The REALIST (REsiduAl risk, Llipids and Standard Therapies) study: an analysis of residual risk attributable to lipid profile in acute coronary syndrome

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Abstract The R3i Foundation (Residual Risk Reduction Initiative), an independent, multinational and academic organization, is conducting the REALIST (Residual Risk, Lipids and Standard Therapies) study in 40 centers in different countries. This is a retrospective epidemiological study, designed to provide new data on the residual risk of major coronary events attributable to lipid abnormalities in patients receiving the current standard treatment. The initial results are expected in mid 2010, and the overall results at the end of 2010.

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PALABRAS CLAVE
Riesgo residual; Dislipemia; Cardiopatía isquémica

Estudio REALIST (REsiduAl risk, Llipids and Standard Therapies): un análisis del Riesgo Residual dependiente del perfil lipídico en el síndrome coronario agudo

Resumen La Fundación R3i (Residual Risk Reduction initiative), una organización académica, multinacional e independiente, está llevando a cabo el estudio REALIST (Residual risk, Lipids and Standard Therapies) en más de 40 centros de diferentes países. Se trata de un estudio epi-
Background and study rationale

Treating LDL cholesterol is not sufficient to decrease residual cardiovascular risk

To date, treatment of dyslipidemia has mainly focused on reduction of LDL cholesterol levels, in addition to control of other modifiable cardiovascular risk factors such as smoking and hypertension. This approach is supported by a broad basis of medical evidence. In large-scale prospective studies in primary and secondary intervention, a 25% to 40% LDL cholesterol reduction was associated to a 9%-38% decrease in the risk of cardiovascular disease (CVD) (4S, CARE, LIPID, ALLHAT, ASCOT, WOSCOPS, AFCAPS/TEXCaps, HPS, and PROSPER studies) depending on baseline cardiovascular risk (CVR) levels.

However, while statin treatment is effective for reducing CVR and decreasing the progression rate of atherosclerosis, it is not able to prevent a majority of subsequent cardiovascular events. Even in patients who achieve their goal LDL cholesterol levels, the residual risk of subsequent cardiovascular events during the 5 following years continues to be high, ranging from 65% and 75% of the risk in control groups. In a published meta-analysis, 14.1% of patients treated with statins (approximately 1 out of every 7 patients) experienced subsequent or recurrent cardiovascular events during a 5-year period. This absolute risk was even greater in patients with pre-existing coronary heart disease (CHD) (21.2%) or with diabetes mellitus (19.1%).

These data have promoted research of a “treating to new targets” strategy based on the hypothesis that an increased dosage of statin therapy would result in a greater reduction of the risk of CVD. Studies such as PROVE-IT-TIMI 22 (Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction) and TNT (Treating to New Targets) showed that high-dose statin therapy aimed at decreasing LDL cholesterol to levels lower than 80 mg/dL (such as in the TNT study) or 70 mg/dL (such as in the PROVE-IT TIMI-22 study) was associated with a greater reduction in the cardiovascular event rate. However, more than 50% of patients continued to be at risk of experiencing subsequent cardiovascular events.

In addition, every increase in clinical benefit associated with high-dose statin therapy should be assessed in the light of a potential increase in the risk of side effects, particularly in the elderly. In two studies, TNT and PROVE-IT TIMI-22, the incidence of high transaminase levels (more than three times the upper normal limit) was greater among patients treated with high-dose statins than in those given conventional doses: 1.2% with atorvastatin 80 mg/day versus 0.2% with 10 mg/day in the TNT study and 3.3% with atorvastatin 80 mg/day as compared to 1.1% with pravastatin 40 mg/day. However, no differences were found in the incidence of creatine kinase elevation (10 times the upper normal limit) and rhabdomyolysis. Similarly, while high-dose statin therapy reduced the risk of recurrent stroke according to the SPARCL study, treatment was also associated with a small increase in hemorrhagic stroke.

