsausschuss beim Gemeinsamen Bundesausschuss, G-BA)
Author details {5a}	1 Institute of Family Medicine and General Practice, Medical Faculty of the University of Bonn, Venusberg-Campus 1, 53127 Bonn, Germany 2 Center for Clinical Trials, University Hospital Essen, University of Duisburg-Essen, Hufelandstr. 55, 45147 Essen, Germany. 3 Institute for General Medicine, University Hospital Essen, University of Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany 4 Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, University of Duisburg-Essen, Hufelandstr. 55, 45147 Essen, Germany
Name and contact information for the trial sponsor {5b}	Institute for Family Medicine and General Practice, University of Bonn; Prof. Dr. Birgitta Weltermann, birgitta.weltermann@ukbonn.de
Role of sponsor {5c}	The sponsor conceptualized the trial and is responsible for the setup of the consortium, as well as the management of the study and respective publications.

Introduction

Background and rationale {6a}

Hypertension is a global public health problem with an estimated number of more than one billion people affected. Despite evidence-based therapeutic options available, it is a leading cause of premature death [1]. Reaching blood pressure (BP) targets of < 140/90 mmHg is associated with significant reductions in cardiovascular events [2, 3]. A meta-analysis of 47 randomized controlled trials with 153,825 patients showed that a BP reduction of 10 mmHg systolic and 5 mmHg diastolic reduces the relative risk for major outcomes after 5 years: heart failure by 43%, stroke by 36%, cardiovascular death by 18%, and coronary heart disease by 16% [3]. However, guideline-recommended BP targets are not reached by 49% of family medicine practice patients in Germany [4]. A variety of well-documented factors play a role, e.g., insufficient adherence to diagnostic and therapeutic algorithms by physicians, poor medication adherence by patients, lack of organizational concepts supporting recall, and delegation to non-physician staff [5–8].

A Cochrane review of various interventions showed the best effects on hypertension control if strategies targeting patients, physicians, and organizations are combined [8]. Recently, complex interventions integrating information and communication technologies (ICT) and delegation to non-physician personnel were successful [9]. Margolis et al. [9] developed an ICT-supported case management involving a delegation model to pharmacists: patients transmitted BP self-monitoring results electronically to a clinical pharmacologist who adjusted drug regimes. After 12 months, intervention effects of − 9.7/− 5.1 mmHg systolic/diastolic were observed; the BP control rate in the intervention group was 18% higher than that in the control group (71% vs 53%) [9]. A meta-analysis of 33 studies on hypertension management delegated to non-physician staff (nurses) showed better BP reductions than standard care (systolic − 8.2 mmHg) [10]. Interventions with nurses who were allowed to prescribe and adjust medications achieved effects of − 8.9/− 4.0 mmHg [10]. Similar results were achieved in a physician-guided, nurse-managed hypertension management which used patient self-measurements and drug algorithms: after only 6 months, an intervention effect of − 8.5/− 3.1 mmHg was observed [11]. This effect was achieved by four times more frequent drug adjustments in the intervention group compared to the control with standard care ($p < 0.01$).

Based on these results, the PIA-Intervention was designed as an ICT-supported case management for the German general practice setting: the PIA-Intervention allows for a highly secured, electronic communication between patients (PIA-App for smartphone/tablet) and practices (PIA practice management center, PIA-PrMC). Patients learn to obtain and transmit reliable BP readings to the practice using the PIA-App; trained practice personnel provide electronic feedback with adjusted medication plans. The concept includes a physician-supervised delegation to practice assistants who manage recall, electronic communication with patients, and stepwise medication adjustments under physician supervision.

Objectives {7}

The main study objective is to investigate if the PIA-Intervention improves BP control rate (BP ≤ 140/90 mmHg) after 12 months in patients with uncontrolled hypertension at baseline.

The PIA-Intervention comprises the following:

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1. The PIA-ICT (PIA-App for patients and PIA-PrMC for practices) for patient-physician communication, recall, and step-wise medication adjustments
2. eLearning for general practitioners and practice assistants
3. Patient education on valid BP readings by practice staff and access to information on hypertension by PIA-App

The concept realizes a physician-supervised delegation model for hypertension management.

Trial design {8}

The study is designed as a prospective cluster randomized controlled trial (cCRT) with an intervention and a waiting list control group. A 1:1 randomization takes place at the practice level, i.e., all patients of a practice are assigned to either the intervention or the control group (30 practices per study arm). The cluster approach is chosen to avoid contamination between the intervention and control groups.

While the control group receives standard care, the intervention group will use the PIA-Intervention for 12 months. After collection of the follow-up data, the control group will receive access to the PIA-ICT for 3 months (waiting list control). The framework is a superiority approach. For details, see Fig. 1.

Methods: participants, interventions, and outcomes

Study setting {9}

The study is conducted in German general practices with certified general practitioners (GP) who are eligible to serve patients insured in the statutory health insurance.

Eligibility criteria {10}

Eligibility criteria on practice level

All of the following inclusion criteria apply: (a) certified GP eligible to serve patients insured in the statuary health insurance, (b) practice is equipped with at least one practice computer with Internet access (Windows 7 or higher), and (c) participation of at least one GP and up to three practice assistants per practice.

The exclusion criteria are as follows: (a) GP has an additional qualification in hypertensiology and/or (b) participated in the development of the intervention.

Eligibility criteria on patient level

All of the following inclusion criteria apply: (a) age 40 to 79 years, (b) diagnosed with essential hypertension (ICD I10), (c) resting practice BP > 140/90 mmHg (calculated as the mean value of the 2nd and 3rd BP readings obtained by trained personnel), (d) need or use at least ≥ 1 antihypertensive substance (drug), (e) insured by the statutory health insurance, (f) equipped with smart devices (tablet or smartphone with android 6 or higher), (g) sufficient skills to use the smartphone or tablet (defined as device use at least 3 times a week), and (h) has sufficient language skills to understand the study documents.

The exclusion criteria are as follows: (a) known white coat hypertension, (b) critical health conditions at the time of inclusion (e.g., hypertensive crisis, BP-related symptoms such as dizziness or headache), (c) chronic renal failure requiring dialysis, (d) being pregnant or breastfeeding, (e) hyperkalemia, (f) secondary hypertension (e.g., renal artery stenosis), and (g) heart failure NYHA III or IV.

Who will take informed consent? {26a}

The research team will obtain written informed consent from all participating practice owners, employed physicians, and practice assistants. The physicians and/or practice assistants obtain written informed consent from all patients during practice visits.

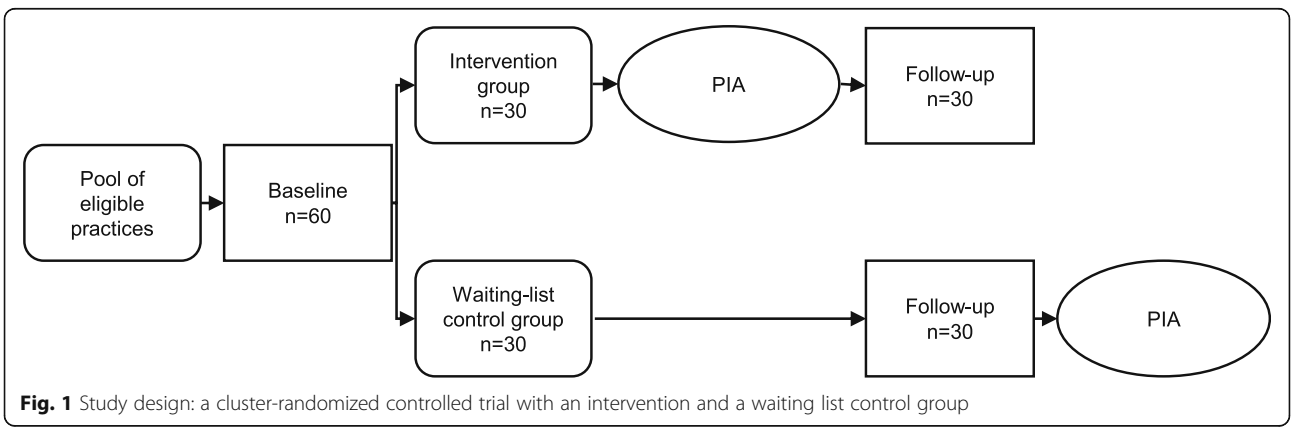

Fig. 1 Study design: a cluster-randomized controlled trial with an intervention and a waiting list control group

Additional consent provisions for collection and use of participant data and biological specimens {26b}
Not applicable.

Interventions

Explanation for the choice of comparators {6b}

The PIA-Intervention is compared to usual care. Usual care is the standard comparator for ICT-based interventions for hypertension management [12], including those implementing a delegation model to non-physician staff [10].

Intervention description {11a}

As a complex intervention, the PIA approach to improve hypertension management comprises the PIA-ICT (PIA-App and PIA-PrMC) and PIA-Education (eLearning/on-site trainings for practice teams and patients) with four elements (for details, see Fig. 2 and Table 1).

The concept realizes a physician-supervised delegation model for hypertension management. The PIA-ICT was conceptualized by researchers of the Institute of Family Medicine and General Practice of the University of Bonn. It was realized together with experts for medical informatics from a private company following an agile design. The software solution was piloted in primary care practices with GPs, practice assistants and patients prior to its use in this cCRT.

