

Feasibility and performance of a device for automatic self-detection of symptomatic acute coronary artery occlusion in outpatients with coronary artery disease: a multicentre observational study

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Summary

Background Time delay between onset of symptoms and seeking medical attention is a major determinant of mortality and morbidity in patients with acute coronary artery occlusion. Response time might be reduced by reliable self-detection. We aimed to formally assess the proof-of-concept and accuracy of self-detection of acute coronary artery occlusion by patients during daily life situations and during the very early stages of acute coronary artery occlusion.

Methods In this multicentre, observational study, we tested the operational feasibility, specificity, and sensitivity of our RELF method, a three-lead detection system with an automatic algorithm built into a mobile handheld device, for detection of acute coronary artery occlusion. Patients were recruited continuously by physician referrals from three Belgian hospitals until the desired sample size was achieved, had been discharged with planned elective percutaneous coronary intervention, and were able to use a smartphone; they were asked to perform random ambulatory self-recordings for at least 1 week. A similar self-recording was made before percutaneous coronary intervention and at 60 s of balloon occlusion. Patients were clinically followed up until 1 month after discharge. We quantitatively assessed the operational feasibility with an automated dichotomous quality check of self-recordings. Performance was assessed by analysing the receiver operator characteristics of the ST difference vector magnitude. This trial is registered with ClinicalTrials.gov, number NCT02983396.

Findings From Nov 18, 2016, to April 25, 2018, we enrolled 64 patients into the study, of whom 59 (92%) were eligible for self-applications. 58 (91%) of 64 (95% CI 81·0–95·6) patients were able to perform ambulatory self-recordings. Of all 5011 self-recordings, 4567 (91%) were automatically classified as successful within 1 min. In 65 balloon occlusions, 63 index tests at 60 s of occlusion in 55 patients were available. The mean specificity of daily life recordings was 0·96 (0·95–0·97). The mean false positive rate during daily life conditions was 4·19% (95% CI 3·29–5·10). The sensitivity for the target conditions was 0·87 (55 of 63; 95% CI 0·77–0·93) for acute coronary artery occlusion, 0·95 (54 of 57; 0·86–0·98) for acute coronary artery occlusion with electrocardiogram (ECG) changes, and 1·00 (35 of 35) for acute coronary artery occlusion with ECG changes and ST-segment elevation myocardial infarction criteria (STEMI). The index test was more sensitive to detect a 60 s balloon occlusion than the STEMI criteria on 12-lead ECG (87% vs 56%; $p < 0·0001$). The proportion of total variation in study estimates due to heterogeneity between patients (I^2) was low (12·6%). The area under the receiver operator characteristics curve was 0·973 (95% CI 0·956–0·990) for acute coronary artery occlusion at different cutoff values of the magnitude of the ST difference vector. No patients died during the study.

Interpretation Self-recording with our RELF device is feasible for most patients with coronary artery disease. The sensitivity and specificity for automatic detection of the earliest phase of acute coronary artery occlusion support the concept of our RELF device for patient empowerment to reduce delay and increase survival without overloading emergency services.

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Introduction

Patient delay during acute coronary artery occlusion is a pervasive problem worldwide. It is associated with out-of-hospital ventricular fibrillation and irreversible loss of myocardial viability. According to the global incidence of acute myocardial infarction,¹ the incidence and risk

factors of primary ventricular fibrillation,^{2,3} and the effect of treatment delay,⁴ an estimated 1000 deaths or more a day could have been avoided in 2017 by decreasing patient delay by 90 min.

A scientific statement from the American Heart Association⁵ describes the sociodemographic, clinical,

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Research in context

Evidence before this study

Patient delay is a substantial unsolved problem causing avoidable deaths in patients with acute coronary artery occlusion. Reliable self-detection of acute coronary artery occlusion might reduce patient doubts and delay during ongoing chest pain. Invasively placed intracardiac ischaemia monitors have been developed for earlier identification of ischaemia in patients with a high risk of acute coronary syndrome and alert patients of a potential occlusive event. We did a systematic literature review of PubMed on Jan 29, 2019, using the search terms ((sensitivity OR specificity) AND (infarction OR (acute coronary occlusion))) AND (Device)) and found that no self-applicable device can accurately detect acute coronary artery occlusion non-invasively. We have shown that an automatic algorithm based upon a self-applicable three-lead system (RELF method) can accurately detect acute coronary artery occlusion. We then developed a handheld device for self-application of this RELF method.

Added value of this study

This is the first clinical study that supports the proof-of-concept of self-detection of acute coronary artery occlusion in outpatients with coronary artery disease. Our prospective, multicentre study shows that most patients with coronary artery disease who can use a mobile phone or smartphone can reliably use our handheld device. We illustrate how our device can integrate patient skills with anticipatory plans from health-care providers into more time-efficient self-triage during chest pain.

Implications of all the available evidence

Monte Carlo simulations that include our study findings predict that patients with an annual risk for acute coronary artery occlusion of more than 0.5%, who are well informed and empowered with a validated device, will be alerted without delay during acute coronary artery occlusion. The median patient delay during acute coronary artery occlusion can potentially decrease to less than 20 min. For 100 patients with an acute coronary artery occlusion this could save 150 quality-adjusted life-years. We provide new data to calculate how emergency services will economically benefit from the empowered self-triage of the patient with chest pain. With the evidence from our study and an expected cost of less than €300 for the device, policy makers can calculate the economic benefit to empower patients in relation to their annual risk for acute coronary artery occlusion. It is feasible to assess whether the introduction of the RELF device in the management of coronary artery disease will effectively reduce patient and system delay. Handheld devices and implantable intracardiac ischaemia monitors might be complementary solutions to reduce patient delay. Handheld devices are targeted for a large population with low or moderately increased risk for an acute coronary artery occlusion, whereas the implantable monitors are targeted for more selected patients at very high risk for acute coronary artery occlusion or who have an additional indication to implant an intracardiac device.