Data from the TNT and PROVE-IT TIMI-22 studies showed that high-dose statin therapy, despite achieving an intensive reduction in LDL cholesterol levels, provides less cumulative absolute benefits. This effect is consistent with a non-linear model of maximum effects, with markedly decreasing recurrence (i.e. a reduction in the CVD event rate) and progressively lower LDL cholesterol levels. Overall, these data suggest that other factors, in addition to LDL cholesterol, contribute to cardiovascular risk and are therefore involved in the burden of residual cardiovascular risk.

Other lipid abnormalities prevalent in high-risk patients

As suggested in the INTERHEART study, dyslipidemia is not a single condition. This study defined dyslipidemia as the ratio of apoB, which is a part of the atherogenic lipoproteins, to apoA-1, which has an atheroprotective effect. These data suggest the importance of treating both lipoprotein types, and not only apoBs of LDL cholesterol, in CVR reduction.

In the US, data from 1.512 patients with CHD or CHD risk equivalents collected from the screening of 44.052 electronic primary care clinical histories suggested that 66% of these patients had low HDL cholesterol levels (40 mg/dL or less in males and 50 mg/dL or less in females). Low HDL cholesterol levels were very common at all LDL cholesterol levels, but especially among patients with LDL cholesterol levels of 70 mg/dL or less, even when treated with statins (64%). In an epidemiological study of 22.323 patients followed up by 4.000 primary care physicians and 927 cardiologists, 50% of patients with dyslipidemia had elevated triglyceride levels and low HDL cholesterol levels.

On the other hand, an assessment of trends in lipid-lowering treatment suggests that changes in the overall lipid profile are not always taken into account when CVR is addressed. In lipid samples collected from 6.098 of the 15.719 patients examined in five cross-sectional surveys conducted in the US from 1960 to 2000, no significant changes were seen in HDL cholesterol levels and only a small (and not significant) increase was seen in triglycerides despite a substantial LDL cholesterol reduction, particularly in elderly and female patients. Data from a retrospective, observational study of 30.348 patients, more than half of whom (57%) had CHD or CHD risk equivalent, showed that 78% did not achieve the combined goals of the different
lipid fractions (such as elevated HDL cholesterol and triglycerides) at three years of follow-up.

**HDL cholesterol, triglycerides, and cardiovascular risk**

There is broad-based evidence to show that low HDL cholesterol levels and high triglyceride levels (including postprandial hypertriglyceridemia) are independently associated with an increased cardiovascular risk.

**Low HDL cholesterol levels and cardiovascular risk**

Epidemiological studies such as the Framingham and PROCAM (Prospective Cardiovascular Münster) studies have established that low HDL cholesterol levels (lower than 40 mg/dL and 50 mg/dL in males and females respectively) are an independent risk factor for CHD. A meta-analysis of data from four large scale prospective studies in the US, two of them observational studies (the Framingham and Lipid Research Clinics Prevalence Mortality Follow-up studies), and two other studies based on data from the control groups of randomized clinical trials (the Coronary Primary Prevention Trial and the Multiple Risk Factor Intervention Trial) significantly showed that for every 1 mg/dL reduction in plasma HDL cholesterol levels there is a 2%-3% increase in CHD risk, irrespective of other risk factors, such as plasma LDL cholesterol levels. These data are supported by the results of the ARIC study (The Atherosclerosis Risk in Communities), showing a strong and continuous association between HDL cholesterol and CHD risk, particularly in elderly women. Studies show that the strength of the relationship between HDL cholesterol and CVD risk is maintained in elderly subjects.