1. PIA-App for patients (PIA-App): The PIA-App is a patient-facing application for smart devices (smartphone or tablet with Android operating system) that allows a secured communication between patient and practice. The key communication feature is the transmission of BP readings from the patient to the practice and the transfer of adjusted medication plans from the practice to the patient, paralleled by short text messages in both directions. The patient receives a push notification when the practice has sent a new medication plan. To motivate patients' adherence, a graph displays BP data over time including systolic BP (SBP), diastolic BP (DBP), pulse rate, and the BP target range. The BP target is set at < 135/85 mmHg per standard but can be individualized by the GP. In addition, the PIA-App enables patients to request prescription refills and access to a video on how to obtain a valid BP measurement as well as web links related to hypertension.
2. PIA practice management center (PIA-PrMC): The PIA-PrMC is a Windows application, which is used by GP and practice assistants to manage patients' hypertension therapy. It allows for reviewing patients' BP records and to adjust drug regimes. Integrated into the application, processes realize a delegation model: First, the GP enters his individual preferences regarding medication regimes. These can be individualized as needed for each patient. Second, the practice assistant reviews the incoming BP readings and—as long as target BP values are not reached and medication is tolerated—adjusts the pre-set medication regime and writes a suggestion for a short note to the patient. Third, the GP reviews these suggestions and, if approved, initiates the electronic transmission to the patient's PIA-App using a physician personalized identification number (PIN). If a GP does not agree with the practice assistants' suggestions and prefers a different medication regime or text message, the physician communicates this to the practice assistant who executes these physician orders with identical subsequent procedures. Fourth, the PIA-PrMC supports the electronic recall of patients who did not

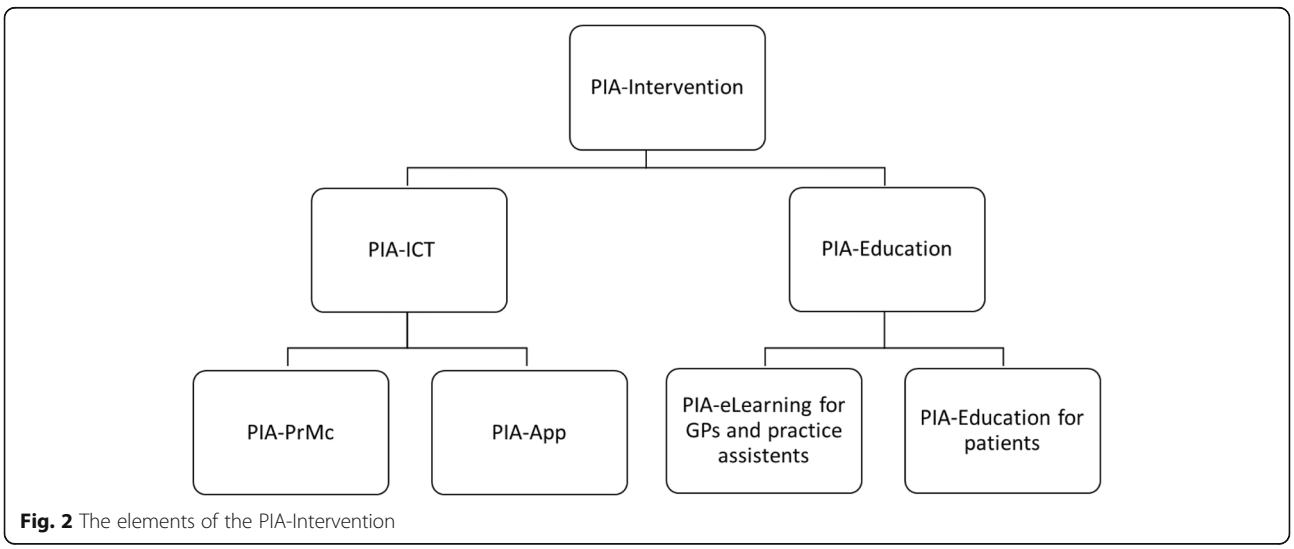

Fig. 2 The elements of the PIA-Intervention

Table 1 The PIA-Intervention: elements and target groups

	PIA-ICT		PIA-Education		
	PIA-Practice management center (PIA-PrMC)	PIA-App	PIA-eLearning and on-site teaching		PIA-Patient-Education
Setting	Secured system in practice	On patients' smartphone/tablet	PIA-Website for practices (secured login) and on-site teaching		In practice and PIA-App
Target croup	GPs and practice assistants	Patients	GPs	Practice assistants	Patients
Functions/ content	1. Secured patient-practice communication 2. Recall and step-wise medication adjustments 3. Communication GP and practice assistants 4. Pre-defined algorithms for medication regimes 5. Graphic display of BP data and target range over time 6. Electronic transmission of medication plan, physician PIN required 7. Data transfer to the trial center 8. Data download for the practice	1. Secured patient-practice communication 2. Transfer of BP values 3. Display of current medication plan 4. BP history displayed as a graph for different time grids 5. Request for prescription refill	1. Evidence-based information on hypertension 2. How to use the PIA-PrMC 3. Details of the delegation model 4. Information on the study processes	1. Evidence-based information on hypertension including medication classes 2. How to use the PIA-PrMC 3. How to use the PIA-App 4. How to obtain valid BP measurements in practice and at home 5. Information about the study processes	1. How to use the PIA-App 2. How to obtain valid BP measurements (in practice training and video) 3. Access to websites with evidence-based information on hypertension

transmit BP readings or have questions regarding their BP care.

The medication options offered to GPs follow the current hypertension guidelines as issued by the European Society of Hypertension [2]. For convenience, pharmaceutical agents are displayed according to the regional prevalence of their use in previous years. For each pharmaceutical agent, a typical regime for step-up dosing is integrated, thus allowing for an advanced treatment plan for each patient. In case of adverse drug reactions or other needs to adjust medication choices, the patient's medication plan can be adjusted individually by the GP.

Data management for the study is facilitated by an export function of aggregated, pseudonymized data in a data file format.

3. PIA-eLearning for GPs and practice assistants:

(a) *PIA-eLearning for physicians*: An audio-visual learning video with about 35 slides introduces GPs to the PIA-Intervention: how to use the software and the delegation concept with the new role for practice assistants (PIA practice assistant) within the German legal frame. The latter allows for the delegation of specific tasks to practice assistants and nurses, but not substitution, i.e., no issuing of prescriptions and no independent medication adjustments.

(b) *PIA-eLearning and PIA certificate to qualify practice assistants (PIA practice assistant)*: Audio-visual learning videos with about 50 slides and a video on BP self-measurements trains practice assistants on the following topics: how to measure BP according to standard, hypertension as so-called silent killer, sequelae of untreated hypertension, BP targets, drug regimens according to guidelines, how to implement the medication step-up based on physician-defined algorithms, short text message communication via the PIA-PrMC, patient management, and recall using the PIA-PrMC. In addition, practice assistants learn how to conduct the study at their practice site and how to educate patients regarding home BP readings. After the eLearning, practice assistants take a written examination and, if passed, receive the PIA certificate. eLearning material will be provided for download via a secured web space.

4. PIA in-practice and in-app education of patients: After informed consent and study inclusion, the PIA practice assistant will teach each patient individually how to obtain valid BP readings and how to use the PIA-App including the in-app video on valid BP home measurements and further web links.

Criteria for discontinuing or modifying allocated interventions {11b}

Patients unable to use the PIA-App for any reason despite having received appropriate training (e.g., worsening overall health status, admission to nursing home,

participant withdrawal) will discontinue the trial. The reasons will be recorded and analyzed.

Strategies to improve adherence to interventions {11c}

Patients in the intervention group will receive an upper arm electronic BP measuring device (BOSO family 4) for use in the study that they may keep afterwards. The PIA practice assistants will analyze the patients' submitted BP readings at least once a week and will provide appropriate feedback under supervision. Patients not answering to electronic reminders will be contacted by phone if no BP data are transmitted for several weeks. Practices in both study arms will receive financial reimbursement per participating patient.

Relevant concomitant care permitted or prohibited during the trial {11d}

Not applicable.

Provisions for post-trial care {30}

A study insurance is covering all study-related adverse patient outcomes.

Outcomes {12}

The following primary and secondary outcomes will be analyzed for each patient, both study groups (intervention, control) and the total population, if appropriate.

Primary outcome

The primary outcome is the BP control rate (% of patients with controlled BP). The BP is defined as "controlled" if the practice BP reading is in the target range, i.e., ≤ 140/90 mmHg (calculated as the mean value of the 2nd and 3rd BP readings, 3 successive measurements at intervals of 1 min each in a seated position).

The selected outcome "BP control" is internationally recognized as a surrogate parameter for the prevention of secondary diseases [13]. A meta-analysis of 47 randomized controlled trials with 153,825 patients showed that a BP reduction of 10 mmHg systolic and/or 5 mmHg diastolic reduces the relative risk for major outcomes after 5 years: heart failure by 43%, stroke by 36%, cardiovascular death by 18%, and coronary heart disease by 16% [3].

Secondary outcomes

The following are the secondary outcomes: (1) changes of SBP and DBP practice measurements per patient, (2) medication use and changes over time (number, kind, and dosing of antihypertensive medications used), (3) frequencies and kind of cardiovascular events (myocardial infarction, stroke, other) or death within the study period, (4) number of hospitalizations (emergency room treatments and/or in-hospital stays) and their causes care, (5) quality of life, (6) patients' satisfaction regarding hypertension treatment by GP practice, (7) time to BP control, (8) patients' health literacy, (9) medication adherence, (10) perceived time to invest for hypertension management in general (by physicians, practice assistants, and patients) (e.g., estimated duration of office consultation including waiting time, BP measurements, and prescription refills), (11) number of physician consultations and practice visits, and (12) perceived workload of the GPs and practice assistants by hypertension management and, for the intervention group only, (13) number of contacts between the practice assistant and patients via PIA-ICT including use of safety functions if applicable and (14) satisfaction and acceptance of PIA-Intervention by patients, GPs, and practice assistants. For details on time points, see Additional File 1: Table S2.

The following secondary data will be provided for patients insured in the respective statutory health insurance, which is a consortium partner: (1) emergency room treatments, (2) hospitalizations (e.g., in-hospital days), (3) prescription details, and (4) death (date and cause of death).

Participant timeline {13}

The schedule of enrollment, intervention, and assessments is shown in Additional File 1: Table S2.

Sample size {14}

The sample size was calculated based on the primary outcome. Using data from the study of Margolis et al. [9], we assumed a BP control rate of 65% in the intervention group and 50% in the control group after 12 months. The sample size calculation was performed in PASS V14, using an unpooled 2-sided Z-test to compare two proportions in a cluster-randomized design. Assuming that both study arms comprise the same number of clusters (practices), the inter-cluster coefficient is 0.055 [14] and the mean cluster size is 15 patients, 2 × 405 = 810 patients (27 clusters per study arm) are required to detect a group difference of 15% (65% vs 50%) with a power of 90%. Although the case number calculation is based on a 2-sided Z-test with an unpooled variance in a cluster-randomized setting, there is sufficient power for the calculation of generalized linear mixed models (GLMM) with additional covariates. Assuming a case number of 810 patients and incidence rates of cardiovascular events between 2 and 5% [3], it is a probability of 100% to observe at least one such event (PASS V14). Based on experience from a previous CRT on hypertension management by GP [15], a 10% drop-out rate in the practices is assumed; therefore, 3 more

practices are recruited per study arm. Therefore, the study aims for a cluster-randomized trial with 60 GP practices (30 intervention, 30 control) with one physician, two practice assistants, and 17 patients each (total 1020 patients).