and social cognitive emotional factors that are associated with patient delay during acute coronary artery occlusion and advises that health-care providers assist patients with coronary artery disease in making anticipatory plans for timely recognition and response to an acute event. However, even well-informed patients are often undecided and left with doubts.⁵ In an up-and-coming era of patient empowerment with digital medical sensors,⁶ a rapid rule-in tool (ie, a tool that confirms acute coronary artery occlusion without delay) has been proposed as a potential strategy to avoid delay during symptoms of acute coronary artery occlusion.⁷

To improve outcome in patients with coronary artery disease, such a tool should fulfil some conditions. First, during ongoing chest pain the device should first display, as a reminder, the individual's anticipatory plan for timely recognition and response to an acute event, which was made with their health-care provider. Second, for those with doubts or a high threshold for the proposed action, the tool should additionally empower the patient by a rapid test for acute coronary artery occlusion. Finally, the device should be safe and generate a quick automatic response at any given time and place because onset of symptoms is unpredictable.

We developed over the past 7 years a three-lead system and automatic algorithm (RELF method) that can

accurately detect acute coronary artery occlusion when applied by experienced medical personnel.⁸ We then developed the first handheld device for automatic self-detection of acute coronary artery occlusion. Patients at risk of this disorder could carry our device and electrodes in their pocket or have them constantly in their vicinity to self-apply the RELF method immediately during symptoms to avoid delay in case of acute coronary artery occlusion. Self-applicability is the most crucial step to establish the potential of the device to reduce patient delay in the very early phase of acute coronary artery occlusion. Therefore, the aim of this study was to formally assess the proof-of-concept and accuracy of self-detection of acute coronary artery occlusion in the hands of patients during daily life situations (specificity) and during the very early phase of acute coronary artery occlusion (sensitivity).

Methods

Study design and participants

In this multicentre observational study, patients with planned elective percutaneous coronary intervention were recruited at Ghent University Hospital, Ghent, Belgium; AZ St-Jan Hospital, Bruges, Belgium; and AZ Nikolaas Hospital, Sint-Niklaas, Belgium. Patients were included if they were admitted to the hospital with

angiographically proven significant (>50% diameter stenosis) coronary artery disease and were discharged with planned elective percutaneous coronary intervention. Patients were excluded if they had a pacemaker or implantable cardioverter-defibrillator implant, a history of coronary artery bypass grafting, an ST-segment elevation myocardial infarction (STEMI) within the past 7 days, an intolerance for skin electrodes, prolonged hospitalisation after diagnostic angiography, and an inability to use a cell phone or smartphone in the past month. Patient screening for eligibility was performed once a day by the study nurse or clinical investigator guided by an updated list of planned coronary angiographies. Shortly before discharge, patients were invited by the study nurse or clinical investigator to participate in the study after a 10–15 min introduction and demonstration of the RELF device. After signing informed consent, a first self-recording was performed under supervision of the study nurse or clinical investigator.

This multicentre clinical trial was approved by the central and local ethical committees (Belgium Registration Number: B670201628891). The device was approved for clinical investigation trial by the Federal Agency for Medicines and Health Products (AFMPS/80M0648/). The trial is registered with ClinicalTrials.gov (NCT02983396). All patients provided written informed consent.

The RELF method and the study device

In a previous clinical study⁸ we introduced and validated the RELF method, which is an easy, self-applicable, three-lead configuration, with its associated automatic algorithm to calculate ST vectors. In brief, the RELF leads record the voltage differences from the right shoulder (R) to an exploratory electrode (E), to the left shoulder (L), and to the left iliac crest (F). The algorithm calculates an individualised ST reference vector based on the average of the most recent 13 reference measurements in asymptomatic daily life conditions. For an index test (decision test), it calculates the magnitude of the ST difference vector (STDV; the difference between the reference vector and the index vector) in an ortho-normalised coordinate system (STDVn; expressed in normalised units [nu]). An a priori-defined cutoff for STDVn was set at 2.947 nu, which is the 95th percentile of all previously recorded values of healthy participants in the previous RELF study.⁸

The RELF study device consists of a handheld RELF recorder with standard self-adhesive skin electrodes (appendix). It is a custom-made electrocardiogram (ECG) device designed for self-application of the RELF method. The device was connected by Bluetooth to the dedicated study smartphone, on which the custom-made user interface app was installed (and other apps were disabled), to start a recording, send data to the study server, and receive automated feedback within 1 min. Two feedback responses may be generated: either successful recording or check electrodes and muscle activity and repeat

recording. After the final study visit the devices were returned for re-use.

Outcomes

We quantitatively assessed the operational feasibility of self-recording with an automated dichotomous quality check. The quality was not accepted if the interquartile range of ST level was above 200 μ V for lead RE, above 100 μ V for lead RL, and above 230 μ V for lead RF.

We assessed the accuracy of the device in the hands of patients in settings that were most representative for intended use. Therefore, we analysed the use of the device in daily life situations (specificity) without acute coronary artery occlusion (absence of target condition). After demonstration of the device functionalities and signing informed consent, a device instruction flyer was given to the patients. They were asked to perform random self-recordings at home preferably 5 times a day or more for at least 1 week. They were encouraged to remove electrodes after each recording and reapply new ones for the next recording. A maximum of 12 h of electrode application to the body was allowed. Before each recording the app requested the patient to indicate the body position (standing, lying, or sitting) and the presence or absence of physical activity in the past 5 min before the recording. After each measurement, the patient received immediate automated feedback (appendix) regarding the recording quality.

In case of bad electrode contact or noise due to muscle activity during a recording, the user received a warning on the smartphone within 1 min to check the electrodes and relax muscles during the measurement. If a positive result was detected, the patient received an automated request to do a repeat measurement. The trial safety monitor also received the measured data instantaneously as a safety precaution in the background of the study.