**Hypertriglyceridemia and cardiovascular risk**

There is also a lot of information to suggest that high triglyceride levels are an independent risk factor for CVD, which provides information about other underlying risk factors apart from LDL and HDL cholesterol. A recent meta-analysis of data from the European Reykjavik and EPIC-Norfolk studies showed that the OR (odds ratio) for CHD associated with high triglyceride levels was 1.76 (95% CI: 1.39-2.11) in the Reykjavik study and 1.57 (95% CI: 1.10-2.24) in the Norfolk study, after adjustment for baseline triglyceride levels and established risk factors. In addition, a meta-analysis of 10,158 cases of CHD among 262,525 participants in 29 studies reported an OR of 1.72 (0.5% CI: 1.56-1.90) when patients with triglyceride levels in the upper tertile were compared to those with values in the lower tertile. This analysis, the most complete to date, showed a significant association between elevated triglycerides and CHD risk. The impact of high triglyceride levels on CHD risk was similar in males and females, and persisted even after adjustment for HDL cholesterol levels. These data support evidence from the PROCAM study, which showed that elevated triglyceride levels were a significant risk factor for CHD, particularly in patients with an LDL:HDLC ratio higher than 5.0.

**Atherogenic dyslipidemia**

The combination of hypertriglyceridemia and low HDL levels increases cardiovascular risk even more. In the PROCAM study, male patients with a combination of elevated triglyceride levels higher than 200 mg/dL and a high LDL:HDLC cholesterol ratio (higher than 5) had a six-fold greater cardiovascular risk. Similarly, data from the Helsinki Heart Study showed that males with elevated triglyceride levels (higher than 204 mg/dL) and low HDL cholesterol levels (lower than 42 mg/dL) had a 71% increase in the relative risk of cardiovascular events. In a study of 284 patients with established CHD and a mean follow-up of 7.8 years, serious cardiovascular adverse events (defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, recurrent angina, or revascularization) were seen to occur more frequently in patients with atherogenic dyslipidemia (51%) than in those who only had low HDL cholesterol levels or high triglyceride levels (33%) or normal HDL cholesterol and elevated triglyceride levels (29%) (p < 0.01 for the trend analysis). A Kaplan-Meier survival analysis also suggested a significant decrease in event-free survival in patients with atherogenic dyslipidemia as compared to those with no atherogenic dyslipidemia (p = 0.006). After adjustment for potential confounding variables, the presence of atherogenic dyslipidemia (elevated triglyceride and low HDL cholesterol levels) was associated with a significant increase in cardiovascular risk (hazard ratio 1.58, 95% CI: 1.12-2.21, p = 0.008).

A meta-analysis of 37 longitudinal studies enrolling 172,573 patients provided additional data about the association of atherogenic dyslipidemia and CVD risk. In this analysis, metabolic syndrome was associated with a relative risk of cardiovascular events and death of 1.78 (95% CI: 1.58-2.00). Some additional investigations of the relative risk associated with each of the individual components of metabolic syndrome showed that high triglyceride levels (OR 1.51, 95% CI 1.04-2.20) and low HDL cholesterol levels (OR 1.1, 95% CI 1.03-1.95) were the only two components significantly associated with CVD risk.

These data emphasize the importance of atherogenic dyslipidemia, the combination of high triglyceride levels with low HDL cholesterol levels, as a determinant of cardiovascular risk.

**Impact of components of atherogenic dyslipidemia on residual risk**

Pooled data from the CARE and LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) studies, including 13,173 patients with CHD, suggested that patients with baseline LDL cholesterol levels in the lowest quintile of the LDL cholesterol range (less than 125 mg/dL) did not achieve a significant benefit with pravastatin treatment. According to analyses of this group, these patients had a greater prevalence of diabetes mellitus (15% versus 9% in patients with LDL cholesterol levels of 125 mg/dL or higher) and arterial hypertension (46% versus 41%), as well as higher mean triglyceride levels (169 versus 154 mg/dL) and lower HDL cholesterol levels (36.5 versus 38 mg/dL). The combination of these effects contributed to a higher coronary event rate (23% over 6 years), similar to that seen in patients with higher HDL cholesterol levels (125 mg/dL or greater). Subsequent analyses showed that HDL cholesterol and triglyceride
levels were good predictors of coronary risk in patients with low LDL cholesterol levels, in whom the impact of other lipid changes is greater. For each 10 mg/dL increase in baseline HDL cholesterol value, coronary event rates decreased by 29% in patients with LDL cholesterol levels less than 125 mg/dL, but by only 10% in those with LDL cholesterol levels of 125 mg/dL or higher. Similarly, each 10 mg/dL increase in baseline triglyceride values caused a 1% increase in the coronary event rate in patients with LDL cholesterol levels less than 125 mg/dL, but only a 0.1% increase in those with high LDL cholesterol levels. Multifactorial analyses revealed that HDL cholesterol and triglyceride levels are two independent predictors of the occurrence of CHD events.

