CLINICAL STUDY PROTOCOL

ICTU ADOPTED

Full Study Title: Implementation of a Decision Support System and its effect on early optimisation of Lipid-Lowering Therapies in patients with Acute Coronary Syndrome: a cluster Randomised Controlled Trial

Short Study title / Acronym: OptimiZation Of lipid lowering therapies using a Decision support system In patients with Acute Coronary syndrome (ZODIAC).

Sponsor: Imperial College London

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This protocol describes an implementation trial which assesses whether availability and use of a Decision Support System (DSS) improve achievement of guideline recommended control of cholesterol levels in patients after an acute coronary syndrome (ACS). This protocol provides information about procedures for enrolling participants into the trial. The protocol should not be used as a guide for the treatment of other participants (not participating in the trial); every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling

participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

ACS	Acute Coronary Syndromes
ADR	Adverse Drug Reaction
AE	Adverse Event
ASCVD	Atherosclerotic Cardiovascular Disease
CI	Chief Investigator
CV	Cardiovascular
CVD	Cardiovascular Disease
CRF	Case Report Form
DSS	Decision Support System
eCRF	Electronic Case Report Form
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
HRA	Health Research Authority
GPvP	Good Pharmacovigilance Practice
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
ITT	Intention to Treat
LDL-C	Low-density lipoprotein cholesterol
LLT	Lipid Lowering Therapy
LMT	Lipid Modifying Treatment
MI	Myocardial Infarction
NSTEMI	Non-ST segment elevation myocardial infarction
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SoC	Standard of Care
SOP	Standard Operating Procedure
STEMI	ST segment elevation myocardial infarction
TEC	Trial Executive Committee
UA	Unstable Angina

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TRIAL SUMMARY

TITLE
Implementation of a Decision Support System (DSS) and its effect on early optimisation of Lipid-Lowering Therapies in patients with Acute Coronary Syndrome: a cluster Randomised Controlled Trial.

OBJECTIVES
To compare implementation of a DSS (aligned to the 2019 ESC/EAS Guidelines) in addition to routine clinical care versus routine clinical care without availability of a DSS, to assess whether the availability of a DSS to current practice results in an increase in the early initiation of combination lipid lowering therapies (LLTs) or intensification of LLT regimens compared to current practice alone over a 16-week period after an ACS event.
To evaluate the potential benefits of guideline-based LLT intensification via simulation-based methods using estimates of baseline risk: LLT utilisation, additional LDL-C reductions and LDL-C goal achievement, on simulated risk of CV events through modelling.

DESIGN
A cluster randomised, parallel arm trial with a maximum of 48 sites randomised to Standard of Care (SoC) [24 sites] or DSS [24 sites] across 3 countries: the United Kingdom (UK), Spain and Italy. We plan to recruit 16 sites per country; 8 DSS sites; 8 SoC sites. In the event of under-recruitment of sites in Italy or Spain, up to 6 replacement sites may be recruited from the UK. DSS sites will receive a standardised period of training prior to commencing patient recruitment. Patients will be followed up for a maximum of 16 weeks.

SAMPLE SIZE
1584 participants across a maximum of 48 sites (792 over 24 clusters per arm).

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:
Sites:

- Manage ACS patients as defined by: Symptoms of myocardial ischemia with an unstable pattern, occurring at rest or with minimal exertion, within 72 hours of an unscheduled hospital admission due to presumed or proven obstructive coronary disease and at least one of the following:
    - Elevated cardiac biomarkers
    - Resting electrocardiographic changes consistent with ischemia or infarction, plus additional evidence of obstructive coronary disease from regional wall motion or perfusion abnormality, 70% or more epicardial coronary stenosis by angiography, or need for coronary revascularization procedure
- Mange post ACS follow up care of patients including risk factor control
- Ability to provide follow up information on patient care for a maximum of 16 weeks including blood tests
- Willing/ able to access and undertake training for the DSS
- Adequate internet connection at site and the ability to access the DSS
- No restrictions on use of LLTs (within national guidelines/ reimbursement)
- Patient information essential for DSS input on all of the following:
    - LDL-C, TC, HDL-C measurements.

- Record of corresponding lipid-lowering therapy at the time the LDL-C is measured.
- Estimated GFR (eGFR), e.g. available or derived using MDRD, or its component, the serum creatinine.

Patient's demographics (age, gender), prior clinical history (ASCVD, coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm, peripheral artery disease, Diabetes Melitus), systolic blood pressure, smoking status.