We analysed the sensitivity of the device for the detection of the very early phase of acute coronary artery occlusion, simulated by 60 s of coronary balloon occlusion (the target condition). In the catheterisation laboratory, the patients were requested to make a preprocedural self-recording similar to a home recording. During the percutaneous coronary intervention procedure, the RELF device was kept in place and was connected via Bluetooth to a laptop for continuous recording. Custom-made software on the laptop enabled the study coordinator or nurse to mark timestamps corresponding to baseline and end of the 60 s balloon occlusion (just before deflation). At each given timestamp a 12-lead ECG was recorded simultaneously.

All standard 12-lead ECGs were recorded according to the European Society of Cardiology guidelines⁹ and quality certificates of ECG equipment were collected. In each study centre, at least one study nurse was instructed on the standard 12-lead ECG configuration. Printouts of all ECGs were collected and the interpreting cardiologists were masked to labelling. Five cardiologists independently

See Online for appendix

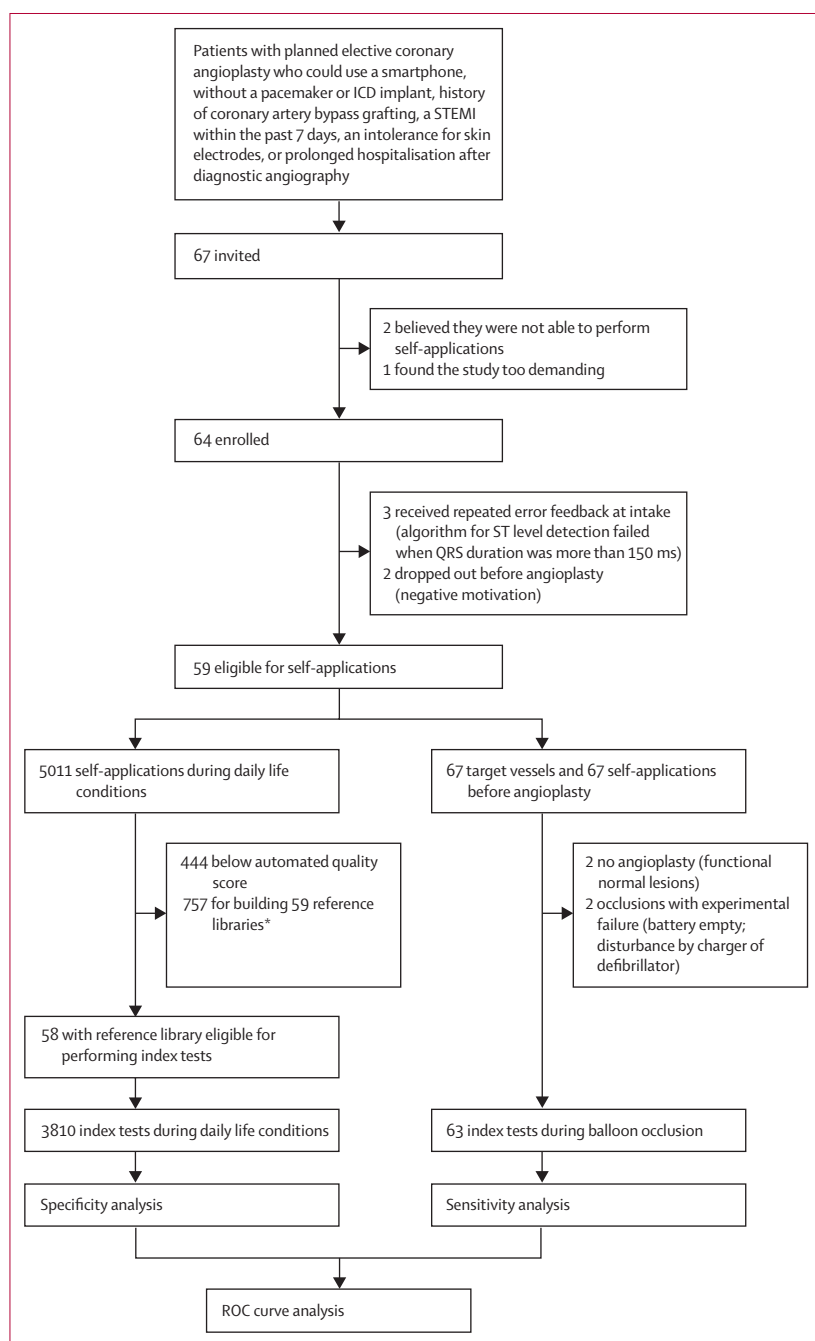


Figure 1: Experimental set up for detecting acute coronary artery occlusion

Operational feasibility (upper panels), specificity during daily life conditions (left panels), and sensitivity during acute balloon occlusions (right panels) were the main outcomes. ROC=receiver operating characteristics.

*57 × 13 reference recordings; one patient performed only 12 reference recordings before angioplasty and one patient performed only four reference recordings and therefore no index tests. ICD=implantable cardioverter defibrillator. STEMI=ST-segment elevation myocardial infarction criteria.

assessed each ECG for presence of ST elevation criteria according to the third international definition of myocardial infarction criteria,¹⁰ including the ST depression criteria for posterior myocardial infarction as STEMI equivalent.⁹ In case of mismatch, the assessment of the

majority was used for further analysis. Three other cardiologists independently assessed ECG pairs consisting of unlabelled ECGs at baseline and at 60 s balloon occlusion. The ECG pairs were simultaneously presented and in random order within pair for the assessment of any ECG change. To categorise a pair of ECGs as no change a matching between all three cardiologists was mandatory. ECGs at 60 s of balloon occlusion were categorised as no ECG change compared with baseline, ECG change without STEMI criteria, or ECG change with STEMI criteria.

Adverse events were collected at each visit during the study inclusion period and were reported to the principal investigator.