The REALIST Study

The R3i Foundation (Residual Risk Reduction initiative), a multinational, independent, academic organization is conducting in more than 40 centers from different countries the REALIST study (REsidual risk, Lipids and Standard Therapies), promoted by its international organization and through its national organizations. REALIST is a retrospective, epidemiological study designed to provide new data on the residual risk of major coronary events attributable to lipid changes in patients who receive the current standard treatments. Its initial results are expected in mid 2010, and the overall results at the end of 2010.

Objectives

Primary objective
This study will be based on the records of specific variables in the current clinical patient histories available at the participating centers.

The study objective is to assess the following in patients who have achieved the LDL cholesterol goal, having been treated or not for high LDL cholesterol levels, and who have been admitted to hospital with a first CHD event:

1) Prevalence of low HDL cholesterol levels or high triglyceride levels. Descriptive analyses will be used to achieve this objective.
2) Whether low HDL cholesterol levels or high triglyceride levels are associated with a significant risk of a coronary event.

Achievement of these objectives will be based on a descriptive analysis and a case-control study, as well as on the categorical and continuous analyses performed.

For this protocol, patients with residual risk attributable to lipid changes are defined as those whose lipid profile, as measured within 8 hours of symptom start, is characterized by a controlled, on target LDL cholesterol value (3.36 mmol/L or 130 mg/dL or less), HDL cholesterol levels less than 1.03 mmol/L (40 mg/dL) in males and less than 1.29 mmol/L (50 mg/dL) in females, or triglyceride levels higher than 1.7 mmol/L (150 mg/dL). An additional limit for triglycerides corresponding to marked hypertriglyceridemia (triglyceride levels higher than 2.3 mmol/L or 200 mg/dL) will be analyzed.

Secondary objectives
If the collected data are sufficient, descriptive and case-control analyses will be repeated in patients divided by age group, sex, LDL cholesterol levels, and geographic region.

Overall study design

Patients
The study will be conducted based on the clinical records from adult male and female patients with on target LDL cholesterol, either treated or not with statins. Patients with LDL cholesterol levels higher than 3.36 mmol/L (130 mg/dL) will be excluded from the study. In patients who have achieved the LDL cholesterol goal, the presence or absence of treatment to decrease LDL levels will not be considered as an inclusion or exclusion criterion.

Cases selected for descriptive analysis and case-control study will not be patients with a first episode of acute coronary syndrome admitted for this reason to the corresponding departments or clinical units.

For patients with CHD events (cases), all clinical histories of patients aged 50 years or older (regardless of stay duration or patient survival at the hospital) which meet one of the following diagnoses at discharge will be eligible for inclusion:

- Unstable angina pectoris.
- Non-ST segment elevation myocardial infarction (NSTEMI).
- ST segment elevation myocardial infarction (NSTEMI).

A diagnosis will be considered as confirmed if supported by electrocardiographic (ECG) criteria and adequate cardiac biomarkers. Otherwise, diagnosis will not be considered to be definitively confirmed.

All of these clinical histories will be included in the study provided the following lipid parameters have been measured within 8 hours of symptom start: total cholesterol, HDL cholesterol, LDL cholesterol (direct or calculated determination), triglycerides. If a calculated LDL cholesterol value is available, TG level should be less than 4.5 mmol/L (400 mg/dL).

Controls selected for the case-control study will be patients with no CHD events admitted to hospital for other reasons and also with on target LDL cholesterol levels, whether or not treated for high LDL cholesterol. Except for data relating to ECG and cardiac enzymes, which will not be routinely searched for in the medical records of control patients, the variables reported below will be taken from the clinical records of patients, whether cases or controls.

