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REVIEW

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Implementation of smart technology to improve medication adherence in patients with cardiovascular disease: is it effective?

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ABSTRACT

Introduction: Medication adherence is of key importance in the treatment of cardiovascular disease. Studies consistently show that a substantial proportion of patients is non-adherent.

Areas covered: For this review, telemedicine solutions that can potentially improve medication adherence in patients with cardiovascular disease were reviewed. A total of 475 PubMed papers were reviewed, of which 74 were assessed.

Expert commentary: Papers showed that evidence regarding telemedicine solutions is mostly conflictive. Simple SMS reminders might work for patients who do not take their medication because of forgetfulness. Educational interventions and coaching interventions, primarily delivered by telephone or via a web-based platform can be effective tools to enhance medication adherence. Finally, it should be noted that current developments in software engineering may dramatically change the way non-adherence is addressed in the nearby future.

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KEYWORDS
e-Health; medication adherence; medication reminders; prevention; mobile phones; smart pill boxes

1. Introduction

Over the past decades, advantages in pharmacological treatment have dramatically improved the prognosis of patients with cardiovascular disease (CVD). Multiple randomized controlled trials (RCTs) have shown a significant decrease in mortality in patients after acute myocardial infarction using beta-blockers [1], angiotensin-converting enzyme (ACE) inhibitors [2], and statins [3] on a daily basis. Also in patients with heart failure, the introduction of numerous drugs has improved prognosis significantly [4,5]. In patients with atrial fibrillation, new oral anticoagulants have decreased the risk of developing stroke [6,7]. A recent trial showed that new oral anticoagulants may also decrease the risk of developing acute myocardial infarction in patients with stable coronary artery disease [8]. Moreover, cholesterol-lowering medication has significantly lowered the risk of recurrent adverse cardiovascular events [9–14]. However, for treatment to be successful, patients have to adhere to their daily intake of medication [15]. However, several publications have shown that this is often not the case and compliance rates are in general low and partly depend on the medication taken [16–19]. Low adherence to intake of medication is associated with higher mortality rates than if patients do adhere to prescribed daily intake schemes. However, causality could not be confirmed as this was a retrospective study. The authors acknowledge that patients who take medication consistently are different from patients that do not in other risk factors for mortality [20].

Ever since the introduction of the iPhone in 2007, it has been recognized as a potential tool to improve healthcare delivery and improve outcomes [21–24]. Smart technology solutions have been developed and investigated for the improvement of medication adherence in various patient populations [22]. These solutions are characterized by using technology, predominantly smartphones, tablets, and/or computers, to remotely monitor and/or coach patients to be more adherent [25]. Advantages of using these systems are the relatively low costs of these systems, the use of existing infrastructure (such as smartphones), and the ease of use [26]. It is the primary purpose of this paper to discuss telemedicine interventions that have been investigated in an experimental design with the goal to improve medication adherence in patients with CVD who take medication orally for more than 180 days consecutively. This period of days was chosen to enhance the chance that patients were taking medication chronically.

2. Methods

2.1. Article selection and categorizing

A search strategy was developed by an experienced librarian (JS). The search strategy was developed using patients-interventions-comparison-outcomes. The patient population was defined as patients that had a CVD or and were, as a consequence of their CVD, taking medication orally for 180 consecutive days or more. The intervention was defined as any

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Table 1. Inclusion and exclusion criteria.

