Study Report	
Drug Substance	APP Mein Herz und ich
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Evaluation of an Electronic Device Based Support Tool for ACS Patients: Brilique™ (Ticagrelor) Treatment Adherence (eMocial)

Study dates: First subject enrolled: 11 February 2016
Last subject last visit: 10 April 2019
The analyses presented in this report are based on a database lock date of 03 May 2019

Phase of development: NA

National Co-ordinating Investigator: [redacted]

Sponsor's Responsible Medical Officer: [redacted]
AstraZeneca Mölndal
[redacted]

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

2 SYNOPSIS

Study centre(s)

In total, 30 study centres in one country (Germany) participated.

Publications

The design concept has been published in Clinical Cardiology, "Design and rationale for the 'Me & My Heart' (eMocial) study: A randomized evaluation of a new smartphone-based support tool to increase therapy adherence of patients with acute coronary syndrome, Clin Card, 42, (11), 1051-1135, 2019

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To evaluate the effect of patient support through an electronic device application on treatment adherence in acute coronary syndrome (ACS) patients prescribed to Brilique™ (ticagrelor) in Germany	Adherence to prescribed treatment according to questions 1-4 in the Brilique™ Adherence Questionnaire (BAQ) including a scoring system for quantification from 0-14 (i.e. one deduction for every missed Brilique™ (ticagrelor) tablet per week with 7 days and twice daily dosing). The BAQ was administered via electronic device every 4 weeks. The percent of tablets taken from the last week asked for in BAQ, was representing the last 4 weeks of Brilique use.
Secondary	Efficacy	To evaluate the effect of patient support through an electronic device application on adherence to Brilique™ (ticagrelor) medication*	Percentage of tablets taken during the 48 weeks observation phase measured by a MEMS to record a time stamp for every tablet taken.*
Secondary	Efficacy	To evaluate the effect of patient support through an electronic device application on the change from baseline to Visit 2 in key risk factors	Blood pressure, laboratory parameters (if available: Low Density Lipoprotein (LDL) cholesterol, High Density Lipoprotein (HDL) cholesterol, haemoglobin A1c (HbA1c), body weight, and body mass index (BMI).
Secondary	Efficacy	To evaluate the effect of patient support through an electronic device application on the Quality of Life	Assessed by SF-36v2®

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	To evaluate the effect of patient support through an electronic device application on the patient reported lifestyle changes	Assessed by Lifestyle Changes Questionnaire (LSQ)-V1 and -V2
Secondary	Efficacy	To evaluate the effect of patient support through an electronic device application on the patient reported disease understanding and treatment awareness	Assessed by questions 5-11 in the BAQ. The BAQ was delivered via electronic device every 4 weeks.
Secondary	Efficacy	To evaluate the effect of patient support through an electronic device application on the health care utilization	Assessed by questions 12-15 in the BAQ. The BAQ was delivered via electronic device every 4 weeks.
Exploratory	Efficacy	To evaluate the effect of patient support through an electronic device application on treatment gaps*	Missed tablets (based on MEMS) compared between randomised groups*
Exploratory	Efficacy	To evaluate the effect of patient support through an electronic device application on the use of alternative medication reminder or health APPs	Usage of other Medication reminder or health APPs
Exploratory	Efficacy	To evaluate whether the cardiac risk score at baseline is relevant for the effect of patient support tool on adherence to Brilique™ (ticagrelor) medication	The impact of GRACE 2.0 risk score at baseline on adherence as assessed by BAQ.
Exploratory	Efficacy	To explore the use of the electronic device application and functionality over time*	For the active group: The number of times the electronic device application was used during the study period through an analysis of the recorded user data.* System Usability Scale

*these data were not available at the time of drafting the report

ACS, acute coronary syndrome; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; HbA1c, haemoglobin A1c; BMI, body mass index; LSQ, Lifestyle Changes Questionnaire; PRO, patient reported outcome; BAQ, Brilique™ Adherence Questionnaire; MEMS, Medical Event Monitoring System; APP, application

Study design

This was a randomised investigation according to §23b *Medizinproduktegesetz* (German Medical Device Law) examining the impact of an electronic device based patient support tool on drug adherence, drug persistence and lifestyle changes in patients who had been prescribed

Brilique™ (ticagrelor) as part of normal clinical practice in a 12 month timeframe after an acute coronary syndrome (ACS) episode.

The aim of this study was to evaluate the effectiveness of this tool, called “Mein Herz und ich”.