Statistical analysis

We aimed to include at least 60 balloon occlusions, in line with our previous study,⁸ to compare the sensitivity of self-applications with the sensitivity of the RELF method as applied by medical personnel.

For paired comparison of STDVn values before and at 60 s of balloon occlusion, we used the Wilcoxon Signed Ranks Test. We dichotomised the RELF tests at a prespecified cutoff of 2.947 nu based on the 95th percentile of all normal STDVn values from our previous study.⁸ We used the McNemar test for paired comparison between the dichotomised RELF method and the conventional STEMI criteria. p values of less than 0.05 were considered statistically significant. We calculated boxplot summaries in SPSS Statistics 25. We analysed the receiver operating characteristics (ROC) curve in SigmaPlot.

We made group and subgroup summaries of the false positive rate taking into account the different sample sizes of the individuals. We multiplied the individual false positive rates with a weight factor that represents the individuals' sample size. Since we assume that variability is not only due to sampling error but also to variability between patients we used a random effect model, for which the weight of the individual false positive rate is further adjusted with a constant that represents it.¹¹ We conducted the calculations necessary for the forest plot, including weighting of cases according to sample size and variance, using a previously published template.¹¹ Significance for heterogeneity was quantified with the I^2 statistics.¹²

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author (FVH) had full access to all the data in the study. FVH, MDB, and PG had final responsibility for the decision to submit for publication.

Results

Between Nov 18, 2016, and April 25, 2018, 67 patients were invited to participate in the study (figure 1). Three

patients were not enrolled as they believed that they were not able to perform self-measurements or that the study was too demanding. Thus, 64 patients signed informed consent. Patient and baseline ECG characteristics are summarised in table 1.

58 (91%) of 64 patients (95% CI 81·0–95·6) were able to perform ambulatory self-recordings. Five (8%) patients were unable to build their own reference library as the algorithm rejected the presence of left bundle branch block (n=3) or the patient was not motivated to perform self-recordings (n=2; figure 1). One patient had an incomplete reference library, including only four reference recordings, but was included in the sensitivity analysis as he participated with the balloon occlusion phase. 59 (92%) patients performed 5011 ambulatory self-recordings of 12 s each; with a median of 71 recordings per patient (IQR 44–102; figure 1). Most patients (68%) spontaneously performed more than the requested number of measurements, supporting the ease of use of the device. Of all 5011 recordings, 4567 (91·1%) were immediately and automatically classified as successful and the patient received positive confirmation from the server within 1 min. The main reason for an unsuccessful recording was interfering noise either from unstable skin contact of the electrodes or from muscle activity. Both have overlapping signal characteristics that were not separable by the algorithm. Of all recordings, 757 (15·1%) were used to build the personal reference libraries consisting of 13 successful recordings for each individual (one patient had only 12 reference recordings before the angioplasty; after discharge, the patient further completed the reference library and performed further index tests during daily life conditions). As such, 3810 home recordings were labelled as index tests during daily life conditions. After an unsuccessful recording (444 [8·9%]), the patient received an automated message from the server within 1 min, requesting to check electrodes and muscle activity and repeat recording. After an unsuccessful recording, all patients performed a repeat recording which went on to be successful after one attempt in 70% (181/258), two attempts in 14% (37/258), or three attempts in 7% (18/258). 22 (0·44%) of all 5011 self-recordings went on to be successful after more than three attempts and were marked as failed.

All 59 patients self-applied the device before entering the catheterisation laboratory or immediately after positioning on the x-ray table. One patient switched the L and F electrodes and another patient accidentally placed the F electrode on the right iliac crest. Both wrong applications were corrected by the study nurse. All patients performed a successful baseline RELF recording in the correct position for the percutaneous coronary intervention procedure and before local anaesthesia. Simultaneously, a 12-lead ECG was recorded. Eight patients had a second lesion planned for percutaneous coronary intervention. For each of these lesions a new baseline recording with the RELF device and 12-lead ECG was taken before crossing the percutaneous

Patients with ambulatory self-recordings (n=59)*	
Sex	
Male	43 (73%)
Female	16 (27%)
Age, years	64·4 (9·7)
Weight, kg	82·6 (14·8)
Height, cm	171·1 (14·8)
Body-mass index, kg/m ²	28·2 (5·0)
Atrial fibrillation	3 (5%)
First degree atrioventricular block	3 (5%)
Right bundle branch block	5 (9%)
Left anterior hemiblock	7 (12%)
Right bundle branch block and left anterior hemiblock	3 (5%)
Left bundle branch block	0
Q waves	11 (19%)
Any abnormal QRS†	19 (32%)

Data are n (%) or mean (SD). *Five patients who were enrolled but who could not carry out self-recordings are not included. †Abnormal QRS was any bundle branch block or Q wave.

Table 1: Patient characteristics

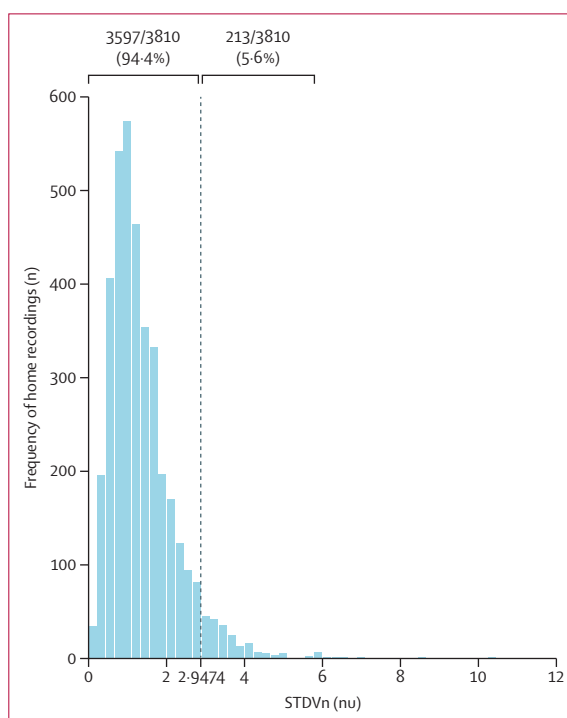


Figure 2: STDVn expressed by home recordings

3810 home recordings were obtained, 94·4% of which were lower than the prespecified STDVn cutoff value of 2·947 nu and 5·6% of which were higher than the cutoff. nu=normalised units. STDVn=ST difference vector in an orthonormalised coordinate system.