Participants:

- Aged ≥18 to < 80 years old
- Provide written informed consent
- Presenting to a study site with ACS as LLT naïve, monotherapy or combination therapy (defined as more than one LLT agent)
- Willing to take lipid lowering treatments for the secondary prevention of cardiovascular disease
    - Attending the same study site (or same clinical team) for ACS follow up to ensure follow up data can be collected; or ensure that follow up data can be collected from other clinical institutions as part of the clinical pathway.

Exclusion criteria:

Sites:

- Unable to capture/ provide data on patients with ACS during admission and follow up
- Unable or unwilling to use lipid lowering treatments other than statins for ACS care

Participants:

- Unable to provide written informed consent
- LDL-C measurement < 1.8 mmol/L at admission

MAIN STUDY PROCEDURES

Those sites randomised to standard of care will continue with routine clinical practice. For those sites randomised to the DSS, there will be no patient intervention. The DSS generates a patient-specific recommendation on the value of initiation of add-on lipid lowering therapy for reducing the risk of recurrent Cardiovascular (CV) events. Based on the patient-specific profile and a benefit calculator plus other evidence-based tools, the DSS generates a patient-specific recommendation on the expected clinical benefit from combination therapy and is designed to support clinical decision making at the time of ACS in-line with EAS/ ESC guidelines. Implementing the patient-specific recommendation remains at the clinicians' discretion.

OUTCOME MEASURES

PRIMARY ENDPOINT

Proportion of patients treated with combination therapy, or who receive escalated monotherapy, or escalated combination therapy, within 16 weeks of the index ACS. Combination therapy is defined as two or more drug combination regimens using commercially available licenced LLTs (statins, selective cholesterol-absorption inhibitors, adenosine triphosphate-citrate lyase (ACL) inhibitors, bile acid sequestrants, PCSK9 monoclonal inhibitors or PCSK9 siRNA therapy). Escalated therapy includes increase in

statin potency, switching to a more potent combination regimen e.g. statin plus ezetimibe to statin plus PCSK9 Mab, or two drug combination therapy increased to triple therapy.

SECONDARY ENDPOINTS

1. Time to initiation of combination therapy or escalation of Lipid lowering therapy as defined in the primary endpoint.

2. LDL-C by Week 16

3. Proportion of patients reaching target LDL-C level (<1.4 mmol/L (<55 mg/dL) by Week 16.

EXPLORATORY ENDPOINTS

1. Proportion of patients achieving a decrease from baseline LDL-C level of more than 50% by Week 16 for LLT naïve patients
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5. Percent change from baseline in triglycerides by Week 16 for LLT naïve patients
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12. Proportion of patients with goal achievement (LDL-C <1.4mmol/L by Week 16 or 55mg/dl) in each trial arm stratified by institution setting (secondary/tertiary/mixed), country (UK/Spain/Italy) and by subpopulations defined by whether patients had experienced one or more CV events in the 2 years prior to admission.
13. LDL-C levels by 16 weeks among LLT naïve (at ACS), monotherapy and combination therapy patients, within the DSS arm.
14. Quantitative evaluation as evaluated by the DSS Evaluation Questionnaire of the DSS by the clinicians at DSS sites

1. BACKGROUND

Acute coronary syndromes (ACS) represent conditions compatible with acute myocardial ischemia and/or infarction. These include ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). Following hospitalisation for an ACS, patients who survive to hospital discharge are at high-risk of recurrent non-fatal and fatal atherosclerotic cardiovascular disease (ASCVD) events, including myocardial infarction (MI), ischemic stroke, cardiovascular (CV) death, UA requiring hospitalisation, and coronary revascularization.[1] Risk factors/markers which

identify those at greater risk for recurrent ASCVD events include the characteristics of the index ACS event itself (e.g. whether MI or UA), management strategies (revascularization, use of preventive therapies), prior history of ASCVD or polyvascular disease, other comorbidities (e.g. diabetes), and demographic characteristics.[1,2]