Changes required due to the SARS-CoV-2 pandemic The scheduled recruitment period was influenced by the pandemic, which led to more SARS-CoV-2-related workloads and perceived insecurities on behalf of practices as well as fewer practice visits by patients due to social distancing and lockdown regulations. Accounting for this unexpected interference, the scheduled recruitment period for both practices and patients needed to be prolonged. To support recruitment, statutory health insurances involved in the project applied several patient information strategies. In addition, given an overall limited project time, the target number of patients was reduced based on a re-calculation of the sample size by the evaluator assuming a power reduction from 0.9 to 0.8 (with all other parameters kept identical) resulting in a target patient number of 2 × 300 = 600 patients (20 clusters per study arm) to detect a group difference of 15% (65% vs 50%). Assuming a 10% drop-out rate for practices and a 10% dropout rate for patients, three more practices and 2 more patients in each practice will be recruited. In summary, this cluster-randomized trial will be conducted with 46 GP practices (23 intervention, 23 control) with one GP, two practice assistants, and a mean of 17 patients each (total 782 patients). In addition, the minimum duration of the intervention was reduced to at least 6 months. This is justified by international studies of ICT delegation models which showed significant improvements in hypertension control already after this shorter period [9, 16, 17].

Recruitment {15}

Recruitment of practices Recruitment follows a multistage procedure. Based on the contact data available, practices are invited by mail, fax, and/or email. Invitation materials include the study information and the consent form for participating GPs. Subsequently, practices are contacted by phone. After written consent of the participating GP, each practice is randomized. Afterwards, a clinical monitor visits each intervention and control practice to provide detailed information on the study and the study materials. Practices declining participation or not providing feedback receive a standardized non-responder questionnaire by fax for subsequent quantitative analysis.

Recruitment of patients Within each practice, the recruitment of patients is coordinated by practice assistants supported by the GP as needed. To avoid selection bias, practices are requested to list all patients with a diagnosis of essential hypertension in their electronic patient management system. Practices are asked to screen all these patients regarding the inclusion criteria and, if applicable, to ask for study participation during their next routine visit. Each practice follows this approach up to the inclusion of at least 17 patients. Practices are asked to systematically document the recruitment including reasons for non-participation.

Changes due to the SARS-CoV-2 pandemic As described in the "Sample size {14}" section, the pandemic interfered with the recruitment of practices and patients. Thus, a much larger number of practices needed to be contacted to recruit the target number. Also, lock-down periods in Germany from fall to spring 2020/2021 led to dropouts of recruited practices requiring additional practice recruitments. Thus, the total recruitment time had to be extended from 6 months to 12 months in total. Given large regional and inter-practice variations of pandemic burden, practices from both groups were asked to include additional patients if possible, to compensate for practices with lower patient recruitment. Nonetheless, approaches for recruitment of practices and patients remained identical over time.

Assignment of interventions: allocation

Sequence generation {16a}

The randomization is conducted by the independent trial center responsible for data management and monitoring. The allocation sequence is computer-generated based on random numbers. Stratified block randomization (1:1) is used to ensure a balanced distribution of urban and rural localized practices in the intervention and control arm.

Concealment mechanism {16b}

For each practice recruited, the trial center will communicate the allocation in written form to the researchers of the Institute of Family Medicine and General Practice.

Implementation {16c}

The trial center, which is not involved in recruitment processes, generates the allocation sequence. The Institute of Family Medicine and General Practice enrolls physicians/practices. After a practice is randomized by the trial center, the institute informs the practice about the allocation. All practices enroll patients.

Assignment of interventions: blinding

Who will be blinded {17a}

Blinding of involved scientists, practice personnel, and patients is not possible due to the ICT-based intervention which is offered to the intervention group only. Data analysts will follow predefined standard operating procedures for analysis to avoid bias.

Procedure for unblinding if needed {17b}

Not applicable.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Measurement instruments address patients, GPs, and practice assistants. For details on points in time, see Additional File 1: Table S2.

The following are the patients' measurements:

1. Blood pressure measurements: All patients receive standardized practice BP measurements by trained practice assistants. For details, see the "Outcomes {12}" section. In the intervention group, only BP measurements from home BP measurements will be analyzed as transmitted electronically to the PIA-PrMC.
2. Mental well-being during the last 14 days is assessed using the WHO-Five Well-Being Index (WHO-5,1998 version, in German) [18–20]. It consists of 5 items on a 6-point Likert scale (5 = "all of the time" to 0 = "at no time"). The scores are added to a sum score ranging from 0 to 25, which is multiplied by 4 to achieve the final score with 0 denoting the worst and 100 representing the best subjective well-being [18].
3. The usability of the PIA-ICT is measured using the standardized and validated System Usability Scale (SUS) which consists of 10 questions on a 5-point Likert scale (1 = "strongly disagree" to 5 = "strongly agree") [21, 22]. The total score ranges from 0 to 100, with a higher score indicating greater usability. An average SUS score of 70 or more is considered appropriate [22].
4. Medication adherence is measured using the standardized and validated Medication Adherence Rating Scale (MARS-D, German version) [23]. It consists of 5 items on a 5-point Likert scale (1 = "always" to 5 = "never") which yields a sum score between 5 and 25 points with a higher score indicating better medication adherence [23].
5. Acceptance and use of the PIA-ICT are measured using the Unified Theory of Acceptance and Use of Technology model (UTAUT) which consists of 18 questions on a 5-point Likert scale (1 = "strongly disagree" to 5 = "strongly agree"). It assumes that behavioral intentions (3 items) and effective use of technology are influenced by four determinants for acceptance: performance expectancy (4 items), effort expectancy (4 items), social influence (3 items), and facilitating conditions (4 items) [24, 25].
6. Patients' characteristics: Sociodemographic characteristics, risk factors (for example, physical activity and smoking behavior), medication adherence, management of BP self-readings, and state of general health are requested. For each patient, the GP completes a sheet addressing the patients' medical history regarding hypertension, hypertension-related diseases, hospitalizations, other diagnoses, and details on medication and their changes during the study.

The following are the measurements addressing physicians and practice assistants:

1. Occupational self-efficacy of physicians is measured using a short version of the Occupational Self-Efficacy Scale [26, 27]. The instrument consists of 8 items on a 6-point Likert scale (6 = "totally disagree" to 1 = "totally agree") with a higher sum score indicating a higher occupational self-efficacy.
2. Sociodemographic and professional characteristics of GPs and practice assistants: age, sex, professional degree(s), additional qualifications, number of years in practice, and working full-time or part-time.
3. Intervention group only: SUS [22] and UTAUT [24, 25] questionnaires as described above (see section 18a, patients' measurements).
4. Given the SARS-CoV-2 pandemic, two questions were added for physicians and practice assistants addressing the perceived burden due to the pandemic.

Plans to promote participant retention and complete follow-up {18b}

Patient-directed strategy Patients in the intervention group will be contacted by the practice via PIA-App, subsequently by phone, if no BP values are transmitted for several weeks.

Practice-directed strategy Regular faxes by the institute ask for practices' actual patient recruitment numbers and if any support is needed. The research team offers practice-specific support including practice visits regarding recruitment and use of the PIA-ICT. The institute will record all questions and support measures.

Discontinuing patients and the respective reasons are recorded by the practices; the research team records discontinuing practices and respective causes. All data

available from discontinuing patients and/or practices will be analyzed.

Data management {19} Data management will be carried out by the trial center according to standardized procedures as defined in the current standard operating procedures (SOPs). The data management system used by the trial center has an integrated audit trail and is Good Clinical Practice (GCP)-compliant. Data will be entered by appropriately trained data entry staff who are familiar with the study specifics. Double data entry will be used to ensure data quality for paper-based information. Data from the PIA-PrMC will be transmitted electronically to the study centers. Missing data will be addressed by imputation methods according to standard [60]. All personal data will be kept confidential in an access-restricted database. All analyses will be performed using pseudonymized data. The pseudonymized data will be stored at the ZKSE, University Hospital Essen, and the Institute of Family Medicine and General Practice, University of Bonn. The latter institute will manage the access to the data set.

Confidentiality {27} Confidentiality issues and data protection issues are part of the ethics statement. The data protection agency of the University Hospital Bonn had agreed to the following approaches:

1. Confidentiality regarding patients' and practices' data

Contact data of practices and personnel involved are stored in access-restricted data files at the institute and the trial center. GPs' and practice assistants' questionnaire data will be managed as pseudonymized data files.

All personal information of patients will remain in the practices. The names of enrolled patients will be kept at the practices in a separate access-restricted paper file. The data analysis will be performed with pseudonymized data only to allow for maximum protection of participants. Information on potential participants which were not enrolled will remain solely in each practice. Before, during, and after the trial, all data will be stored in the institute and the trial center in access-restricted files according to their standard operating procedures.

2. Confidentiality in PIA-ICT (PIA-App and PIA-PrMC software)

The PIA-App will not store any personal data on the patient's smart device. The regularly transmitted BP data does not contain any personal data. The communication between the PIA-App and the PIA-PrMC, i.e., data transfer and transmission, takes place via a secured server at the University Hospital Bonn. This communication and data transfer is encrypted by using https/Transport layer Security (TLS) with encryption algorithms on the elliptic curve and perfect forward secrecy (TLS negotiation BSI TR-021202-2). After the user (GP, practice assistant) logs on to the PIA-PrMC, a token is generated for encrypted communication with the PIA-App (Bearer Token). This token is transmitted with every communication.

3. Data transfer to trial center and the institute

Pseudonymized patient and practice data will be exported from the PIA-PrMC. This data is first stored on the GP's practice computer. Exports will only contain pseudonymized data, i.e., personal data such as surname, name, and date of birth of the patients are removed prior to export. The export is a zip file with AES (Advanced Encryption Standard) password encryption. This file is transmitted electronically to the Institute for Family Medicine and General Practice as well as the trial center.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Descriptive data will be used for all participant characteristics and scales as applicable (e.g., frequencies, means). Analyses of all scales will follow scale-specific recommendations. The confirmatory analysis for the primary endpoint is based on a generalized linear mixed models (GLMM) with a significance level of 5% (2-sided).