coronary intervention wire through the second lesion. In two lesions, no angioplasty was performed because the functional assessment of the lesion was not significant. In

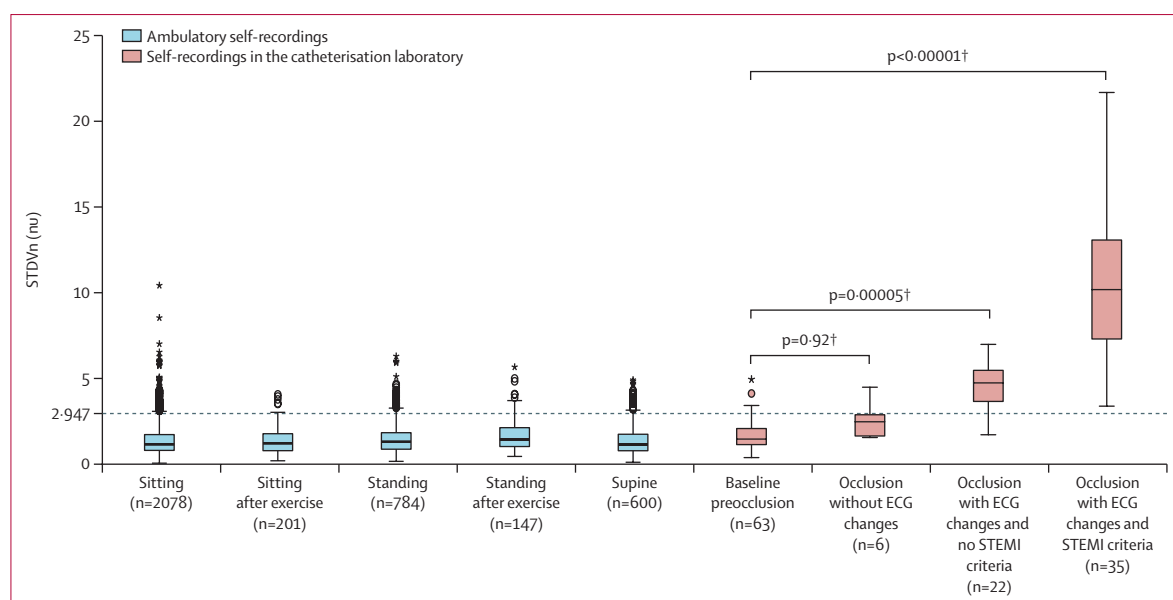


Figure 3: STDVn of all test recordings according to physical condition

The horizontal line represents the prespecified STDVn cutoff value of 2.947 nu. All STDVn values during ST elevation (occlusions with ECG changes and STEMI criteria, n=35) were higher than the cutoff. ECG=electrocardiogram. nu=normalised units. STEMI=ST-segment elevation myocardial infarction. STDVn=ST difference vector in an orthonormalised coordinate system. *Extreme outliers. †Wilcoxon Signed Ranks Test for paired comparison of preocclusion and occlusion STDVn values. Note that all extreme outliers of the ambulatory self-recordings are higher than the prespecified cutoff and are false positives.

	Total number of occlusions	RELF positive	RELF negative	Sensitivity (95% CI)
Acute coronary artery occlusion	63	55	8	0.87 (0.77–0.93)
LAD occlusion	33	30	3	0.91 (0.76–0.97)
RCA occlusion	15	13	2	0.87 (0.62–0.96)
CX occlusion	15	12	3	0.80 (0.55–0.93)
With ECG changes on 12-lead ECG	57	54	3	0.95 (0.86–0.98)
With STEMI criteria on 12-lead ECG	35	35	0	1.00*

Data are number of occlusions. Subgroups are defined by vessel territory or by ECG changes during occlusion. Cutoff for RELF positive status was 2.947 normalised units. LAD=left anterior descending artery. RCA=right coronary artery. CX=left circumflex artery. ECG=electrocardiogram. STEMI=ST-segment elevation myocardial infarction. *95% CI not calculated as sample sensitivity was 1.

Table 2: Sensitivity at 60 s of acute coronary artery occlusion

total, 65 lesions were balloon occluded for 60 s (figure 1). At 60 s of balloon occlusion, a second RELF recording and 12-lead ECG were taken simultaneously. Two recordings at 60 s of balloon occlusion technically failed, one due to high frequency interference from the catheterisation laboratory's external defibrillator (unintended charging of capacitors) and the second due to low battery of the RELF device. Finally, 63 index tests (in 55 patients) at 60 s of occlusion were available (figure 1).

The length of the STDVn was used as a decision parameter to detect ST elevation with the RELF device. The ambulatory self-recorded STDVn measurements (n=3810) are summarised in figure 2. The mean value was 1.39 nu (SD 0.876) and the median value was

1.17 nu (IQR 0.80–1.75). The distribution was not normal (Kolmogorov-Smirnov 0.109; $p<0.00001$). The 90th percentile was 2.49 nu and 95th percentile was 3.06 nu.

The distribution of the ambulatory self-recordings and the recordings in the catheterisation laboratory before and at 60 s of balloon occlusion is summarised in figure 3. Neither postural changes nor presence of physical activity within 5 min before recording, or installing the patient on the x-ray table, influenced the distribution of STDVn, taking into account that the false positives are excluded from the distribution. All outliers are above the prespecified cutoff and therefore represent false positive recordings (figure 3). Balloon occlusions without observed changes in simultaneous 12-lead ECG (n=6) had no significant increase of STDVn (paired analysis $p=0.92$). Occlusions with changes in simultaneous 12-lead ECG but without STEMI criteria (n=22) had a highly significant increase of STDVn (paired analysis $p=0.00005$). Occlusions with STEMI criteria on 12-lead ECG (n=35) had the highest increase of STDVn (paired analysis $p<0.00001$).