Patients hospitalised with ACS (ST elevation myocardial infarction [STEMI], non-ST elevation myocardial infarction [NSTEMI], or unstable angina pectoris [UA]) and treated with Brilique™ (ticagrelor) co administered with low dose acetylsalicylic acid (ASA) were randomised 1:1 into an active group receiving the patient support tool under investigation via electronic device application (APP) and a control group without the patient support tool. In addition, both groups – active and control – consisted of two 1:1 randomised subgroups, one that used a Medical Event Monitoring System (MEMS) to record when the patients had taken their medication, and one without MEMS available. Patient questionnaires for evaluation of lifestyle changes and quality of life were administered at the beginning (Visit 1) and end (Visit 2) of the observation period. In addition, questionnaires for adherence, treatment attitudes, health care utilization and risk factors were administered at monthly intervals.

Target subject population and sample size

The target population was ACS patients 18 years or older with access to an electronic device compatible with the patient support tool, diagnosed with STEMI, NSTEMI or UA treated with twice daily Brilique™ (ticagrelor) co-administered with ASA once daily according to the prescription recommendation, within 14 days following the diagnosis of an ACS event. Excluded were patients on treatment with oral anti-platelet drugs other than Brilique™ (ticagrelor), with planned coronary artery bypass grafting (CABG) or any other elective surgery, or with serious/severe co-morbidities which might limit life expectancy (<1 year).

The number of evaluable patients needed was set according to the intervention with 231 evaluable patients per arm, so for the whole study 462 patients were planned. Based on literature data and data on file the drop-out rate was estimated to 30% resulting in a total of 660 patients. This will then give the primary objective a power of 85%, with an assumed effect of 7% improvement on adherence and a SD of 0.25.

The revised sample size of 660 patients was achieved in this study. In total, 677 patients from 30 centres were enrolled and statistically analysed.

The active group, patients receiving the patient support tool via a smarthphone-based application, included 343 patients (50.7%) whereas the control group without the patient support tool encompassed 334 patients (49.3%).

Both groups – active and control – consisted of two 1:1 randomised subgroups, one that used the MEMS to record when the patient had taken their medication, and one without MEMS.

165 patients (48.1%) of the active group and 171 patients (51.2%) of the control group were randomised to the MEMS subgroups.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

In this study no investigational products were dispensed to the study participants.

An electronic device APP, “Mein Herz und ich”, had been developed by the sponsor specifically for ACS patients who were prescribed Brilique™ (ticagrelor) to increase adherence to treatment (medication and lifestyle changes) by a combination of reminders on medication intake, information on the importance of treatment, motivation by supportive messages, and visualisation of individual lifestyle choices’ effect on cardiovascular risk. In addition, questionnaires were delivered to the patients in intervals of 4 weeks via the APP.

The device has a CE-mark. Patients needed to provide their own Brilique™ (ticagrelor) supply from the pharmacy, as in common clinical practice. Furthermore, assessments in this study were not to be used for guiding the treatment of the patients participating in the study.

Brilique™ (ticagrelor) is approved and marketed in Germany. Brilique™ (ticagrelor) was not considered an investigational product for this study. The Brilique™ (ticagrelor) prescription used by patients in this study was NOT provided by AstraZeneca, i.e., patients had to purchase their medication as commonly practiced.

Duration of treatment

The observation period per patient was 12 months from the date of the ACS.

Statistical methods

Statistical analysis was performed using the Full Analysis Set which includes all randomised patients. Patients were followed for one year after the ACS. For primary outcome variables, a hypothesis test of equal means was performed at 5% significance level (one-sided). For all secondary outcome variables descriptive statistics are presented.

Subject population

In total, 677 adult ACS patients, diagnosed with STEMI, NSTEMI or UA treated with Brilique™ (ticagrelor) from 30 centres in Germany were enrolled and randomised. Mean number per centre was 22.6 (±24.0, median 12.0) patients with a minimum of one patient (5 centres) and a maximum of 71 patients (2 centres).

All patients fulfilled the inclusion criteria and none of the patients met any of the exclusion criteria.

The active group included 343 patients (50.7%) whereas the control group encompassed 334 patients (49.3%). 165 patients (48.1%) of the active group and 171 patients (51.2%) of the control group were randomised to the MEMS subgroups.

At Visit 1, data of 677 patients and at Visit 2, data of 605 patients were available. The number of patients withdrawn from the study was 193, whereas 484 patients completed the study as per the clinical investigation plan (CIP).

The majority of enrolled patients was male in each group (active group, 83.0%; control group, 86.5%). Mean age of both groups was almost similar with 56.6 (active group) and 56.0 (control group) years, respectively.

With regard to co-morbidities including risk factors, such as hyperlipidemia, diabetes mellitus, obesity and smoking, a comparable proportion of patients of both groups was affected.