Inclusion criteria
All papers that were shown in PubMed as result of the search strategy given in the Appendix
Exclusion criteria
The study does not describe a randomized controlled trial
Medication adherence is not listed among the primary or secondary outcomes in the Section 2
The solution described does not involve one of the following items: a computer, smartphone, tablet, or Internet
The study is not concerned with patients taking medication orally
Paper is not written in English and no English translation is available
Survey papers

remote intervention targeting medication adherence. This could be compared to either regular follow-up, a non-digital intervention, or another digital intervention. The outcome of the trial had to be medication adherence, either measured by a questionnaire (e.g. Morisky MMAS-8) or by pharmacy claim data. For this strategy, only articles describing the results of a RCT were included in the paper selection that served as the basis for this review. The complete search strategy is presented in the Appendix. For this paper, a PubMed search was carried out. Of the resulting papers, titles and abstracts were screened by one of the investigators (RT) and papers not matching the inclusion criteria or matched the exclusion criteria were excluded. These inclusion and exclusion criteria are given in Table 1. Briefly, papers that did not describe a RCT, only described the rationale and design of a RCT, articles not written in English, articles not including medication adherence as primary or secondary outcome, or articles not specifically designed to address medication adherence were excluded. In case of doubt, the full text was evaluated, and after reading of the full text, it was decided whether the paper could be included. After the selection, articles were divided into subcategories, based on the technology the intervention was delivered with (Table 2). These categories were mobile applications, short message service (SMS), smart pill boxes, web-based interventions (e-Learning), and telephone calls (Figure 1). Per category, a qualitative overview of the existing literature is given in the Section 3.

For this review, mobile applications were defined as an intervention delivered by an application on a mobile phone with iOS or Android OS as operating system. SMS interventions were defined as any intervention that used SMS to deliver content to the patient. Smart pill boxes were defined as boxes for medication that are equipped with a timer, alarm clock, or are Bluetooth enabled and that register whether the medication box has been opened or not. Web-based interventions were defined as any content that was delivered to the patient via a web browser or data delivered from the patient to the hospital via a web browser. Finally, telephone interventions were defined as coaching, reminders to take medication, or education delivered via the telephone. Papers were classified in one of the categories by one of the authors (RT).

3. Results

3.1. Paper selection

The search strategy, executed on September 15, 2017, yielded 475 hits in PubMed. Of these 475 papers, 401 were not further assessed for this study. Reasons for exclusion were only describing the rationale and design of an RCT (100/401), RCTs not being primarily concerned with medication adherence (95/401), not describing an RCT at all (93/401), papers describing a systematic review (28/401), papers of which no full text could be retrieved (27/401) or narrative review (17/401), targeting healthcare professionals (15/401), not describing an telemedicine solution to improve medication adherence (11/401), papers not in English (9/401), papers describing a cost-effectiveness analysis (5/401), and papers that described results from a previously published RCT ('salami slicing', 1/401).

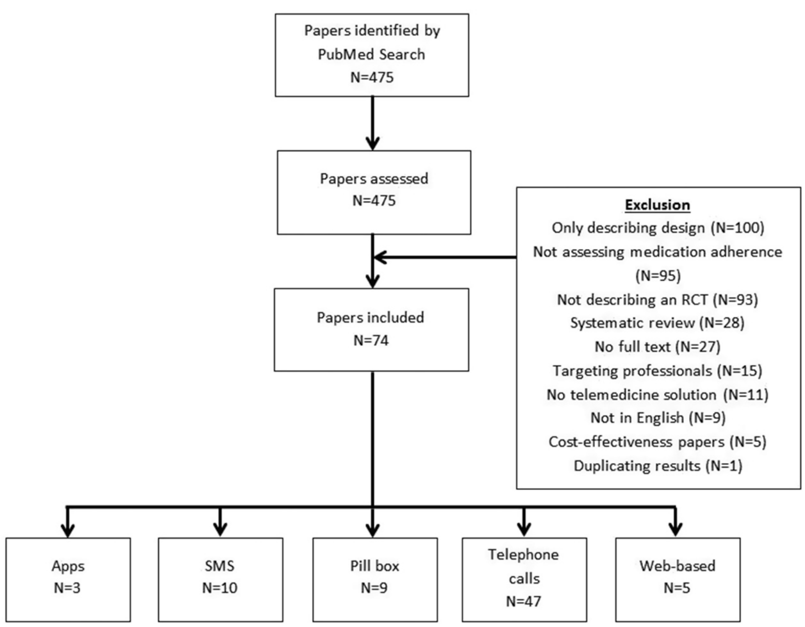

Figure 1. Flow of the inclusion and classification of the papers.