The STDVn values of the 3810 daily life recordings were less than the a priori set cutoff of 2.947 nu in 3597 (94.4%) of 3810 cases. To estimate the mean false positive rate we weighted the individual contributions with a random effect model meta-analysis (appendix). Barring one patient who performed only four measurements, the mean false positive rate in 58 patients was 4.19% (95% CI 3.29–5.10) corresponding to a mean specificity of daily life recordings of 0.96 (0.95–0.97).

All index STDVn at 60 s of balloon occlusion were dichotomised into positive or negative (table 2) according to the predetermined cutoff of 2.947 nu. The sensitivity for the target conditions was 0.87 (55 of 63; 95% CI 0.77–0.93) for acute coronary artery occlusion, 0.95 (54 of 57; 0.86–0.98) for acute coronary artery occlusion with ECG changes, and 1.00 (35 of 35) for acute coronary artery occlusion with ECG changes and STEMI criteria. Additionally, the index test was more sensitive to detect a 60 s acute coronary artery occlusion than the STEMI criteria on 12-lead ECG (87% vs 56%; paired comparison with McNemar test $p < 0.0001$).

The proportion of total variation in study estimates due to heterogeneity between patients (I^2) was low (12.6%). The mean false positive rates in clinical subgroups according to age, sex, body-mass index, and abnormal QRS is summarised in figure 4 and revealed no subgroup with a significantly different mean false positive rate. The algorithm triggered a repeat recording if a positive result ($n=213$) was detected. 160 (75%) of these false positive recordings triggered a repeated recording effectively within 5 min. 109 (68%) of these repeated false positive recordings were normal within 5 min.

The accuracy of self-recordings at other cutoff values is presented in the empirical ROC calculated with the 3873 recordings without acute coronary artery occlusion and the 63 index recordings with acute coronary artery occlusion (appendix). The area under the ROC curve was 0.973 (95% CI 0.956–0.990). No patients died during the study.

Discussion

In our multicentre, observational study, we found that the use of our RELF device for self-detection of acute coronary artery occlusion was feasible, with high sensitivity and specificity. Patient and system delay in reperfusion strategies highlight the need for a rapid rule-in tool (ie, a tool that rapidly confirms acute coronary artery occlusion) to guide patients at risk of acute coronary artery occlusion towards optimal decision making, without overloading emergency services. To our knowledge this is the first clinical study of an automatic handheld device for self-detection of acute coronary artery occlusion.⁷

We found that in the hands of patients with coronary artery disease our newly developed device is highly sensitive (0.87) and specific (0.958) for detecting acute coronary artery occlusion at 60 s of onset. This early stage of acute coronary artery occlusion was simulated by 60 s of coronary balloon occlusion. Of interest, at 60 s of occlusion our device was more sensitive than the current STEMI criteria on 12-lead ECG (87% vs 56%).

We documented that self-applications are operationally feasible (91%) for a broad range of patients with coronary artery disease, provided patients have a basic knowledge of smartphone use and absence of cardiac implantable electronic devices or left bundle branch block at baseline.

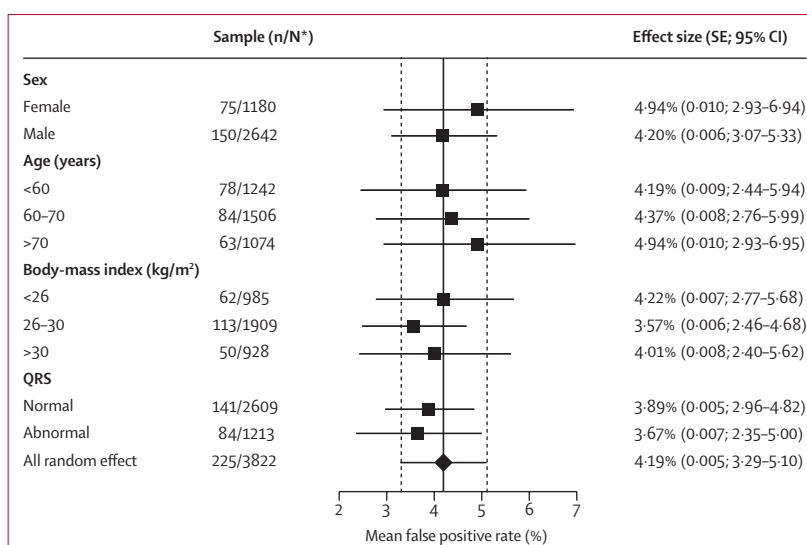


Figure 4: Mean false positive rates of RELF measurements in predefined subgroups

Rates are presented with 95% CIs and were similar between subgroups. *12 cases without false positive recordings were given one false positive recording and their sample size was increased with one to allow calculation of the weighted individual contributions.

The presence of left bundle branch block with QRS more than 150 ms is automatically detected at intake by the RELF device and these patients are automatically excluded from further recordings.

Our device might be suitable both for use in trials and in clinical practice. The high sensitivity and specificity of the current device suggest that it might serve in trials as the gold standard for early detection of ECG evidence of STEMI, allowing comparison with novel devices. However, the main purpose of the device will be everyday application by patients with 0.5% annual risk of symptomatic acute coronary artery occlusion, such as patients with multiple risk factors for coronary artery disease, patients with proven coronary artery disease, or patients during 6 months after a first unexplained chest pain episode. The device consists of a sensor part, connected via Bluetooth to a medical app on a smartphone. The sensor part, as used in our study, is operationally feasible and can be even further reduced in size and weight. It can remain in the patients' pockets or in their vicinity and be applied on the body any time when in doubt about ongoing chest pain (see online video, appendix). After taking some reference recordings (ideally 13), the app is ready for use and can be applied at any time. A checklist of the story table is provided in the appendix.