Primary endpoint

A GLMM is used because the primary endpoint is a patient-related outcome and these are embedded in the clusters. The model will include relevant patient covariates (e.g., age, gender). Taking the data's cluster structure into account, the affiliation of patients to practice is included in the model as a random effect. The null hypothesis (no difference in BP control rate) will be rejected if the p-value for the Wald test statistics for the intervention effect is < 0.05. The p-value for the Wald test statistics for the intervention effect is < 0.05. The p-value for the Wald test statistics for the intervention effect is < 0.05. The adjusted odds ratio (OR) and the associated 95% confidence interval will be reported.

Secondary endpoints

All secondary analyses will be performed exploratively, i.e., without adjustment, using GLMM and adequate statistical standard procedures, taking into account the cluster structure of the data. A significance level of 5% will be assumed for all statistical analyses. Under individual randomization, an OR of 1.5 could be detected with 2 × 405 patients and a power of 80% and an OR of 1.6 with a power of 90% (Fisher's exact test; PASS V14). We expect similar, probably slightly higher ORs for this CRT design.

Interim analyses {21b}

No interim analyses are planned.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analyses will consider the age, gender, and socioeconomic status of the patients as well as practice and practice personnel characteristics.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Robustness and sensitivity analyses with imputation procedures for the missing values will be performed.

Plans to give access to the full protocol, participant level-data, and statistical code {31c}

After study publication, the statistical code and trial data, including deidentified participant data, will be made available on request after approval of a formal written proposal. To gain access, researchers need to contact the corresponding author. This manuscript is the full study protocol, which is publicly available.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The Institute of Family Medicine and General Practice is the coordinating center. The project management group consists of representatives from the coordinating center, the trial center, and the supporting statutory health insurances. A steering and review board with three national and international specialists is set up and will review all harms and reported adverse events.

Composition of the data monitoring committee, its role, and reporting structure {21a}

Data management and data monitoring are provided by the trial center (Center for Clinical Trials, University Hospital Essen, University of Duisburg-Essen, https://zkse.de/), which is independent from the sponsor and has no competing interests. All data-related procedures are carried out according to the standardized procedures defined in current SOPs. The data management system applies an integrated audit trail and is GCP compliant. All unexpected findings will be reported to the principal investigator (BW) who will decide upon the procedure together with the study's advisory board.

Adverse event reporting and harms {22}

If adverse events or other unintended effects of the intervention occur during the course of the study, they will be documented, evaluated, and reported. All patients and physicians are asked for adverse events in the follow-up questionnaires. Throughout the study, safety analyses are performed for all patient-relevant endpoints. A steering and review board with three national and international specialists is set up and will review all harms and reported adverse events.

Frequency and plans for auditing trial conduct {23}

The documentation in the study folders is audited at baseline and follow-up by clinical monitors from the trial center responsible for data management and monitoring. This center is independent from the investigator and the sponsor.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

In case of modifications to the protocol, the ethics' committee and participants will be informed.

Dissemination plans {31a}

The results will be disseminated to participating practices, regional and national physician agencies and professional associations, statutory health insurances, patient representatives, and the scientific community and the public. Information channels will include websites, journal publications, conference presentations, newsletters to relevant stakeholders, and press releases. The study is supported by three statutory health insurances which will contribute to the dissemination.

Discussion

The PIA-Intervention as a complex telemedicine intervention realizes an ICT-supported delegation model for German primary care. Involving physician-supervised medication adjustments by practice assistants, the project is a step towards more task delegation in German GP practices and advancement of practice assistants' professional roles. Aiming at a high fit accuracy for GP practices, the development of the intervention applied three participatory strategies: (1) the project was initiated by a practicing, academic family medicine specialist; (2) agile software development with close interaction of medical software engineers, information system and

implementation scientists, and an academic GP; and (3) repetitive testing and software adjustments involving practice personnel (GPs and practice assistants). Thus, it followed state-of-the-art principles of the implementation sciences [28].

During study conduct, several practical and operational issues evolved due to the SARS-CoV-2 pandemic requiring described protocol adjustment. First, there was a need for over-recruitment of practices due to unusual numbers of dropouts after the target number of practices had been successfully recruited initially. The consistently reported reasons were pandemic-related duties and strains. Given a limited overall project duration and the need for a prolonged recruitment period, the primary outcome was adjusted to a minimum follow-up of at least 6 months. This is justified by international studies of ICT-delegation models which showed significant improvements in hypertension control already after this shorter period [9, 16, 17]. Second, patient recruitment by practices is more difficult as patients visit the practices less frequently given recommendations for social distancing and lock-down regulations. Therefore, the targeted power was adjusted from 0.9 to 0.8 leading to a reduced target sample size. Third, there was a higher need for individual support of practice teams by the research team due to the pandemic, e.g., active support for patient recruitment and telephone reminders for motivation.

The project is supported by the Federal Joint Committee (G-BA) within a legal framework allowing for special contracting option (so-called selective contracts) according to the German social security code V (SGB V, §75a Selektivvertraege). This implies not only a scientific evaluation of new care models but also a preparation for potential implementation in routine care by special contracts which regulate health services (here PIA-ICT) including reimbursement. Thus, if proven effective, the PIA-ICT will be considered for the benefit catalog of the statutory health insurance funds (GKV) by the Federal Joint Committee (G-BA).

Trial status

Recruitment started on May 1, 2020, and is scheduled to be completed by March 31, 2021.

Abbreviations

AES: Advanced Encryption Standard; BP: Blood pressure; DBP: Diastolic blood pressure; GCP: Good Clinical Practice; GLMM: Generalized linear mixed models; GP: General practitioner; ICT: Information Communication Technology; MARS-D: Medication Adherence Rating Scale – Deutsch; OR: Odds ratio; PIA: PC-gestütztes Fallmanagement von Hypertonikern zur Implementierung einer Leitlinien-konformen Hypertonietherapie anhand eines Arzt-definierten und – supervidierten, patientenindividuellen Therapiealgorithmus (= official German title which stands for a "PC supported case management of hypertensive patients to implement guideline-based hypertension therapy using a physician-defined and -supervised, patient-specific therapeutic algorithm"); SBP: Systolic blood pressure; SOP: Standard operating procedure; SUS: System Usability Scale; TLS: Transport Layer Security; UTAUT: Unified Theory of Acceptance and Use of Technology; WHO: World Health Organization; WHO5: World Health Organization-Five Well-Being Index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-021-05660-4.

Additional file 1: Table S2. Overall schedule of enrolment, intervention, assessments, and time commitment for trial participants. Is an overview for overall schedule of enrolment, intervention, assessments, and time commitment for patients, general practitioners and practice assistants.

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Authors' contributions {31b}

BW had the study idea and drafted the grant application together with CK, CO, and KHJ. BW, AK, and FL developed and piloted the intervention. AK drafted the first version of the manuscript together with BW and FL. All authors contributed to the study protocol and/or development of the intervention. All authors provided feedback on the manuscript and approved the final version.

Funding {4}

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Availability of data and materials {29}

After study publication, the statistical code and trial data, including deidentified participant data, will be made available on request after approval of a formal written proposal. To gain access, researchers need to contact the corresponding author. This manuscript is the full study protocol which is publicly available.

Authors' information

Not applicable.

Declarations

Ethics approval and consent to participate {24}

Ethical approval was obtained from the lead Ethics Committee of the Medical Faculty of the University of Bonn (reference number: 156/18, date of approval: 02/08/2018). Written, informed consent to participate is obtained from all participants.

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare that they have no competing interests.

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9.2 Publication 2

Digital redesign of hypertension management with practice and patient apps for blood pressure control (PIA study): A cluster-randomised controlled trial in general practices

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Digital redesign of hypertension management with practice and patient apps for blood pressure control (PIA study): A cluster-randomised controlled trial in general practices

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Summary

Background Long-term hypertension control prevents heart attacks and other cardiovascular diseases, yet implementation is insufficient worldwide. The redesign of hypertension management by information and communication technology (ICT) improved hypertension control, e.g., by transmission of blood pressure (BP) measurements to a central webspace. However, an easy-to-use secure patient app connected with a practice management centre is lacking. This study evaluates the effectiveness of the newly developed PIA (PC-supported case management of hypertensive patients to implement guideline-based hypertension therapy using a physician-defined and -supervised, patient-specific therapeutic algorithm) intervention with PIA-ICT and eLearning for general practices.

Methods The effectiveness of the PIA intervention was evaluated in a cluster-randomised study. Practices were randomly allocated (1:1) to the intervention or the control group (usual care). Group allocation was unmasked for participants and researchers. The primary outcome was the BP control rate (BP < 140/90 mmHg) after 6–12 months. Secondary outcomes included BP changes and satisfaction with PIA-ICT. The trial is registered in the German Clinical Trials Register (DRKS00012680).

Findings Starting from December 1, 2019, 64 general practices were recruited over 1 year during the COVID-19 pandemic. Overall, 848 patients were enrolled between April 15, 2020 and March 31, 2021. The study was completed Sept 30, 2021. At baseline, 636 patients (intervention: 331; control: 305) of 50 general practices met the inclusion criteria. The final dataset for analyses comprised 47 practices and 525 patients (intervention 265; control 260). In the adjusted hierarchical model, the PIA intervention increased the BP control rate significantly by 23.1% points (95% CI: 5.4–40.8%): intervention 59.8% (95% CI: 47.4–71.0%) compared to 36.7% (95% CI: 24.9–50.3%) in the control group. Systolic BP decreased by 21.1 mmHg in the intervention and 15.5 mmHg in the control group.

Interpretation The PIA redesign of care processes improved BP in an outcome-relevant way. Prospectively, it may constitute an important model for hypertension care in Germany.

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Keywords: Hypertension; Blood pressure; Telemedicine; Family medicine; General practice; Home blood pressure monitoring; Delegation; mHealth; Information technology; eHealth

Introduction

Hypertension is a major risk factor for cardiovascular disease, and a leading cause of morbidity and mortality worldwide.[1,2] High blood pressure (BP) is responsible for 8.5 million deaths from hypertension comorbidities worldwide.[1,3] In 2019, the worldwide prevalence of hypertension in adults aged 30–79 years was 32% in women and 34% in men.[4] On the other hand, the

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Research in context

Evidence before this study

We searched PubMed and Google scholar for studies on randomized controlled trials published in English, using the search terms 'hypertension', 'hypertension management', 'telemonitoring', 'digital health', 'eHealth' and 'mHealth', with the last update on May 13, 2022. We screened papers by title and abstract to identify studies, which used an ICT-supported hypertension management. Of eight studies identified, five showed a significant improvement of blood pressure in the intervention arm after 6 and/or 12 months. None of the eight studies used an app with patient-physician chat communication, BP readings and medication plans in connection with the electronic health record.