Papers that were included predominantly described phone interventions (47/74). Other interventions that were described were SMS based (10/74), smart pill boxes (9/74), web-based interventions (5/74), or mobile apps (3/74).

3.2. Mobile app

The number of mobile apps has skyrocketed after the initiation of commercial sales of the iPhone in 2007 [27]. Currently, there are over 150,000 health apps available for download in the different App Stores [28]. Some of them address medication adherence and have been tested in RCTs. In a multicenter study by Johnston et al. [29], 174 ticagrelor-treated myocardial infarction (MI) patients were randomized to either an interactive patient support tool (app) or control. The smartphone app gave patients the possibility to log their medication intake. A reminder SMS was send in case a patient forgot to take his medication. Furthermore, patients received educational messages about the benefits of ticagrelor after MI. At 6 months, larger patient-registered drug adherence was found in the active compared to the control group [non-adherence percentages (based on self-reported medication intake): 16.6% vs. 22.8%, P = 0.025] (Table 2) [29].

Another clue that mobile apps with educational purposes might work is found in a pilot study by Guo et al. [30]. In total, 113 patients in the treatment group received the 'mAF' (mobile app atrial fibrillation) app versus 96 patients in the control group (usual care). The app educated patients about their condition and the importance of drug intake. Furthermore, patients could record vital signs with their app. Primary outcome was drug adherence measured with the Pharmacy Quality Alliance adherence (a questionnaire for patients to fill in). Scores were 0 (indicating low risk of non-adherence) in the intervention group and 4 in the control group (indicating moderate risk of non-adherence). Drug adherence was therefore significantly better in the group of patients using the app [30].

A very promising technology using mobile technology is described in a small study by Labovitz et al. [31] They randomized patients with ischemic stroke, who received anticoagulant therapy, to an Artificial Intelligence (AI) platform group (n = 15) or control group (n = 13). The AI platform recognized the patient via the smartphone camera with face recognition. Subsequently, the actual ingestion of medication could be recognized and confirmed. The interesting part of using this technology is that it can confirm the actual ingestion of the pill. If an ingestion was not registered, the app gave an automated reminder. Patients randomized to the treatment group received mobile devices with the AI app to provide medication reminders and dosing instructions. Medication adherence based on measured plasma levels was 100% in treatment group and only 50% in control group [31].

Table 2. Summary of the results per technology.

Mobile apps	Mobile apps with educational content might enhance medication adherence. Artificial intelligence is a promising technology.
Smart pill boxes	Evidence regarding the use of smart pill boxes is conflictive. More research needs to be done to pinpoint which interventions using smart pill boxes result in better medication adherence .
Short message service	Short message services seems a good technology for simple medication reminders.
Telephone calls	Telephone calls are effective if they are made by a human being. Automated phone calls show little improvement. Interactive voice recording might be a promising technology.
Web-based interventions	Web-based tools are relatively cheap and therefore an interesting technology. E-Learnings might be beneficial because patients are better informed.