Low-density lipoprotein cholesterol (LDL-C) is a causal risk factor for incident and recurrent risk of ASCVD events.[3] Reduction in LDL-C with lipid-lowering therapy (LLT) reduces the risk of ASCVD events across broad group of patients, including those with a recent or a history of a prior ACS event.[4] The relative risk reduction derived with sustained LDL-C lowering via LLT has been observed to be time-dependent in randomised controlled trials (RCTs) with the relative risk-reduction gradually improving over time with continued and persistent treatment with LLT over longer durations.[4] This is consistent with data from Mendelian randomisation studies where a larger relative risk reduction is observed per 1 mmol/L reduction in LDL-C (approximately 52% over 52 years) as compared to RCT data where over 5 years the benefit per 1mmol/L is approximately 22%, reinforcing the importance of longer-term cumulative reductions to benefit from LDL-C lowering.[3] Moreover, as the benefit per 1mmol/L reduction in LDL-C is half (approx. 10-11%) in the first year of therapy versus later years, this underscores a strategy of immediate, intensive and sustained reduction in LDL-C in very high-risk individuals such as those with an ACS event. Furthermore, as the required reductions in LDL-C and the recommended goals are unachievable for the vast majority without use of combination therapy, recent expert consensus statements recommend combination LLT as first-line strategy in this population rather than a step-wise approach.[5]

The 2019 European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) dyslipidaemia guidelines categorise patients with an ACS event as very-high risk and recommend an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) and >50% reduction in LDL-C in this population.[1] Several studies of populations in Europe have highlighted gaps between clinical practice and implementation of recommended LLTs as compared with evidence based guideline recommendations. A national registry including several thousand individuals admitted to hospital with a MI in Sweden concluded that approximately 77% patients had no evidence of past statin treatment at the time of admission for the MI event.[6] In the 6-10 weeks after the MI event, there was insufficient treatment intensification. For instance ~25% of patients who were admitted saw little or no change in cholesterol levels, with LDL-C levels of about 2.1mmol/L at admission and ~ 2.3 mmol/L post discharge. Most of these patients were on statins, had prior history of ASCVD and high-risk comorbidities. The use of ezetimibe was 1% at the MI event increasing to 7% post event suggesting a shortfall in optimisation/ intensification of therapy beyond statin based monotherapy. Even among the 77% of patients newly initiated onto statins at the time of the ACS event, LDL-C levels ranged between 1.8-1.9 mmol/L with approximately 13% of those initiated onto statin therapy discontinuing at 8-12 months. In the DA VINCI study representing 5,888 patients prescribed LLT in 18 countries across Europe, LDL-C goal achievement in very-high risk patients per 2016 and 2019 ESC/EAS guidelines was 39% and 18%, respectively.[7] Use of statin monotherapy and combination of statin and ezetimibe was 84% and 9.0 % respectively. Use of PCSK9 monoclonal antibodies in combination with oral LLTs were 1% Similar findings regarding gaps in treatment compared with guideline recommendations have been reported in several country-specific studies across Europe including the United Kingdom (UK), France, Italy, Germany, and the Netherlands, representing a collective failure of public health in implementing guidelines.[8-13]

Barriers to achieving guideline recommendations for control of lipid-levels via LLT therapy are multi-factorial. These may include perceived side effects, health literacy (lack of patient education) relating to benefits of therapy for an essentially silent risk-factor, complexity of treatment regimens including polypharmacy in patients requiring multiple medications, and challenges related to reimbursement. Implementation of effective lipid lowering strategies in patients at highest risk, such as those with ACS, is poor globally, heterogeneous, and often relies on unwieldy multiple steps, delaying the time to optimisation of effective control of LDL-C. Moreover, to achieve guideline based lower LDL-C levels, combination therapy is required. Extensive contemporary data demonstrates that combination therapy will be essential in order for the vast majority of ACS patients to reach new guideline target of LDL-C. A study based on patients with an ACS hospitalisation in Switzerland concluded that approximately 76% will require combination therapy to achieve LDL-C < 1.4 mmol/L (note the additional requirement of > 50% LDL-C reduction from baseline was not modelled in this analysis making this estimate relatively lower), with 35% requiring only statin + ezetimibe and 51% requiring an add-on PCSK9 inhibitor.[14]

Another study based on the SWEDEHEART registry in Sweden representing individuals with hospitalization for an MI event indicated that 80% of the patients will require treatment with combination therapy (approximately 29% requiring only statin + ezetimibe and approximately 51% requiring an add-on PCSK9 inhibitor) to achieve 2019 ESC/EAS guideline recommendation of LDL-C level of < 1.4 mmol/L and ≥ 50% reduction in LDL-C.[15] Another study based on the INTERCATH registry in Germany representing a stable ASCVD population indicated that approximately 70% of the patients will require statin and ezetimibe to achieve LDL-C goals with approximately 42% also requiring add-on PCSK9i in order to achieve the 2019 ESC/EAS guideline recommendations.[11] These estimates predicting that approximately 70% to 80% of very high-risk patients will require combination LLT to achieve LDL-C levels < 1.4mmol/L are analogous to scenarios for antihypertensive therapies where approximately 75% to 80% of individuals are estimated to require combination therapy for achieving guideline recommended blood pressure control. Based in part on this rationale the 2018 European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) guidelines for the management of arterial hypertension recommend initiating treatment with a combination therapy in most people with hypertension.[17]

The aim of this trial is to assess whether the availability and use of a DSS system is more likely to result in implementation and achievement of EAS/ESC lipid lowering goals in ACS patients.