Added value of this study

To our knowledge, the PIA-ICT is the first hypertension management with a patient app and a practice management centre that allows a secure transmission of BP readings and comprehensive medication plans as well as chat communication. Using a safety-by-design approach, data transmission is securely encrypted, pseudonymised and fulfils current national data protection requirements.

Implications of all the evidence

This study provides convincing evidence that the PIA-ICT for hypertension management improves blood pressure control significantly after 6–12 months. The PIA-ICT with PIA-app was well accepted and rated very user-friendly by GPs, practice assistants and patients.

benefit of blood pressure control by widely available antihypertensives is well documented: in a meta-analysis of randomised controlled trials, each 10 mmHg reduction in systolic blood pressure (SBP) resulted in significant risk reductions of major cardiovascular events (–20%), coronary heart disease (–17%), stroke (–27%), heart failure (–28%) and all-cause mortality (–13%).[5] However, routine implementation remains a challenge with improvement shown by IT-supported strategies.

In eight studies with ICT (information and communication technology)-supported hypertension management, BP was reduced significantly by –6.0 to –21.4 mmHg systolic and –2.3 to –9.4 mmHg diastolic after 6 months.[6–13] The ICT systems studied differ in their degree of ICT support for the complex care processes of hypertension management. All systems operate with an IT-based case management and a secure webspace/application with central data collection of patients' BP measurements, while other aspects vary considerably, e.g., access for care providers and/or patients, delegation models, modes of physician-patient communication and integration into the electronic health record (EHR). A 2013 landmark study by Margolis et al.[6] showed a significant BP improvement (71.8% controlled BP in the telemonitoring group and 45.2% in the usual care group after 6 months) using a delegation model to a clinician pharmacist who evaluated BP readings of 380 US patients, uptitration medications following a written algorithm and informed patients of medication changes by phone. In a 2013 study by McKinstry et al. with 401 Scottish patients, practices and patients had access to a secure webspace, which sent automated responses (SMS) to patients depending on BP results. If medications needed to be optimised, the system suggested contacting the general practitioner (GP) with whom patients communicated by email or SMS outside the ICT.[10] A system used by McManus et al., 2018 provided an automated weekly message to the participating 393 patients depending on BP readings. Practices were asked to log into the platform monthly to adjust medications; any changes could be communicated to patients from within the system by text messages (SMS).[7] In two studies by the same research group, patients received paper-based algorithms for medication self-titration if the electronic platform told them to do so, with physician contact at the latest after two adjustments.[8,9] All described BP monitoring systems lack easy patient-practice chat communication on BP readings, well-being and medication plans. Also, most systems require additional input outside the EHR, resulting in double documentation of medication adjustments. To facilitate care, there is a need for ICTs that simplify more steps of the complex hypertension management tailored to practices' and patients' needs.[13] Similar to other countries, BP control in German GP patients is poor (prevalence of uncontrolled BP 49%)[14] and no ICT-supported hypertension management is available. This cluster-randomised, controlled study describes the effectiveness of the PIA-ICT for BP control in German general practices. The acronym PIA refers to a PC-supported case management of hypertensive patients to implement guideline-based hypertension therapy using a physician-defined and -supervised, patient-specific therapeutic algorithm. Following above mentioned international experiences, the IT solution was developed in a participatory approach with patients, GPs and practice assistants (PrA). It allows for a highly secure, electronic communication of blood pressure readings, medication plans and chats between patients (PIA app for smartphone/tablet) and practices (PIA practice management centre, PIA-PrMC). Physician-defined medication electronic algorithms are implemented stepwise by trained

PrAs under physician supervision. Medication plans from the practice's EHR are electronically transmitted to the PIA app via the PIA-PrMC.

The main study objective was to investigate whether the PIA intervention improves BP control (BP ≤ 140/90 mmHg) after 6–12 months in patients with uncontrolled hypertension at baseline.

Methods

Study design

The study was designed as a cluster-randomised controlled trial (cRCT) in 60 German GP practices from the Greater Bonn region which were randomised 1:1 to an intervention group (PIA-ICT) and a waiting-list control group (usual care). The waiting list control group obtained access to PIA-ICT for 3 months after the collection of follow-up data (see Figure 1 in study protocol[15]). Further information is published in the study protocol.[15] Ethics approval was obtained from the Ethics Committee of the Medical Faculty of the University of Bonn (reference number: 156/18, date of approval: 02/08/2018). An advisory and review board with three international researchers in the field and one national GP specialist was implemented.

Participants

Board-certified GPs accredited for the statutory health insurance system were eligible to participate in the study. Patients were eligible if they had an uncontrolled practice BP (≥140/90 mmHg). The exclusion criteria for age are based on the European Guidelines for the Management of Hypertension (ESH/ESC): patients younger than 40 years need routine evaluation for potential secondary hypertension; for patients older than 80 years higher target values are recommended.[16]

For details on the inclusion and exclusion criteria, see Table 1. All participants (GPs, PrA, patients) provided written informed consent. Recruitment of practices followed a multi-stage procedure (mail, fax, and/or email, phone). Participating general practices recruited patients.

Randomisation and masking

Randomisation took place at the practice level, i.e., all patients of a practice were assigned to either the intervention or the control group. Randomisation was conducted by the independent trial centre. The allocation sequence was based on computer-generated random numbers. Stratified block randomisation (1:1) was used to ensure a balanced distribution of urban and rural practices in the intervention and control arms. Masking of involved scientists, practice personnel and patients was not possible due to the ICT-based intervention, which was offered to the intervention group only. Data analysts followed predefined standard operating procedures for analysis to avoid bias.

Practice level	
Inclusion criteria	Certified GP accredited for the statutory health insurance system
	Practice computer with internet access (Windows 7 or higher)
	Participation of at least one GP and up to three practice assistants per practice
Exclusion criteria	GP has an additional qualification in hypertensiology
	GP/practice participated in the development of the intervention
Patient level	
Inclusion criteria	Age 40–79 years
	Diagnosed with essential hypertension (ICD I10)
	Resting practice BP ≥ 140/90 mmHg (second of two BP readings)
	Need for or use of ≥1 antihypertensive substance
	Insured in the statutory health insurance
	Smart device with Android 6 or higher
	Sufficient skills to use the smart device at least 3 times a week
	Sufficient language skills to understand the study documents
Exclusion criteria	Known white coat hypertension
	Critical health condition at the time of inclusion (e.g., hypertensive crisis, BP-related symptoms such as dizziness or headache)
	Chronic kidney disease requiring dialysis
	Pregnancy or breast-feeding
	Hyperkalaemia
	Secondary hypertension (e.g., renal artery stenosis)
	Heart failure NYHA III or IV

Table 1: **Inclusion and exclusion criteria.**

Procedures

PIA is a complex intervention comprising two elements: the PIA-ICT (PIA app and PIA-PrMC) and the PIA education (eLearning/on-site training for practice teams and patients).[15]

The following features characterise the electronic PIA intervention:

1. PIA communication: Highly secure communication between patients (PIA app) and practices (PIA-PrMC):
   a. PIA app for patients: transmission of BP measurements, graphic display of BP over time with individual target range, medication plan, ordering of prescription refills, video education and links to BP related information;
   b. PIA-PrMC with delegation model: recall and step-wise medication adjustments, predefined and guideline-oriented algorithms for

medication regimens, graphic display of BP over time with individual target range, electronic transmission of medication plan to PIA app, predefined process with colour scheme for delegation to PrAs, option to export data from the PIA-PrMC to the EHR for documentation.
2. PIA medication plan transfer: electronic transmission from the EHR to the PIA-PrMC and the PIA app;
3. PIA medication safety: the GP signs each medication plan electronically (required by German law as PrAs have no prescribing privileges);
4. PIA eLearning for GPs and PrAs: videos present evidence-based information on hypertension management including medication classes, how to use the PIA-PrMC and the PIA app, how to obtain valid BP measurements in the practice and at home, and the study details. PrAs complete a short, written exam to qualify as a PIA-PrA.

After randomisation, all practices received information on the patient recruitment procedure and standardised blood pressure measurements. Practices in the intervention group received access to eLearning, on-site training if needed, and the PIA-PrMC.

In each practice, patients were approached and recruited using pre-specified criteria. The practices created lists of patients with the ICD diagnosis hypertension who were eligible for the study. By protocol, the practices were asked to approach patients on this list consecutively as they visited the practice. Due to the pandemic, not all practices followed this approach rigidly. However, a comparison of patients' characteristics (age groups, sex, history of coronary disease/myocardial infarction) with national data suggest that this did not lead to a systematic error. Recruited patients received two blood pressure measurements in the office (5 min rest, then two measurements taken with 1-min in-between). In addition to an automatic upper arm blood pressure monitor (BOSO® medicus family 4), patients in the intervention group received access to the PIA app and training on its use and blood pressure measurement.

The PIA intervention used repetitive cyclic communication: Patients measure their resting blood pressure daily at home two times in the morning and in the evening, each time with an interval of 1-min in-between, and manually entered the readings into the PIA app. These BP values are transmitted to the PIA-PrMC in real time. The PIA-PrA analyses the values on a weekly basis and makes medication suggestions based on the physician's instructions. The suggestions are supervised by the physician and signed with an electronic PIN. Modified medication plans are automatically sent to the PIA app. The patient receives a push message when new information is available in the PIA app. The practice and patients can exchange information electronically via the PIA-ICT. After patients reached the target value, the practices defined an individual interval for further blood pressure measurements. For the follow up survey, blood pressure measurements were performed according to the same scheme at baseline.