3.3. Smart pill boxes

Smart pill boxes, also called 'electronic medication-packaging devices' [32], are devices meant for packaging of medication that are equipped with a timer, alarm clock, or are Bluetooth enabled and that register whether the medication box has been opened or not. A criticism of these smart pill boxes is that opening of the box does not confirm the actual ingestion of the pill. There are several RCTs that have investigated the effectiveness of these smart pill boxes. Evidence regarding the effect on medication adherence is however conflicting. Three RCTs have found no statistically significant difference in medication adherence. In a study in 1509 post-acute coronary syndrome patients randomized in a 2:1 fashion to electronic pill bottles and social support (N = 1003) or to usual care (N = 506), medication adherence (based on pharmacy claim data) was found not statistically different between the two groups. Furthermore, no statistically significant differences were found between study arms in time to first hospitalization for vascular events or death, or other outcomes [33]. Choudry et al. [32] performed a four-arm four- block-randomized clinical trial in 53.480 enrollees, patients who were using 1–3 different drugs daily. Patients were randomized to receive a pill bottle with toggles, digital timer cap or a standard pill box, or no device (= control). No statistically significant difference was found in medication adherence (based on pharmacy claim data) between control and any of the treatment groups. One of the conclusions of the authors was that devices may have been more effective if coupled with interventions to ensure consistent use. In a multicenter RCT, Kooy et al. [34] studied medication adherence (based on pharmacy claim data) in three patient groups on lipid-lowering medication (statin): smart pill box with reminder system with counseling, smart pill box with reminder system alone, and control (no smart pill box). Results: proportions of adherent patients in both smart pill box groups (69.2%/72.4%) were not statistically higher than in the control group (64.8%) [34].

Two other trials suggest that electronic pill bottles might be beneficial: in one RCT, 150 patients with either hypercholesterolemia, hypertension, or diabetes mellitus were randomized to medication blisters, capable of tracking dosage and timing of medication intake or regular care. There was a statistically significant difference (P = 0.04) in intake of metformin, but no significant difference was found for the other drugs [35]. One trial that showed a significant difference was performed by McKenney et al. [36]. The study population consisted of 70 patients, randomly divided into two groups (phase 1), and then in four groups (phase 2). In phase 1, patients received medication either in vials with time cap, or standard cap. In phase 2, the four groups were A (control):

standard vial; B: vials with timepiece cap; C: same as B, but this group also received tools to record blood pressure (BP) at outpatient clinic visit; D: same as B, but with home BP measurements. In phase 1, the patients in the intervention group had significantly better adherence and significant reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP). In phase 2, patients were even higher significant compliance in groups C and D compared to control. However, there were no further improvements in SBP and DBP [36].

3.4. Short message service

SMS was developed in the 1980s. It was designed to send small size message over the mobile telephone system. The first SMS was sent in 1992 [37]. After the commercial implementation of SMS, RCTs investigating its application for medication adherence were published. The RCTs use the same technology, but vary in the way they implement SMS [38–40]. Several RCTs used a SMS intervention in which they sent a SMS on a fixed time with a fixed text. The SMS was a general reminder to the patient to take his medication. Multiple trials demonstrated a positive effect on medication adherence using this intervention. Of the 10 trials in our study, 9 [38–45] show an increase in medication adherence, while 1 [46] shows no difference in medication adherence. However, these trials all assess short-term outcomes. This is problematic because the effect of simple reminders might decrease over time as messages might become boring and repetitive to patients [38]. Moreover, the intervention only addresses one barrier to adequate medication adherence, namely the patient purely forgetting to take their prescribed medication. Interestingly, one trial did compare a more sophisticated way of implementing SMS with simple reminders. The 'Mobile Phone Text Messages to Support Treatment Adherence in Adults With High Blood Pressure (StAR)' [45] trial randomized 1372 patients with hypertension in a 1:1:1 ratio to either interactive SMS, information-only SMS, or usual care. The information-only group received general reminders to take medication, whereas the interactive SMS group was able to SMS back to the research team, call the research team, and ask specific medication-related questions. Primary outcome was change in systolic BP after 12 months. The SMS-information-only group was superior to usual care (ΔSBP −2.2 mmHg). Interestingly, there was no difference between the interactive SMS group and the SMS-information-only group. Although these were the results of only one RCT, they might indicate that SMS is in general unfit to serve as an interactive way of communicating and that other technologies, most notably telephone and web-based interventions, are necessary to fully benefit from a two-way communication [45].