The expected clinical benefit of treatment with combination LLT depends on: (1.) patient's baseline risk representing existing clinical characteristics, (2.) baseline LDL-C level, (3.) absolute LDL-C reduction with LLT treatment regimens whether monotherapy or combination therapy, and (4.) duration of treatment.[4] Although the baseline risk and LDL-C levels represent characteristics before treatment and vary by patients, a published risk-reduction model combines these with potential treatment choices and treatment duration to provide reliable estimates of the magnitude of the expected clinical benefit. These estimates serve as a framework, helping provide scenarios where the choice and duration of different treatment regimens can be reliably estimated and visualised easily. This serves to inform the health-care professional and may help to better communicate to patients the clinical value of more intensive, continued therapy and relevance of consistent sustained LDL-C reductions over time. The estimation of the baseline risk can be further facilitated by use of the SMART risk prediction model which has been validated in multiple trials, epidemiological

studies and in routine health care records. Combining the overall estimation of baseline risk with estimated treatment benefit from any combination of LLT can be facilitated via a web application developed by Imperial College London and the European Atherosclerosis Society, which allows for graphical and tabular representation of individualised benefits in different scenarios. This web application brings together published validated tools both for estimation of risk and treatment benefits from RCT data.[4]

Subsequent modelling and simulation-based analysis will provide estimates of CV event impact of initiation and continuation of combination therapy over longer time horizons, 1 year, 5 year, 10 years. Several scenarios will be investigated as detailed later in the document.

1.1 Clinical setting

Patients presenting to hospitals with ACS (myocardial infarction (MI)). Of those, approximately 65-75% will be non-ST elevation MI (NSTEMI) and the remainder ST elevation MI (STEMI). Of the ACS cohort, we expect approximately 75% to be statin naïve at the time of presentation with ACS.

1.2 Intervention details

Study sites will be allocated to either SoC group or the DSS group. Both groups will be following routine clinical care including local / national prescribing guidelines during the course of the study. For those sites randomised to the DSS, there will be no patient intervention, but those sites' will be trained on a DSS tool. The DSS is a web application available online intended for clinicians to estimate the clinical benefit of any LLT regimen, whether monotherapy or combination therapies. The DSS does not recommend treatments but shows the expected ASCVD risk, absolute and relative ASCDV risk reductions and number needed to treat for the various treatments selected by the clinical user on the potential value of initiation of an add-on therapy for reducing the risk of recurrent Cardiovascular (CV) events. Implementing the patient-specific recommendation remains at the clinicians' discretion.

This DSS will provide estimates of potential benefits in terms of ASCVD risk reduction (composite endpoint: combined non-fatal myocardial infarction, non-fatal ischaemic stroke and cardiovascular death) as a function of treatment duration and magnitude of LDL-C lowering. This DSS is a graphical and tabular representation of the time-dependent CV treatment benefit model for LLTs published in a peer-reviewed journal article.[18]

The DSS collects the following inputs in a structured format:

i) The patient's ASCVD risk at the time the DSS is used, whether reported as in percentage/year, or 5, or 10y if known. If it is unknown, the 10-year risk can be estimated using an embedded calculator utilising the SMART calculator.[19]

ii) The patient's high-sensitivity C-reactive protein level (a variable included in the SMART calculator), if known is added or imputed if unknown using published data.[20]

iii) The patient's latest LDL-C measurement and corresponding lipid-lowering therapy (if any) at the time the LDL-C was measured.

iv) A hypothetical alternative treatment strategy for which the clinical benefit must be estimated.

v) The patient identifier and email address of the nurse / investigator responsible for entering the data into the “OpenClinica” study database.