Outcomes

The primary outcome was the BP control rate (% of patients with BP < 140/90 mmHg). BP was defined as "controlled" if the second of two resting practice BPs was within the target range. The mean of a second and third BP reading was initially used to define the outcome, but practices refused a third reading to decrease contact times during the COVID pandemic. A literature review showed a difference of 0–1 mmHg between these approaches, which we deemed acceptable as it systematically affected both study arms.[17] Additional sensitivity analyses were performed using the mean of two BP measurements. In addition, the following secondary outcomes are reported for both groups: changes in systolic and diastolic blood pressures (SBP, DBP) between baseline and follow up; medication changes; frequency of cardiovascular events, emergency treatments and hospitalisations; patients' satisfaction with hypertension treatment by their GP practice. For the intervention group only, the number of contacts between the practice and the patients via PIA-ICT, as well as the satisfaction with PIA-ICT among GPs, PrAs and patients were obtained. For details see the study protocol.[15]

Statistical analysis

As detailed in the study protocol, it was estimated that 600 patients from 40 GP practices (300 patients from 20 GP practices per study arm) would be required to detect a 15% difference in control rates between the groups with 80% power. The sample size calculation respected for the clustered design.[15]

The confirmatory analysis for the primary endpoint was based on a generalized linear mixed model (GLMM) with a significance level of 95% (2-sided). The model included relevant patient covariates (four age groups, sex, history of coronary disease/myocardial infarction). The recruitment period was included as covariate because the COVID-19 pandemic delayed patient recruitment. To account for the clustered structure of the data, the patients' practice was entered as a random effect. The null hypothesis (no difference in blood pressure control rate) was rejected if the p-value for the Wald test for the intervention effect was <0.05. The adjusted odds ratio (OR) and associated 95% confidence interval are reported. The secondary outcomes addressing blood pressure measurements (changes in systolic and diastolic BP) were evaluated using GLMM with random effects to account for the clustered design of the data. All other secondary analyses were performed in an exploratory

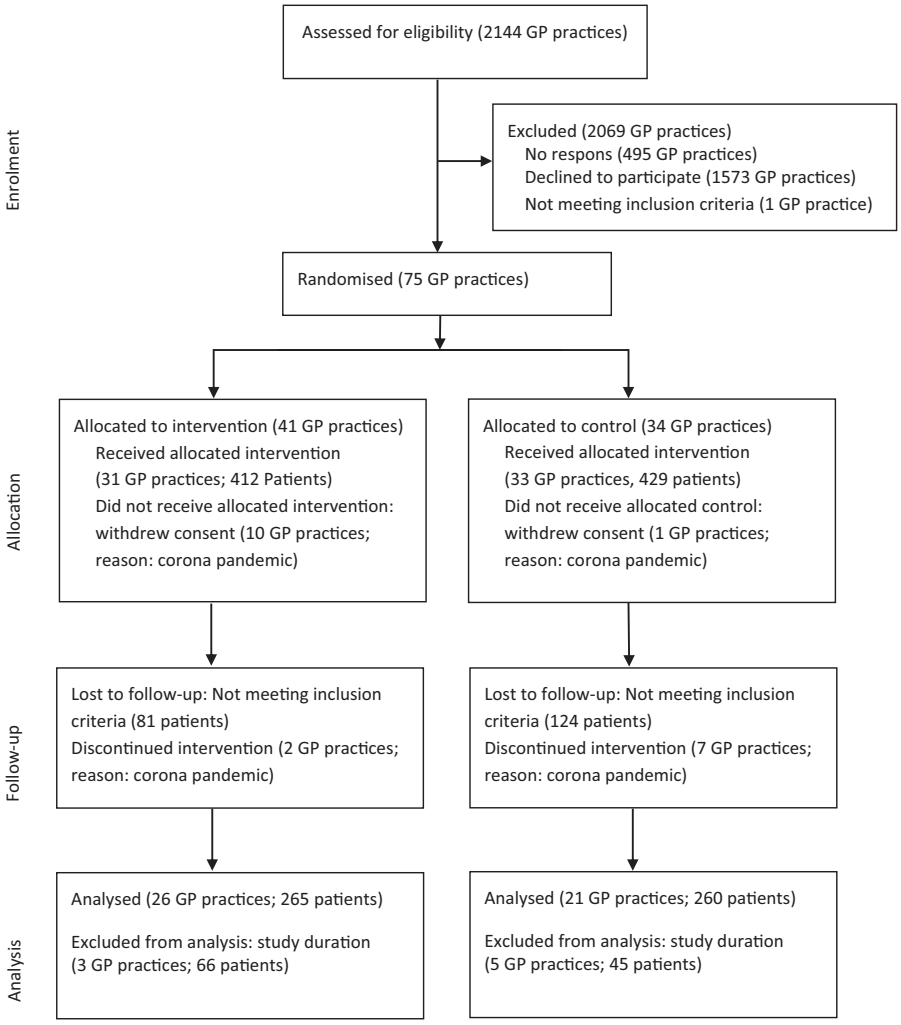

Fig. 1: CONSORT flowchart.

fashion using adequate standard statistical procedures (Mann–Whitney U test, chi-square-test (χ^2), Z statistics). A significance level of 95% was assumed for all statistical analyses which were performed using IBM SPSS 27 on Windows and R 3.6 (GLMM model: lme4 [1.1-26]).

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. All authors had access to dataset and decided to submit the publication.

Results

A total of 64 practices and 848 patients were recruited for the study. Study participants were recruited during the COVID-19 pandemic with three lock-downs in Germany (February 2020 up until March 2021). The recruitment rate was 3.6% which is in line with recruitment rates from other studies.[18] At baseline, 50 primary care practices and 636 patients participated. Reasons for study withdrawal were pandemic-related burden and/or non-compliance with the inclusion criteria for the practice and/or patients. A total of 47 general practices with 525 patients, 51 GPs and 61 PrAs completed the follow up (final study cohort). The details are outlined in the CONSORT flowchart (Fig. 1).

In the baseline evaluation, 50 practices with 636 patients met the study criteria (28 intervention practices with 331 patients; 22 control practices with 305 patients). On average, 12.7 patients were recruited per practice (intervention 11.8 patients [SD 9.9]; control 13.9 [SD 11.2]). At follow up, 525 (82.5%) of these patients from 47 practices (intervention: 26; control: 21) had provided complete datasets with an average of 11.2 patients per practice [SD 10.31].

A comparison between the intervention and control groups at baseline showed no significant differences except that control group participants were 2.3 years older on average. In the final study population, the control group was 0.9 years older on average. The final model controlled for this difference. There were no further significant differences between study participants with complete datasets at baseline (Table 2).

Table 3 presents the BP measurements at follow up. Unadjusted results showed significantly lower first and second SBPs as well as significantly higher control rates for SBP and DBP in the intervention compared to the control group. 62.6% of the patients in the intervention compared to only 44.6% of patients in the control arm reached the BP target range ($p < 0.001$).

The GLMM model for the primary endpoint is detailed in Table 4. The odds ratio for the influence of the intervention versus the control group was 2.57 (95% CI: 1.23–5.37, $p = 0.012$), so that the null hypothesis (intervention has no influence) can be rejected with a probability of error of 5% (2-sided test). The population-adjusted proportion of patients with controlled blood pressure at the end of the study was 59.8% (95% CI: 47.4–71.0%) in the intervention group and 36.7% (24.9–50.3%) in the control group. This results in a difference of 23.1 percentage points (95% CI: 5.4–40.8 percentage points), which is markedly higher for the PIA intervention than the estimated difference of 15% used a priori to calculate the number of cases. The covariates age, sex, and concomitant disease (coronary disease/myocardial infarction) had no influence. Additional analysis showed that BP control rates at follow-up did not differ between urban and rural practices. A bootstrapping with 1000 replications for the systolic SPB (control group) showed a minimum difference in standard errors of the means between the descriptive data and the bootstrapping sample (0.96 vs. 0.98). The bootstrapping confidence interval ranged from 135.86 to 139.67 and did not include the mean of 134.28 from the intervention group.

In a sensitivity analysis, the mean of the results of both BP measurements instead of the results of the second BP measurement alone was in line with the prior result: the odds ratio for the intervention arm was 2.59 (95% CI: 1.35–4.96, $p = 0.004$). For Details, see Table 5.

The validity of the practice BP readings was ensured by comparing the second home and the second practice BP readings at follow up (intervention group only). The measured difference in SBP of 4.85 mmHg (mean home: 129.45 [SD 12.27]; mean practice: 134.3 [SD 14.5] is in agreement with the expected difference between home and practice readings of 5 mmHg reflected in the target values for home and office readings.[16] The difference for the second DBP was 0.34 mmHg (mean home: 82.76 [SD 9.26]; mean practice: 83.1 [SD 9.7]).

At baseline, the mean SBP was 155.4 mmHg in the intervention group and decreased to 134.3 mmHg at follow up. In the control group, baseline SBP was 153.5 mmHg and follow up SBP was 137.8 mmHg. SBP decreased by 21.1 mmHg in the intervention and 15.5 mmHg in the control group.

There were no differences in the frequencies of hospital and/or emergency department and/or emergency service visits between the study arms. Also, the number of serious cardiovascular events (stroke, myocardial infarction, heart failure, renal failure, death) with a need for hospital or emergency service did not differ. For details, see Table 6. Patients receiving the PIA intervention were significantly more satisfied with their BP treatment than patients in the control arm: in the intervention arm, 89.4% of patients rated it as good to excellent, while in the control arm this was significantly lower at 79.5% (χ^2; $p < 0.001$).

Medication changes: The number of drugs and drug categories did not differ significantly between intervention and control group at baseline, but at follow up. The number of patients with a thiazide antihypertensive was significantly higher in the intervention than the control group at follow up ($p = 0.001$). For details, see Table 7.

Utilization of PIA-ICT: The PIA communication tool was frequently used by patients and practices. On average, 10.59 medication plans were transferred to patients (SD 11.25; median 8; min–max 0–48). A mean of 249.79 blood pressure readings were transmitted from patients to practices (SD 228.90; median 164.0; min–max 0–1138). On average 3.71 chats were sent from patients to practices (SD 7.95; median 1.0; min–max 0–91), while practices sent 6.93 messages (SD 8.87; median 3.0, min–max 0–49). These messages included automated ones indicating a new medication plan. For details, see Table 8.

Satisfaction with the PIA-Intervention: Patients scored their satisfaction with the PIA app as 1.76 [SD: 2.00] on a five-point scale (1 = very good to 5 = poor). GPs rated the PIA-PrMC as 1.88 [SD: 0.50] and the PrAs as 1.98 [SD: 0.66] using the same scoring system.