With regard to the educational and professional level, more than half of the patients had a secondary school degree (active group, 51.2%; control group, 53.0%) and was employed or self-employed (active group, 67.3%; control group, 64.1%). A comparable part of both groups was living with a partner (active group, 55.0%; control group, 49.1%). The majority of both patient groups were not on a vegetarian or vegan diet (active group, 99.1%; control group, 99.0%). Most patients stated to eat moderately healthy (active group, 73.8%; control group, 69.8%).

As concerns the number of patients treated with cardiovascular and/or diabetes medication, no considerable differences were detected between patient groups. Furthermore, mean values of vital as well as laboratory parameters were comparable.

In conclusion, the characteristics of both patient groups were very similar. All documented socio-demographic features, key baseline characteristics and co-morbidities were comparable between patient groups.

Summary of efficacy results

The primary endpoint is patient reported adherence to ticagrelor treatment via the BAQ on a monthly basis. During the whole observational period of 12 months the treatment adherence was significantly better in patients receiving the patient support tool via a smartphone-based application than in patients without the patient support tool (average adherence rate of 96.4% versus 91.5%, n=174 in each group, $p<0.05$). The analysis shows a significant improvement of the adherence already during the first 3 months, 99.0% vs 95.8% for active and control groups, respectively (n=174 in each group), $p<0.05$), and the difference is sustained throughout the 12 months period with the adherence data at the end of study (week 37-48) being 93.7% and 87.4%, respectively. The data contain a high degree of missing data in both the active and the control group.

The study data indicate a putative high adherence level in both treatment groups under real life conditions within the observational period of 12 months. The active group showed a high degree of treatment adherence with over 93% of tablets taken during the entire observational time of 12 moths. The percentage of tablets taken was highest within the first 3 months (1st month, 98.6%; 2nd month, 99.3%; 3rd month, 98.9%) and the lowest adherence level (93.3% of tablets taken) was recorded 12 months post study start. Patients of the control group showed a similar pattern with an adherence above 90% of tablets taken during the first seven months. Lowest value for the control group was also recorded at the end of the observational period (87.0% of tablets taken).

During the whole study, the proportion of adherent patients (defined as adherence >90%) in the control group was lower than in the active group. The differences between the two treatment groups already existed in the first quarter and were strengthened during the study. In the first 3 months 97.1% of patients in the active group reported an adherence >90%. The corresponding value for the control group was significantly lower at 91.9% (n=174 in both groups(?), $p<0.05$). The data for month 10-12 was 91.4% and 83.9% (n=174 in both groups(?), $p<0.05$), respectively.

The majority of patients in both groups took Brilique™ (ticagrelor) during the entire course of the study. Only 17 patients (8.2%) of the active group and 23 patients (11.4%) of the control group stated that they had stopped taking Brilique™ (ticagrelor)

On average, mean number of Brilique™ (ticagrelor) tablets the patients had taken during the last 7 days in case they had not taken the pills every day was 12.1 in patients of the active group and 10.5 in patients of the control group.

Overall, treatment adherence was significantly better in patients receiving the patient support tool via the smartphone-based application than in patients without the patient support tool. However, data to determine adherence were present only in a certain part of the participating patients. It is possible that missing data are more frequently those from patients with poor compliance, but the rate of missing data is very similar in both control and active groups. Thus, it cannot be ruled out that available data might have led to allegedly higher adherence rates than they actually would have been if data of all patients had been available. Our study shows a difference in adherence rates between the patient groups when time periods of three months were considered using the pre-defined imputation method for missing data.

Summary of safety results

NA

Conclusion(s)

Overall, adherence to the prescribed medication was high in patients of both groups who provided data. However, adherence during the observational period of 12 month was

significantly higher in patients receiving the patient support tool via the smartphone-based application than in patients without the patient support tool (average adherence rate of 96.4% versus 91.5% (Is there a p-value?)).

The differences between the two treatment groups already existed in the first quarter of the study and were strengthened in the further course. With regard to patients of the active group, percentage of tablets taken was highest within the first 3 months (1st month, 98.6%; 2nd month, 99.3%; 3rd month, 98.9%). The lowest adherence value (93.3% of tablets taken) was recorded 12 months post study start. The proportion of adherent patients declined from quarter to quarter. This was also true for patients of the control group. They showed an adherence of >90% only within the first seven months.

Taken together, the eMocial study contributed to the knowledge of how adherence could be improved under real life conditions. The study evaluated how a novel smartphone-based support tool could help patients with acute coronary syndrome and impact the adherence to medication over a period of 12 months. The results may indicate that patient support via a smartphone-based APP can significantly increase adherence to treatment in a broad cohort of adult patients with acute coronary syndrome and treated with Brilique™ (ticagrelor) co-administered with low dose acetylsalicyl acid.