Invasively placed intracardiac ischaemia monitors have been developed for earlier identification of ischaemia in patients with a high risk of acute coronary syndrome and alert patients of a potential occlusive event. These devices might be beneficial among high-risk patients for potentially identifying asymptomatic ischaemic events.¹³ Handheld devices and implantable intracardiac ischaemia monitors might be complimentary solutions to reduce

	Annual risk for symptomatic acute coronary artery occlusion	Positive predictive values	Negative predictive values
Adult population	0.05–0.15%	57.3% (35.2–71.8)	99.1% (98.0–99.8)
ASCVD score >20	0.5–1.0%	91.0% (85.3–94.7)	93.5% (87.2–98.4)
Stable multivessel coronary artery disease	0.5–1.0%	91.0% (85.3–94.7)	93.5% (87.2–98.4)
Stent implantation <1 year	0.5–1.0%	91.0% (85.3–94.7)	93.5% (87.2–98.4)
Unexplained chest pain <6 months ²³	0.5–1.0%	91.0% (85.3–94.7)	93.5% (87.2–98.4)
Recent acute coronary syndrome <1 year	1.5–3.0%	96.8% (94.8–98.2)	83.1% (69.2–95.6)
Complex stenting <1 year	1.5–3.0%	96.8% (94.8–98.2)	83.1% (69.2–95.6)

Data are % or % (95% CI). The Monte Carlo simulations (n=10 000) are based on the 95% CIs for sensitivity and specificity and on the estimated incidence of chest pain without acute coronary artery occlusion between 1% and 2%^{21–23} in all risk categories. ASCVD score=10-year risk for atherosclerotic cardiovascular disease in adults aged 40–79 years.

Table 3: Positive and negative predictive values for the RELF test when the device would be used during chest pain or discomfort in a priori-defined risk categories for acute coronary artery occlusion

patient delay. Handheld devices are targeted for a large population with low or moderately increased risk of an acute coronary artery occlusion, whereas the implantable monitors are targeted for more select patients at very high risk of acute coronary artery occlusion¹⁴ or who have an additional indication to implant an intracardiac device.¹⁵

A tool to guide patients with acute coronary artery occlusion towards immediate and safe transport (by emergency services and guarded by an external defibrillator) to the catheterisation laboratory could have a substantial effect on mortality of patients with acute coronary artery occlusion.²⁴ A rapid rule-in tool, to rapidly confirm acute coronary artery occlusion, should not overload emergency departments, which could theoretically occur when the positive predictive value of the test in the target population is less than the current probability of acute coronary artery occlusion in patients visiting the emergency department for chest pain. The probability of acute coronary syndrome in patients visiting the emergency department for chest pain varies between 3% and 25%.^{16–20} The (pretest) empirical and theoretical probability for acute coronary syndrome during chest pain in a general population has been estimated to be 2–12%. The theoretical probability is based on the proportion of annual risk of acute coronary artery occlusion (44–142 per 100 000 per year)²¹ and annual risk of chest pain in the general population (1–2% of adults).^{22–24} Indeed, of 1212 consecutive patients with chest pain, aged 35 years and older, attending 74 general practitioners, 3.6% presented with acute coronary syndrome.²⁵ In a general practice setting in the Flemish part of Belgium, significant heart disease was present in only 5% of the chest pain patients.²⁶ Of 172 180 patients who presented with a first consultation for chest pain to 223 general practices in the UK, 4.8% were attributed to coronary artery disease.²³ With the confidence intervals of sensitivity and specificity from our study and an a priori risk of acute coronary artery occlusion for a patient with

chest pain in the general population between 2 and 12%, the positive predictive value for acute coronary artery occlusion will be 0.573 (95% CI 0.352–0.718; Monte Carlo simulation), far exceeding the current probability of acute coronary syndrome in patients visiting the emergency department for chest pain. The positive and negative predictive values for different risk categories are given in table 3. Our device could be useful and economically beneficial for patients with more than 0.5% annual risk for acute coronary artery occlusion, such as patients with proven coronary artery disease, patients with recent stent implantation, or patients with unexplained chest pain.²³ These patients could carry our device and electrodes in their pocket or have them constantly in their vicinity to self-apply the RELF method immediately during acute symptoms to avoid delay in case of acute coronary artery occlusion.

We have previously discussed why the RELF method outperforms other ECG methods to detect acute coronary artery occlusion.⁸ In brief, the RELF method has been developed to be very sensitive for ST deviations perpendicular to the long axis of the left ventricle because these are typically associated with acute coronary artery occlusion (transmural ischaemia). The RELF method is less sensitive for ST deviations parallel to the long axis of the left ventricle, which are typically associated with subendocardial or non-transmural ischaemia and with more physiological shifts in ST segment, such as those related to changes in heart rate or body position. Holter devices and exercise stress treadmills have robust and extensively validated algorithms to detect ST segment deviations but are not designed for self-application and do not specifically target ST changes perpendicular to the long axis of the left ventricle. Therefore, these tests might be less sensitive and specific for the minimal ST changes related to the early phase of acute coronary artery occlusion.

Self-applications of the RELF method applied in our device preserve their accuracy for several reasons. First, the lead system is easy to apply and designed for on-demand self-application of electrodes, preventing electrode switching, or bad positioning. Specifically, the application of the E lead on the chest is guided by the lead design in a way that deviation of more than 3 cm from the target position is avoided (appendix). Second, the automated ECG quality algorithm (appendix) rejects self-recordings with baseline wandering or muscle activity (8.9% of home recordings) and immediately requests a new recording. Furthermore, the algorithm allows a minimum of signal filtering to preserve the characteristics of the ST segment that could otherwise be obscured by the use of high pass and low pass filters or filters in the frequency domain of the ST segment.^{27–29} When the device is used on a larger scale during normal physiological conditions, it might be possible to further lower the detection threshold of the algorithm according to patient specific characteristics.