Discussion

This cluster-randomised controlled trial of the PIA-ICT for hypertension management showed a significant improvement of BP control rates after 6–12 months (adjusted: +23.1%). The finding of this complex intervention is in line with prior studies of various IT-supported hypertension management systems.[6,7,10] However, our PIA system differs from the other systems in several features. First, the IT set-up was developed with the participation of the end users (GPs, PrAs, patients) which led to a thorough understanding and design of the IT-supported care processes, e.g., electronic transmission of the full medication plan from the EHR with antihypertensives and all other

	Baseline			Baseline with complete follow-up data		
	All (N = 636)	Intervention group (n = 331)	Usual care group (n = 305)	All (N = 525)	Intervention group (n = 265)	Usual care group (n = 260)
Social demographic characteristics						
Sex, N (%)						
Women	301 (47.3%)	150 (45.3%)	151 (49.5%)	248 (47.2%)	119 (44.9%)	129 (49.6%)
Man	335 (52.7%)	181 (54.7%)	154 (50.5%)	277 (52.8%)	146 (55.1%)	131 (50.4%)
Age, mean (SD)	58.0 (9.2)	56.9 (8.7)	59.2 (9.7)	59.4 (9.7)	57.7 (8.7)	58.6 (9.2)
Marital status, N (%)						
Married or cohabiting	411 (64.7%)	213 (64.4%)	198 (64.9%)	347 (66.1%)	178 (67.2%)	169 (65.0%)
Divorced or separate living	84 (13.2%)	43 (13.0%)	41 (13.4%)	72 (13.7%)	32 (12.1%)	40 (15.4%)
Widowed	38 (6.0%)	17 (5.1%)	21 (6.9%)	35 (6.7%)	17 (6.4%)	18 (6.9%)
Single	69 (10.8%)	38 (11.5%)	31 (10.2%)	50 (9.5%9	26 (9.8%)	24 (9.2%)
Missing data	34 (5.3%)	20 (6.0%)	14 (4.6%)	21 (4.0%)	12 (4.5%)	9 (3.5%)
School graduation, N (%)						
No school graduation	26 (4.1%)	13 (3.9%)	13 (4.3%)	23 (4.4%)	11 (4.2%)	12 (4.6%)
Finished 9th grade	206 (32.3%)	98 (29.5%)	108 (35.5%)	185 (35.2%)	89 (33.6%)	96 (36.9%)
Finished 10th grade	178 (28.0%)	103 (31.0%)	75 (24.7%)	147 (28.0%)	81 (30.6%)	66 (25.4%)
Finished 12th grade	50 (7.9%)	25 (7.6%)	25 (8.2%)	38 (7.2%)	21 (7.9%)	17 (6.5%)
High school diploma	126 (19.8%)	63 (19.0%)	63 (20.7%)	103 (19.6%)	48 (18.1%)	55 (21.2%)
Graduated from other schools	14 (2.2%)	8 (2.4%)	6 (2.0%)	6 (1.1%)	2 (0.8%)	4 (1.5%)
Missing data	36 (5.7%)	25 (7.6%)	11 (3.6%)	23 (4.4%)	13 (4.9%)	10 (3.8%)
Occupation, N (%)						
Working	347 (54.6%)	196 (59.2%)	151 (49.5%)	280 (53.3%)	153 (57.7)	127 (48.8)
Retired	171 (26.9%)	75 (22.7%)	96 (31.5%)	155 (29.5%)	71 (26.8%)	84 (32.3%)
In early retirement	12 (1.9%)	7 (2.1%)	5 (1.6%)	11 (2.1%)	6 (2.3%)	5 (1.9%)
Searching for work	20 (3.1%)	12 (3.6%)	8 (2.6%)	16 (3.0%)	8 (3.0%)	8 (3.1%)
Housewife or househusband	27 (4.2%)	12 (3.6%)	15 (4.9%)	21 (4.0%)	8 (3.0%)	13 (5.0%)
Not working	23 (3.6%)	9 (2.7%)	14 (4.6%)	19 (3.6%)	7 (2.6%)	12 (4.6%)
Missing data	36 (5.7%)	20 (6.0%)	16 (5.2%)	23 (4.4%)	12 (4.5%)	11 (4.2%)
General health status, N (%)						
Excellent	6 (0.9%)	2 (0.9%)	4 (1.3%)	5 (1.0%)	1 (0.4%)	4 (1.5%)
Very good	53 (8.3%)	25 (8.3%)	27 (8.9%)	45 (8.6%)	21 (7.9%)	24 (9.2%)
Good	347 (54.4%)	175 (54.8%)	172 (56.5%)	290 (55.2%)	142 (53.6%)	148 (56.9%)
Less good	155 (24.3%)	91 (24.4%)	64 (21.0%)	129 (24.6%)	74 (27.9%)	55 (21.2%)
Bad	25 (3.9%)	12 (3.6%)	13 (4.3%)	22 (4.2%)	10 (3.8%)	12 (4.6%)
Missing data	50 (8.2%)	26 (7.9%)	24 (7.9%)	34 (6.5%)	17 (6.4%)	17 (6.5%)
Blood pressure, mean (SD)						
SBP (mmHg), M1	156.9 (14.8)	157.8 (16.2)	155.9 (13.1)	156.9 (14.5)	158.5 (16.4)	155.2 (12.2)
DBP (mmHg), M1	93.7 (9.6)	94.8 (9.8)	92.5 (9.3)	93.6 (9.7)	94.5 (10.1)	92.6 (9.3)
SBP (mmHg), M2	154.1 (14.1)	154.7 (15.7)	153.5 (12.1)	154.4 (13.8)	155.4 (15.7)	153.3 (11.6)
DBP (mmHg), M2	93.1 (9.6)	94.6 (9.8)	91.5 (9.1)	93.0 (9.8)	94.4 (10.2)	91.6 (9.1)
Coronary heart disease and/or myocardial infarction, N (%)						
Without coronary heart disease or myocardial infarction	529 (83.2%)	280 (84.5%)	249 (81.6%)	429 (81.7%)	217 (81.9%)	212 (81.5%)
With coronary heart disease and/or myocardial infarction	107 (16.8%)	51 (18.4%)	56 (18.4%)	96 (18.3%)	48 (18.1%)	48 (18.5%)
Current smoker, N (%)	160 (25.2%)	86 (26.0%)	74 (24.3%)	131 (25.0%)	68 (25.7%)	63 (24.2%)

BP M1 = first measurement after 5 min rest; BP M2 = second measurement after 1 min; DBP = Diastolic blood pressure; SBP = Systolic blood pressure.

Table 2: **Patient characteristics at baseline (n = 636) and at baseline with complete follow-up data (n = 525).**

medications, use of different colours for GPs' and PrAs' tasks, options for individual adjustments by GPs on all levels (BP targets, medication algorithms, medication dosing), easy to use app design manageable also by the elderly. Following Yardley's framework for person-based approaches to intervention development, the three user groups (patients, GPs, PrA) were involved repetitively in intervention development.[19] This participatory approach

	All (N = 525)	Intervention group (n = 265)	Usual care group (n = 260)	P value[a]
SBP (mmHg), M1, mean (SD)	138.6 (17.3)	136.0 (16.4)	141.3 (17.8)	<0.001
Controlled SBP (mmHg), M1, N (%)	282 (53.7%)	173 (65.3%)	109 (41.9%)	<0.001
DBP (mmHg), M1, mean (SD)	84.5 (11.0)	84.1 (10.9)	84.9 (11.1)	0.40
Controlled DBP (mmHg), M1, N (%)	361 (68.8%)	194 (73.2%)	167 (64.2%)	0.03
SBP (mmHg), M2, mean (SD)	136.0 (15.1)	134.3 (14.5)	137.8 (15.5)	0.01
Controlled SPB (mmHg), M2, N (%)	323 (61.5%)	192 (72.5%)	131 (50.4%)	<0.001
DBP (mmHg), M2, mean (SD)	83.3 (10.1)	83.1 (9.7)	83·4 (10.6)	0.73
Controlled DBP (mmHg), M2, N (%)	387 (73.7%)	206 (77.7%)	181 (69.6%)	0.04
BP, M1, N (%)	242 (46.1%)	149 (56.2%)	93 (35.8%)	<0.001
Primary endpoint: BP M2, N (%)	282 (53.7%)	166 (62.6%)	116 (44.6%)	<0.001

BP M1 = first measurement after 5 min rest; BP M 2 = second measurement after 1 min; DBP = Diastolic blood pressure; SBP = Systolic blood pressure. [a]z-Test.

Table 3: **BP measurements at follow-up (unadjusted) (n = 525).**

is reflected in the high acceptance of the system as indicated by the high frequencies of use as well as all users' evaluations. To our knowledge, the publication of such data on utilisation is new and not available for the other IT-supported hypertension management systems. Second, the PIA setup with the secure communication between the patients' PIA app and the PIA-PrMC is novel and much easier for practices and patients to use than logins onto separate platforms. Hammerslay et al., 2020[13] partially addressed this issue by implementing an automated import of BP results into EHRs from the third-party website. Third, we did not use automated BP transmission from the BP monitor device to the electronic platform (e.g., by Bluetooth) as nicely used in the studies of Margolis,[6] McKinstry[10] and McManus,[8] because such BP monitors are more costly and not financed by the statutory health insurance in regular care, which we aimed to reflect as closely as possible. However, the proximity of the first and the second BP measurements in our study indicates that the documentation in the PIA app were easily manageable for patients. Fourth, both the standardisation and individualisation of hypertension management is a challenge for the design of clinical IT systems. To decrease

	Odds ratio	95%-CI	P value
(Intercept)	0.38	0.17–0.81	0.01
Study arm			
Usual care arm (reference)			
Intervention arm	2.57	1.23–5.37	0.01
Age			
40–49 years (reference)			
50–59 years	1.16	0.66–2.03	0.61
60–69 years	1.09	0.59–2.03	0.73
70–79 years	1.38	0.69–2.97	0.34
Sex			
Women (reference)			
Man	1.07	0.67–1.84	0.78
Comorbidities			
Without coronary heart disease and/or myocardial infarction (reference)			
With coronary heart disease and/or myocardial infarction	0.78	0.45–1.34	0.36
Recruiting duration			
Recruiting (first quarter to fourth quarter in 2020) (reference)			
Recruiting (first quarter in 2021)	1.67	0.97–2.88	0.07
Blood pressure (Baseline, M2)			
SBP, mmHg	0.98	0.96–0.99	0.00
DBP, mmHg	0.99	0.97–1.02	0.57

BP M 2 = second measurement after 1 min; DBP = Diastolic blood pressure; SBP = Systolic blood pressure. Statistical measures: Variance of random effects (practice ID) $\tau 00$ = 0.86 (SD: 0.88). Intra-cluster correlation coefficient ICC = 0.21.