3.5. Telephone calls

Telephone calls have been subject for RCTs since the early 1980s. Although the technology is straightforward and easy to use, the RCTs conducted with this technology show significant interstudy variability regarding patient population, implementation of the technology, and outcome assessment. Phone calls can vary from simple, automated reminders to the patient to take their medication to coaching programs via telephone. In various trials, coaching or educating interventions via telephone have been investigated [47–50]. In these RCTs, patients were randomized between a telephone-based intervention or control. The telephone-based intervention consisted of a nurse calling patients to either coach or educate patients. Coaching patients generally consisted of taking medication according to prescription or addressing barriers to adequate medication intake. Education generally consisted of the nurse educating the patients about the condition they were given medication for and the importance of adequately taking the medication. RCTs generally show an increase in medication adherence in the intervention group compared to the control group. Coaching, especially motivational interviewing, has been proven to improve medication adherence in various patient populations [51]. The disadvantage of a nurse-led intervention is that it is labor intensive and relatively costly [26].

Another, less labor-intensive way is automated phone calls, in which the call is initiated by a computer system. The voice can either be a computer voice or a human voice that is recorded previously. The important difference between automated phone calls and calls by healthcare professionals is the lack of interaction in the former. One RCT has compared the effectiveness of automated and in-person phone calls [52]. This trial randomized patients who used a certain commercial pharmacy chain to pick up their prescriptions. Patients of which a prescription was received but not purchased within 8 days were randomized. The control group received no intervention, whereas the intervention group first received two automated phone calls and then one in-person phone call. The RCT found no difference in adherence from the automated phone calls, but found a significant and positive difference in the in-person phone calls group [52]. This RCT provides evidence that human interaction in telephone interventions may be more effective than automated, computer-initiated phone calls.

An interesting technology that, at least partly, overcomes the drawbacks of automated phone calls is interactive voice recognition (IVR). In this technology, the receiver of a call can interact with the computer via speech recognition or input on the keypad. In the RCT study by Vollmer et al. [53], 21,752 patients who had prescriptions for ACE inhibitors or statins were randomized to usual care or IVR [53]. The RCT demonstrated that IVR significantly increased adherence to prescribed medications.

An interesting intervention is the combination of self-measurement and coaching by telephone. In an RCT by Bosworth et al. [48], 636 patients with hypertension were randomized to either usual care, home BP measurement, a tailored behavioral self-management intervention, or a combination of home BP measurement and a tailored behavioral self-management intervention. The self-management intervention consisted of nurse-led education in the risks of hypertension, side effects of medication, and the importance of taking medication. Home BP measurement consisted of measuring and transferring BP three times weekly. Interestingly, BP was significantly better controlled in the intervention groups (an average 3.9 mmHg lower blood pressure in the intervention group compared to the control group), but self-reported medication adherence was not [48]. The authors argue that a behavioral intervention might only be interesting if patients can measure the parameter of interest themselves. The combination of self-management and telephone follow-up is therefore an interesting concept and requires further research.

3.6. Web-based interventions

Web-based interventions have become increasingly popular in scientific literature, mostly because of the high penetration rate of PCs and the Internet. In high-income countries, the average penetration rate of computers is around 85% [54]. Web-based interventions use mostly low-cost technology and, once developed, can be implemented in large numbers of patients simultaneously [26]. Web-based interventions furthermore have the advantage to induce active participation in patients taking medications for longer periods of time. One such example is the introduction of e-Learning in patient groups. The advantage of using e-Learning is the ability to educate patients about the medications they are taking and the reasons they are taking it for. As such, patients become better educated and are therefore more likely to take their prescribed medications [55]. An extended version of e-Learning may be the usage of a web-based counseling program. The advantage of a counseling program is that it can coach the patient on top of educating him. An RCT by Keyserling et al. [56] in 385 patients with a high risk of coronary heart disease (Framingham Risk Score ≥ 10%) demonstrated that this is an effective way of reducing cardiovascular risk. The RCT randomized patients to either live counseling or web-based counseling. The trial showed a reduction of 1.5% in Framingham Risk Score in the web-based counseling group and a 2.3% reduction in the live counseling group. However, it was calculated in the trial that the live counseling was almost twice as expensive as the web-based counseling ($207 vs. $110, respectively) [56]. Therefore, e-Learning programs might be effective and low-cost ways of improving medication adherence. Findings should be corroborated in other patient populations.