One criterion for patients to be excluded from the study was the inability to use a mobile phone or smartphone in the past month. More specifically, the necessary skills were handling (reading and touching) an interface on a touch screen to start a recording and to read the result and attaching wired electrodes to the skin according to an instruction folder consisting of six steps on one page. The technical skills needed to use the study version of this technology are presented in a video in the appendix. To allow maximum participation we thought that the ability to use a mobile phone or smartphone in the past month was an appropriate wording to condense the two necessary skills.

We did not assess the associations between patient characteristics and the proportion of quality rejected recordings, which could be helpful in finding potentially unknown determinants of quality rejected recordings other than electrode–skin contact noise and noise from muscle activity.

The RELF algorithm alerts patients to a potential acute coronary artery occlusion by applying a single cutoff of 2.947 μV , which is based on the 95th percentile of the measurements during normal physiological conditions in our previous study.⁸ We assume that the changes of the ST vectors induced by acute coronary artery occlusion are not specific to individual patients but are inherent to the acute coronary artery occlusion. Conversely, the variations of the ST vectors induced by normal physiological conditions are probably patient specific; if these variations are large and overrule those induced by acute coronary artery occlusion, then the sensitivity will be compromised. From a clinical point of view, we would not increase the cutoff at the expense of sensitivity. However, if the variations between patients are small, then indeed there would be an opportunity to lower the cutoff and thereby increase the sensitivity.

The algorithm calculates an individualised ST reference vector based on the average of the most recent 13 reference measurements in asymptomatic daily life conditions. In a theoretical study (unpublished) we assessed the effect of increasing the number of reference recordings on the 95th percentile of STDVn and documented that generating more than 13 reference recordings did not further reduce the 95th percentile of STDVn.

Any tool to guide patients at risk for acute coronary artery occlusion should start with the advice that whenever the patient feels the need for medical help during chest pain or discomfort, they should not hesitate and seek immediate medical attention without consulting any device. A device such as ours should only be used by patients with chest pain or discomfort who are in doubt for seeking immediate medical help. Such a device should also, in case of absence of ST elevation, further guide the patient with a non-ST segment elevation myocardial infarction or non-coronary cause of ongoing chest pain. These patients generally have a much lower risk of out-of-hospital ventricular fibrillation or irreversible loss of

myocardial viability than those with acute coronary artery occlusion. The device will automatically generate messages on the screen of the device, such as seek medical attendance within two hours from now or seek medical attendance within 12 hours from now. The built-in algorithm will follow either an anticipatory plan from the health-care provider⁵ or guidelines on chest pain management. An example of such an algorithm is included in the appendix.

Because the use of our device must be initiated before an expected clinical event, we will need a larger sample size to capture real-world events, such as ongoing chest pain or myocardial infarction. To assess whether the introduction of the RELF device in the management of coronary artery disease will effectively reduce patient and system delay, we have planned a randomised controlled trial of 5400 patients in 2020, when our device will be manufactured on a large scale. To obtain 80% power to detect an increase from less than 20% to more than 70% of the proportion with very short patient delay (<30 min), defined as time from onset of symptoms to emergency call, 1800 patients with coronary artery disease will be enrolled in the device empowerment group and 3600 in the advice control group. At that time, a medical graded mobile app on the patients' smartphones will capture the data from the sensor and detect acute coronary artery occlusion according to our algorithm.

Our RELF device is, to our knowledge, the first validated device intended for automatic rapid rule-in during chest pain in patients with coronary artery disease. Self-application is operationally feasible for most patients with coronary artery disease. The proof-of-concept is supported by its high sensitivity and specificity for detection of the earliest phase of acute coronary artery occlusion. Even if applied to populations with a low probability of acute coronary artery occlusion during chest pain (2–12%), the positive predictive value remains higher than the current probabilities in patients visiting the emergency department with chest pain. Therefore, our study device fulfils all essential conditions to empower the patient with coronary artery disease towards more efficient use of emergency services for ongoing chest pain. This study further illustrates that digital automated interpretation of individual pre-event data enables precision diagnosis of new events.

Contributors

FVH, MC, JDP, BD, MD, SG, PK, YV, JV, and MEH designed the trial. MEH designed the handheld RELF device. MDB and MEH prepared the study. FVH recruited patients. YV was the investigator at AZ Sint Jan hospital, Bruges, Belgium. JV was the investigator at AZ Nikolaas hospital, Sint-Niklaas, Belgium. FVH, BD, and PK performed PCI. MEH managed the study server. FVH followed up patients. FVH, MC, JDP, BD, and PK independently assessed the ECGs for ST elevation criteria. MD, SG, and YV independently assessed the ECGs for changes during balloon inflation. FVH, MDB, and MEH interpreted the data. FVH, MDB, and MEH analysed the data. FVH and MDB drafted the manuscript. MC, JDP, BD, MD, SG, PK, YV, JV, and MEH commented on the manuscript. PG was the lead researcher and lead the preparation of all analyses and drafts of the manuscript.

Declaration of interests

PG, MEH, and Ghent University declare the patents EP3003140A1 (European Patent Office), CA2912476A1 (Canada), WO2014187998A1 (WIPO [PCT]), US9867577B2 (USA). All other authors declare no competing interests.

Data sharing

All data collected for the study, including individual participant data and a data dictionary defining each field in the set, are available upon request. Data available are de-identified participant data and the data dictionary. Additional available data are the instructions folder containing the six steps on one page for operation of the study device. Data will be made available, on request, by contacting the primary investigator of the study by email at peter.gheeraert@uzgent.be or the first author by email at frederic.vanheuwelswyn@uzgent.be.

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