Table 4: **GLMM model of primary endpoint.**

	Odds ratio	95%-CI	P value
(Intercept)	0.40	0.2–0.81	0.01
Study arm			
Usual care arm (reference)			
Intervention arm	2.59	1.35–4.96	0.00
Age			
40–49 years (reference)			
50–59 years	1.12	0.66–1.91	0.67
60–69 years	1.01	0.56–1.81	0.98
70–79 years	1.1	0.55–2.19	0.78
Sex			
Women (reference)			
Man	1.09	0.74–1.6	0.66
Comorbidities			
Without coronary heart disease and/or myocardial infarction (reference)			
With coronary heart disease and/or myocardial infarction	0.89	0.53–1.49	0.66
Recruiting duration			
Recruiting (first quarter to fourth quarter in 2020) (reference)			
Recruiting (first quarter in 2021)	1.58	0.95–2.62	0.08
BP (Baseline), mean M1/M2			
SBP, mmHg	0.98	0.96–0.99	0.00
DBPe, mmHg	0.99	0.97–1.01	0.48

BP M1 = first measurement after 5 min rest; BP M2 = second measurement after 1 min; DBP = Diastolic blood pressure; SBP = Systolic blood pressure. Statistical measures: Variance of random effects (practice ID) τ00 = 0.66 (SD: 0.81). Intra-cluster correlation coefficient ICC = 0.17.

Table 5: **Sensitivity analysis: GLMM model of the primary endpoint using the mean of the first and second BP readings.**

	All (N = 525)	Intervention group (n = 265)	Usual care group (n = 260)	P value[a]
Treatments in hospital and/or emergency department: frequency of treatments and number of serious cardiovascular events				
Number of inpatient treatments, n (%)	58 (11.0%)	23 (8.7%)	35 (13.5%)	0.10
One hospital treatment	45 (8.6%)	19 (7.2%)	26 (10%)	
Two hospital treatments	9 (1.7%)	3 (1.1%)	6 (2.3%)	
Three hospital treatments	3 (0.6%)	0 (0.0%)	3 (1.2%)	
Inpatient treatment without frequency indication)	1 (0.2%)	1 (0.4%)	0 (0.0%)	
Number of emergency treatments, n (%)	39 (7.4%)	16 (6.0%)	23 (8.8%)	0.21
One emergency treatment	32 (6.2%)	13 (4.9%)	19 (7.2%)	
Two emergency treatments	4 (0.8%)	3 (1.1%)	1 (0.4%)	
Emergency treatment (without frequency indication)	3 (0.6%)	0 (0.0%)	3 (1.2%)	
Number of major cardiovascular events (hospitalizations), n (%)	21 (4.0%)	12 (4.5%)	9 (3.5%)	0.14
Myocardial infarction	4 (0.8%)	1 (0.4%)	3 (1.2%)	
Stroke	3 (0.6%)	3 (1.1%)	0 (0.0%)	
Other cardiovascular events	14 (2.6%)	8 (3.0%)	6 (2.3%)	
Cardiovascular events (emergency treatment), n (%)	12 (2.3%)	9 (3.4%)	3 (1.2%)	0.45
Myocardial infarction	1 (0.2%)	1 (0.4%)	0 (0.0%)	
Stroke	3 (0.6%)	3 (1.1%)	0 (0.0%)	
Blood pressure derailing	4 (0.8%)	2 (0.8%)	2 (0.8%)	
Other cardiovascular events	4 (0.8%)	3 (1.1%)	1 (0.4%)	

SD = standard deviation. [a]Chi-Square-Test.

Table 6: **Treatments in hospital and/or emergency department or emergency service: frequency of treatments and number of serious cardiovascular events (stroke, myocardial infarction, heart failure, renal failure, death) with inpatient or emergency outpatient treatment at follow up.**

	Baseline (N = 492)		P value[a]	Follow-up (N = 501)		P value[a]
	Intervention (n = 248)	Usual care (n = 244)		Intervention (n = 244)	Usual care (n = 257)	
Number of antihypertensives, mean (SD)	2.09 (1.07)	2.04 (1.15)	0.37	2.42 (1.26)	2.19 (1.19)	0.05
Number of prescribed drug classes, mean (SD)	1.75 (0.94)	1.65 (0.88	0.34	2.42 (1.14)	2.20 (1.09)	0.04
Without antihypertensives, N (%)	13 (5.3%)	15 (6.1%)		3 (1.2%)	4 (1.6%)	
One drug class, N (%)	98 (39.5%)	101 (41.4%)		54 (22.1%)	78 (30.4%)	
Two drug classes, N (%)	87 (35.1%)	87 (35.7%)		79 (32.4%)	73 (28.4%)	
Three drug classes, N (%)	39 (15.7%)	36 (14.8%)		64 (26.2%)	72 (28.0%)	
Four drug classes, N (%)	11 (4.4%)	5 (2.0%)		34 (13.9%)	24 (9.3%)	
Five drug classes, N (%)	0 (0.0%)	0 (0.0%)		10 (4.1%)	6 (2.3%)	
Drug classes						
ACE-inhibitors and angiotensin receptor blockers, N (%)	222 (89.5%)	208 (85.2)	0.15	220 (90.2%)	221 (86.0%)	0.15
Beta-blockers, N (%)	116 (46.8%)	107 (43.9%)	0.52	109 (44.7%)	116 (45.1%)	0.92
Calcium channel blockers, N (%)	104 (41.9%)	94 (38.5%)	0.44	123 (50.4%)	117 (45.5%)	0.27
Thiazid diuretics, N (%)	71 (28.6%)	57 (22.0%)	0.18	92 (37.7%)	62 (24.1%)	0.00
Others, N (%)	36 (14.5%)	44 (18.0%)	0.29	46 (18.9%)	50 (19.5%)	0.86

[a]Mann-Whitney-U-Test.

Table 7: **Medication changes.**

the number of antihypertensives according to guidelines, we had initially restricted the list to the 98% most frequently prescribed antihypertensive drugs. However, the reactions of the GPs led us to include even rarely used drugs. Thus, our system was designed to guide an evidence-based path but was simultaneously open fully to adjustments, e.g., in BP targets, medications used and uptitration steps. In contrast to studies by McManus who used paper-based, self-uptitration of BP medication with GP contact after two changes,[8,9] we continuously used physician-initiated uptitration via the ICT. Fifth, our ICT successfully realized a delegation model to PrAs who have a certified vocational training without prescribing privileges, while nurses and clinician pharmacists were involved in care processes from the US, England and Scotland.[6,9,13] Sixth, the transfer of medication plans from the EHR is an important step towards the safe digitalisation of care processes as it prevents transcription errors; this was not applied in prior studies. However, further developments towards even better IT support of hypertension care processes are needed, e.g., artificial intelligence (AI)-supported management including a substitution of delegation models by AI-supported processes, block chain technologies for large scale data protection, full integration of data and processes in EHRs.[13,20] Given the magnitude of the care problem presented by uncontrolled hypertension, systems need to be as simple and reliable as possible to address the populations in need of better care.

This cluster-randomised controlled trial was successfully conducted during the pandemic, although follow up and support of practices and patients required additional time and effort of the study team. The primary outcome was initially based on the mean of the second and third standardised BP reading, but the pandemic forced us to rely on the second measurement only to reduce contact times. Although this approach differs from other studies, the difference is 0–1 mmHg according to an analysis of the NHANES data.[17] As this systematic bias applies to both the intervention and the

	Intervention arm (N = 265)		
	Mean (SD)	Median (IQR)	Min-max
Frequency of use of the PIA ICT by patients and practices			
Number of messages from practice to patient	6.93 (8.87)	3.0 (1.0; 9.0)	0–49
Number of messages from patient to practice	3.71 (7.95)	1.0 (0.0; 4.5)	0–91
Number of transmitted blood pressure values	249.79 (228.901)	164.0 (86.0; 353.0)	0–1138
Number of medication plans sent to patient	10.59 (11.25)	8.0 (1.0; 16.0)	0–48

IQR = interquartile range; SD = standard deviation.

Table 8: **Frequency of use of the PIA ICT.**

control arm, it does not impair the study results. Our sensitivity analyses indicate that patients reliably used a resting position even when the first reading was taken. As 2/3 of smart devices in Germany are android based, the PIA app was developed for this operating system.[21] However, a PIA app for iOS devices is currently being developed. For long-term benefit, the development of the PIA app for iOS devices is currently in the planning process. Although patients self-recording of BPs in the app has the potential for errors, the closeness of the first and second readings recorded does not indicate a problem. Long-term success will need to be evaluated. It is difficult to determine which components of the complex PIA intervention contributed to the final result.

The planned case number for the analyses of 600 patients (300 per study arm) was just not achieved. The recruitment period actually coincided with the outbreak of the Corona pandemic, resulting in a significant burden on GP practices caused by uncertainty and increased workload. This was compounded by patient fears that led to routine visits to the primary care physician's office being avoided. Nevertheless, 525 patients could be included in the analyses. Although the target sample size was not fully reached due to the pandemic, the improved BP can be considered an effect of the intervention but not chance as shown by the additional bootstrapping analysis. The PIA intervention lowered SBP by 6.1 mmHg systolic which is outcome-relevant according to large cohort studies with decreased morbidity and mortality already after SBP reductions of 3 mmHg.[22,23]

Our IT-supported hypertension management PIA with several novel features significantly improved BP control rates and was well accepted by professionals and patients.

Contributors

B.W. had the study idea. B.W., A.K., and F.L. developed the study protocol, detailed the methodology and administrated the project. B.W., A.K. and F.L. developed the intervention materials supported by F.D. und K.K. A.K., F.L., F.D. and K.K. conducted the intervention. T.G. and T.B. verified and analysed the data. A.K., F.L. and B.W. drafted the first version of the manuscript. All authors provided feedback on the manuscript and approved the final version. All authors had access to the data and were responsible for the decision to submit for publication.

Data sharing statement

Data collected for this study will be made available deidentified data with publication upon reasonable written request to the corresponding author. The study protocol is published: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05660-4.[15]

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101712.

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