Patient matching
Cases and controls will be matched in a 1:1 ratio (a 1:2 case:control ratio may also be considered for feasibility reasons) by age (3-5 year interval), sex, LDL cholesterol category (less than 70 mg/dL, 70 mg/dL or higher, 100 mg/dL or less, 130 mg/dL or less), and presence of treated diabetes mellitus. Blood pressure, blood glucose, smoking (current smoker/non smoker), and other cardiovascular risk factors will be considered as covariates in analyses.
The matching mechanism will include calculation of an arithmetic score measuring the distance between each pair of subjects formed from the case and control groups. The pair with the minimum mean distance will be used. This adjustment will be done at the analysis stage. Scoring elements may include demographic variables such as center and clinical variables such as lipid measurements. The biometrics department will determine the weight of the different components before analysis is completed.

Study organization

Patient recruitment
Each participating center will process all consecutive clinical histories which meet the selection criteria and will record all necessary parameters.

The clinical histories of all patients aged 50 years or above (with no upper age limit) admitted in the three years prior to study implementation who meet the ICD-10 diagnostic codes (or the BCS codes or Read codes or equivalent coding) shown in Table 1 will be processed for case selection and enrolment.

These clinical records will then be manually or electronically processed in order to collect the lipid parameters (total, HDL and LDL cholesterol and TG) measured within 8 h of start of symptoms. These clinical records will be considered as selected, and full patient data will be collected from them.

Study investigators will review clinical histories manually (or electronically if full electronic records may be accessed) to recover data. Copies of the ECG and myocardial biomarker records supporting final diagnosis will be available if requested.

Data collected will be entered into an electronic file specifically created for that purpose or will be recorded in an equivalent hard paper format (Case Report Form). This file will include a code algorithm to link data recorded to the identification number of the hospital clinical records. The corresponding list will be kept at the center, and the coordinating center will be blinded to patient identity.

Parameters recorded
Clinical records will be reviewed in detail in order to collect the parameters listed in Table 2. If data required are missing, they will be recorded as NA (not available).

Final considerations

Residual risk in patients who achieve the current LDL cholesterol goals

In patients who achieve very low LDL cholesterol levels, predictors of major cardiovascular events continue to be HDL cholesterol levels or high triglyceride levels, as is shown in the main by the results of the TNT and PROVE-IT TIMI-22 studies. Retrospective analyses show that a 1 mg/dL increase in three months in HDL cholesterol levels could predictably decrease the risk of severe cardiovascular events by 1.1%. In patients who achieve LDL cholesterol levels lower than 70 mg/dL on statin therapy, the prognostic value of low HDL cholesterol levels is significant (p = 0.03) even after adjustment for other conventional risk factors such as body mass index, fasting blood glucose, presence of diabetes mellitus, triglyceride levels achieved with treatment, and baseline LDL cholesterol levels. Analysis of data from the PROVE-IT TIMI-22 study also showed that triglyceride levels are a significant predictor of CHD risk in patients with acute coronary syndrome. Thus, the combination of low TG levels (less than 150 mg/dL) and low LDL cholesterol levels was associated with a significant relative risk reduction of 28% (p = 0.017) in patients who achieve very low LDL cholesterol levels.
Table 1  Diagnostic codes included in the REALIST study