The DSS produces the following outputs over a period of 30 years starting from 0 years (on the x-axis in figures and in rows of tables):

i) Estimated risk of ASCVD for current and alternative therapies, and no therapy, and by duration of treatment (or years without treatment).

ii) Absolute reductions in ASCVD risk due to current and alternative therapies compared to no therapy, by duration of treatment.

iii) Relative reductions in risk due to current or alternative therapies compared to no therapy, by duration of treatment.

iv) Numbers Needed to Treat to prevent one composite endpoint outcome under current and alternative therapies by duration of treatment.

The DSS has been developed with the Angular 10 JavaScript Framework and will be published in a web application that can be accessed on the Internet using the most common Web browsers, namely Google Chrome, Safari, Internet Explorer, Microsoft Edge, or Mozilla Firefox. The DSS has been tested on these web browsers and we cannot guarantee it will work on other unlisted web browsers. The DSS will be protected from unwanted use by asking its users to enter their OpenClinica credentials.

All versions will be run within the users’ devices to enhance data privacy and reduce the risk of malfunctioning. At each use of the DSS, i) a limited amount of information will be collected, anonymised, and stored on a secure server for data and usage monitoring, and ii) the DSS inputs will be sent to the clinical research nurse responsible of inputting these data into OpenClinica, the study database.

No personally identifiable information will be stored in or by the DSS directly, which will be described in a readily available Privacy Notice. The DSS will be accessible to visually impaired users, and this will be described in an accessibility statement.

Prior to the trial taking place, the DSS will be functionally tested by an external software testing company to make sure the risk and benefit are accurate and reliable. The DSS will be hosted on two servers from different cloud providers so if one is not working users will be asked to use the second domain name and access the working server. It is highly unlikely that two data providers are unavailable at the same time. No data will remain on the cloud but only transit for a brief moment until it reaches OpenClinica.

The authors of the original publication[23] have reviewed the implementation of their time-dependent model within the DSS source code and have validated its accuracy.

Once a site has been randomised to receive the DSS tool, study staff and clinicians utilising the DSS will receive training on the tool including a standardised training manual, as well as practical training and simulated clinical scenarios. A study version of the DSS tool will be created (in English) and distributed to site staff after allocation to the DSS and site training has been conducted. Access will be restricted to those site staff who are both trained on the DSS and are on the study delegation log.

DSS sites will also be supported throughout the trial via various formats including regular Webinars with National Leads, and regular automatic communication providing reminders about the availability of the tool. More details about the standard training procedures, FAQs and Trouble Shooting will be documented in the Training Manual.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To compare implementation of a DSS (aligned to the 2019 EAS/ESC Guidelines) added to routine clinical care as compared with routine care without a DSS, to assess whether the addition of a DSS system to current practice increases the likelihood of initiation or combination therapy or escalation of LLT over a 16-week period. To evaluate the longer-term impact of guidelines-based treatment intensification with LLT via simulation-based methods on: LLT utilisation, LDL-C goal achievement, and simulation of CV events.

2.2 Secondary Objectives

1. To compare the time to intensification of LLT in DSS versus routine care.
2. To compare the mean low-density lipoprotein cholesterol (LDL-C) and other key lipid variables by Week 16 in DSS versus routine care.
3. To compare the proportion of patients reaching target LDL-C level (<1.4 mmol/L (<55 mg/dL) by Week 16 in DSS versus routine care.
4. To compare the proportions of patients who receive different types of intensification of LLT: combination therapy by Week 16, escalated monotherapy by Week 16 and escalated combination therapy by Week 16 in DSS versus routine care.

4. Simulation objectives:

   a. Evaluate impact of guidelines-based treatment intensification on the need for combination therapy (e.g. % requiring add-on ezetimibe and PCSK9i)

   b. Evaluate impact of guidelines-based treatment intensification on LDL-C goal achievement

   c. Evaluate impact of guidelines-based treatment intensification on CV events representing composite of nonfatal MI, nonfatal ischemic stroke, and CV death over longer time horizon (e.g., 1-year, 5-years, and 10-years).

2.3 Primary Endpoint

Proportion of patients treated with combination therapy, or who receive escalated monotherapy, or escalated combination therapy, within 16 weeks of the index ACS. Combination therapy is defined as two or more drug combination regimens using commercially available licenced LLTs (statins, selective cholesterol-absorption inhibitors, adenosine triphosphate-citrate lyase (ACL) inhibitors, bile acid sequestrants, PCSK9 monoclonal inhibitors or PCSK9 siRNA therapy). Escalated therapy includes increase in statin potency, switching to a more potent combination regimen e.g. statin plus ezetimibe to statin plus PCSK9 Mab, or two drug combination therapy increased to triple therapy.