Other web-based interventions in study show however less positive results. An RCT by Martin et al. [57] investigated the use of a cyber nurse in 434 low-income patients. The cyber nurse (a recorded female voice) gave general health information and told patients to take their medication. This trial found that 51% of the patients in the intervention group were adherent, while 49% of the patients in the control group were adherent. The authors note that the population in this RCT was a medically underserved patient population with low-income and low socioeconomic status [57]. They acknowledge that their intervention addressed the issue of patients forgetting to take their medication, but that in a low-income, low-socioeconomic status patient population, financial barriers and social influence might be more important causes of the relatively low adherence rates.

4. Discussion

This paper gives an insight into the existing literature of different technologies used to improve medication adherence that have been investigated in an RCT. Several non-RTC studies presented promising technologies; however, in general, evidence comes from RCTs with relatively small sample sizes.

Non-adherence to medication is a major problem. It is associated with higher mortality and morbidity rates. There are various reasons for patients to be non-adherent. A systematic review by Kardas et al. [58] searched 51 systematic reviews to identify determinants of non-adherence. They found 771 determinants of non-adherence, of which 47 were determinants of persistence. These factors were categorized into socioeconomic determinants, healthcare team-related determinants, condition-related determinants, therapy-related determinants, and patient-related determinants. Most interventions however only target a couple of these 771 determinants, and most interventions assume patients forget to take the medication [58].

The authors identified five commonly used technologies to deliver telemedicine interventions for medication adherence. Some remarks have to be made: first, some technologies exist longer than other technologies. Telephones, for example, have been investigated in RCTs for over three decades, while mobile apps have been investigated for 7 years only. This might explain while only three papers were found that described a mobile app for medication adherence, while there were 47 papers describing telephone apps.

The authors would like to argue that the suitability of the technology depends on the determinant of medication adherence that is being addressed with the technology. RCTs using SMS as technology show that for simple medication reminders this might be a suitable technology. However, RCTs that use SMS for educational purposes show no difference in medication adherence. Education and coaching have been proven as an effective method to increase medication adherence. Evidence from our literature search predominantly points to web-based technologies as a cost-effective tool, most importantly because it is not labor intensive [26].

It has to be noted that, as of this moment, software is improving fast. AI and machine learning are very likely to bring new possibilities in this field of research. Therefore, as pointed out in our 5-year view, it might very well be the case that all the techniques in this review will be obsolete within 5 years.

4.1. Limitations

This paper is a narrative review on telemedicine strategies to improve medication adherence in patients with CVD. The 'narrative' aspect of the review makes it subject to certain limitations. First, although some aspects of a systematic review were incorporated into the design of this review, this paper does not describe a systematic review. This means that the results section above might be biased. The selection of papers might be biased because only one investigator selected them. The explanation of the various techniques and their effectiveness might be biased because not all papers could be included in the qualitative analysis. Furthermore, no formal risk of bias analysis was done. Therefore, results could not be weighed against data quality. Finally, inherent to describing the existing literature, there was no assessment nor correction for meta biases such as publication bias. It could very well be that, as in most other scientific fields, papers with a positive effect are more likely to be published. The authors would however like to emphasize that it was not the purpose of this paper to describe a systematic review.

5. Expert commentary

Non-adherence to medication intake according to prescription is a complex problem with various causes. Most technologies focus on simply reminding the patient that he has to take his medication. Evidence regarding this approach is conflictive. It is the authors' opinion that generally these approaches do not take into account the complexity of the problem and the fact that a substantial number of patients are non-adherent for other reasons than simply forgetting to take their medication. Therefore, we believe that further research should not focus on simple reminders.

Approaches that have, in our opinion, huge potential are educational interventions and AI. Educational interventions are a good way to activate patients. It has been proven that involved patients (i.e. patients who are willing and able to manage their own health) are at lower risk of being obese, smoke, or having a high hemoglobin A1c [59]. Most educational interventions show a significant increase in medication adherence. Web-based interventions seem to favor other technologies since they are mostly less expensive [26].

Phone calls can be an effective way of delivering educational interventions. However, with the rise of video-conferencing systems such as Skype (Microsoft, Redmond, Washington, USA), it can be expected that these software systems will take over phone calls. The authors recommend an RCT comparing the effect of the same intervention in an intervention group in which the intervention is delivered by video-conferencing, while in the control group, the intervention is delivered via phone calls.

The benefit of the intervention described by Labovitz et al. [31] is that it actually confirms the ingestion of the pill. Furthermore, it can be seen as the first step in AI, i.e. the development of interaction between human and computer. The app in this study recognizes the ingestion of a pill and gives feedback to its user. Further improvements in AI could have the computer coach and educate the patient based on input received via voice recognition, simulating actual human interaction. Second of all, computers capable of analyzing big data could become increasingly important. As discussed above, pharmacy claim data accurately reflects (non-) adherence. If personal health characteristics can be combined with these databases, non-adherence might be predicted. That way, patients that are likely to be non-adherent could be identified. Interventions addressing non-adherence can be tailored to these patients, thereby enabling personalized medicine [24]. Currently, limited voice recognition is possible. Smartphones are able to recognize clear spoken short instructions. Coaching via smartphones and the Internet is also possible. As demonstrated in this review, e-Learnings are already available. However, a major barrier to implementing this is the very limited interaction that is possible between computers and humans. In order for computer-based coaching to succeed (and not to become boring and repetitive), computers need to 'humanize'. However, the technology at this moment is not advanced enough for clinical implementation.

6. Five-year view

Currently available digital solutions to improve medication adherence are based on available software and technologies. However, in the next 5 years, software will for certain become more advanced and machine learning and AI will be usable in everyday practice. The first important change that will have an impact in the way medication non-adherence is addressed is that in 5 years computers will be able to simulate human interactions adequately. They will most likely be able to read face expressions and react in an appropriate manner. This means that educational interventions can be delivered in an interactive way. Furthermore, new interventions will focus on multiple determinants of medication adherence instead of one per intervention. Advances in software will enable programmers to develop the software in such a way. Machine learning ('the ability of a computer to learn without being explicitly programmed' [60]) will enable another important component: individualization of the way the intervention is delivered. It will take approximately another 5 years before software is sophisticated enough to allow for individualization. Therefore, it can be expected that in the next 5 years the development in digital solutions to address non-adherence will be limited. As software becomes available that is sophisticated enough to replace humans, it can be expected that the way non-adherence is addressed will change radically. These developments may personalize the way patients are addressed, taking socioeconomic status, cultural preferences, and personal characteristics into account.

Key issues

- Medication adherence is of paramount importance in treatment and prevention of cardiovascular disease
- Educational interventions, delivered via internet or smartphone are effective
- SMS might be a suitable technology for simple, automated reminders
- The evidence for the use of smart pill boxes is conflictive
- Developments in artificial intelligence may dramatically alter the way medication non-adherence is addressed

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Appendix
Search strategy (keywords used)

(("digital•[tw] OR "online"[tw] OR digital*[tw] OR mobile*[tw] OR "webbased"[tw] OR "web-based"[tw] OR "remote"[tw] OR "ehealth"[tw] OR "e-health"[tw] OR "mhealth"[tw] OR "m-health"[tw] OR "telehealth"[tw] OR electronic communication*[tw] OR "Internet"[mesh] OR "internet"[tw] OR "Telemedicine"[mesh] OR telemed*[tw] OR "Reminder Systems"[mesh] OR "Reminder Systems"[tw] OR "Reminder System"[tw] OR "Reminder Device"[tw] OR "Reminder Devices"[tw] OR "reminder messages"[tw] OR "reminder message"[tw] OR "Telephone"[mesh] OR telephon*[tw] OR "phone"[tw] OR "phones"[tw] OR "Cell Phones"[tw] OR "Smartphone"[tw] OR "Text Messaging"[tw] OR "Cell Phone"[tw] OR "Smartphones"[tw] OR iphon*[tw] OR "Text Messaging"[tw] OR text messag*[tw] OR "texting"[tw] OR "Electronic Mail"[mesh] OR "Electronic Mail"[tw] OR e-mail*[tw] OR email*[tw] OR "Telecommunications"[mesh] OR "app"[tw] OR "apps"[tw] OR webapp*[tw] OR "SMS"[tw] OR "mass communication"[tw] OR "blogging"[tw] OR "blog"[tw] OR "weblog"[tw] OR "social media"[tw] OR twitter*[tw] OR facebook*[tw] OR webcast*[tw] OR "Webcasts as Topic"[Mesh]) AND ("medication taking"[tw] OR "drug taking"[tw] OR "Medication Adherence"[Mesh] OR "medication adherence"[tw] OR "Medication Nonadherence"[tw] OR "Medication Noncompliance"[tw] OR "Medication Non-Adherence"[tw] OR "Medication Non Adherence"[tw] OR "Medication Persistence"[tw] OR "Medication Compliance"[tw] OR "Medication Non-Compliance"[tw] OR "Medication Non Compliance"[tw] OR ("administration and dosage"[subheading] AND "Patient Compliance"[mesh]) OR (("medication"[tw] OR "medications"[tw] OR "drug"[tw] OR "drugs"[tw]) AND ("adherence"[tw] OR "compliance"[tw] OR "taking"[ti]))) AND ("Cardiovascular Diseases"[Mesh] OR cardiovascular*[tw] OR cardiac[tw] OR "coronary"[tw] OR "Myocardial Infarction"[Mesh] OR "Myocardial Infarction"[tw] OR infarct*[tw] OR "Heart Attack"[tw] OR "Acute Coronary Syndrome"[mesh] OR "Angina Pectoris"[mesh] OR "Acute Coronary Syndrome"[tw] OR "Angina Pectoris"[tw] OR "Angina"[tw] OR "Heart Valve Diseases"[mesh] OR "Heart Valve Diseases"[tw] OR "Aortic Valve Insufficiency"[tw] OR "Aortic Valve Stenosis"[tw] OR "Subvalvular Aortic Stenosis"[tw] OR "Supravalvular Aortic Stenosis"[tw] OR "Heart Valve Prolapse"[tw] OR "Aortic Valve Prolapse"[tw] OR "Mitral Valve Prolapse"[tw] OR "Tricuspid Valve Prolapse"[tw] OR "Mitral Valve Insufficiency"[tw] OR "Mitral Valve Stenosis"[tw] OR "Pulmonary Atresia"[tw] OR "Pulmonary Valve Insufficiency"[tw] OR "Pulmonary Valve Stenosis"[tw] OR "LEOPARD Syndrome"[tw] OR "Pulmonary Subvalvular Stenosis"[tw] OR "Tricuspid Atresia"[tw] OR "Tricuspid Valve Insufficiency"[tw] OR "Tricuspid Valve Stenosis"[tw] OR "Atrial Fibrillation"[Mesh] OR "Atrial Fibrillation"[tw] OR "Atrium Fibrillation"[tw] OR "Heart Failure"[Mesh] OR "Heart Failure"[tw] OR "Hypertension"[mesh] OR "hypertension"[tw] OR hypertens*[tw] OR "blood pressure"[tw]) AND ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR random*[tw] OR "Placebos"[mesh] OR placebo*[tw] OR "Double-Blind Method"[Mesh] OR double blind*[tw]))