<table>
<thead>
<tr>
<th>Terms proposed by the British Cardiology Society</th>
<th>ICD-10 code</th>
<th>IDC-10 or equivalent term</th>
<th>Read code</th>
<th>Read code or equivalent term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific ACS</td>
<td>I200</td>
<td>Unstable angina</td>
<td>G3111</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>ACS with unstable angina (troponin 2ve)</td>
<td>I200TN</td>
<td>Unstable angina:</td>
<td>G3111</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>ACS with myocyte necrosis (troponin+ve)</td>
<td>I200TP</td>
<td>Troponin-ve</td>
<td>G31y1</td>
<td>Microinfarction of heart</td>
</tr>
<tr>
<td>ACS with aborted MI</td>
<td>I200AB</td>
<td>No equivalent ICD-10 term</td>
<td>G3110</td>
<td>Aborted MI</td>
</tr>
<tr>
<td>ACS with clinical MI</td>
<td>I21</td>
<td>General ICD-10 code for AMI</td>
<td>G30</td>
<td>General ICD-10 code for AMI</td>
</tr>
<tr>
<td>Anterior wall acute myocardial infarction with ST segment elevation</td>
<td>I210</td>
<td>Acute transmural myocardial infarction of anterior wall</td>
<td>G301 z</td>
<td>Anterior MI, unspecified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute transmural myocardial infarction of anterior wall</td>
<td>G300</td>
<td>Acute anterolateral myocardial infarction</td>
</tr>
<tr>
<td>Inferior wall acute myocardial infarction with ST segment elevation</td>
<td>I211</td>
<td>Acute transmural myocardial infarction of inferior wall</td>
<td>G308</td>
<td>Inferior MI, unspecified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute transmural myocardial infarction of inferior wall</td>
<td>G302</td>
<td>Acute inferolateral myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute transmural myocardial infarction of inferior wall</td>
<td>G303</td>
<td>Acute inferoposterior myocardial infarction</td>
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<td></td>
<td>Acute transmural myocardial infarction of inferior wall</td>
<td>G30y2</td>
<td>Acute septal myocardial infarction at other sites</td>
</tr>
<tr>
<td>Acute myocardial infarction at other sites with ST segment elevation</td>
<td>I212</td>
<td>Acute transmural myocardial infarction at other sites</td>
<td>G304</td>
<td>Acute septal myocardial infarction at other sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute transmural myocardial infarction at other sites</td>
<td>G305</td>
<td>Lateral MI, unspecified</td>
</tr>
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<td></td>
<td></td>
<td>Acute transmural myocardial infarction at other sites</td>
<td>G306</td>
<td>Posterior MI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute transmural myocardial infarction at other sites</td>
<td>G30y2</td>
<td>Acute septal myocardial infarction at other sites</td>
</tr>
</tbody>
</table>
in cardiovascular morbidity could only be seen in primary prevention patients. In the more recently published ACCORD study\textsuperscript{53}, the combination of a fibrate plus a statin in patients with atherogenic dyslipidemia brought about an additional 31% reduction in cardiovascular events as compared to the statin alone. This effect was particularly evident in the subgroup of patients with high triglyceride levels and low HDL cholesterol levels\textsuperscript{54}.

It therefore appears important to more precisely assess the prevalence of residual risk attributable to lipid changes and to ascertain the frequency with which this is associated with additional groups of risk factors in order to suggest more efficient strategies to decrease cardiovascular risk.

The REALIST study will be conducted in order to assess the impact of residual lipid factors on episodes of ischemic heart disease, assessed as a first episode of acute coronary syndrome.

**Conflict of interest**

The authors state that they have no conflict of interest.
Table 2  Parameters and variables of the REALIST study

Admission and discharge dates

Demographic data
- Patient age and sex
- Weight and height at admission
- Race

Optional:
- Waist circumference

Personal and family cardiovascular history
- Stroke or transient ischemic attack
- Arterial hypertension
- Symptomatic arterial insufficiency in lower limbs
- Left ventricular hypertrophy
- Lifestyle before hospital admission: smoking and alcohol consumption
- Family history (parents) of sudden death or MI before 65 years or stroke before 45 years

Diagnosis of acute coronary syndrome and course during hospital stay
- Nature of coronary event (with ICD-10 or equivalent code) and
- Final clinical outcome at hospital (dead or alive at discharge from the participating unit)

Optional:
- Results of
  - Coronary angiography
  - Myocardial scan
  - Stress ECG
  - Stress echocardiogram
  - Carotid ultrasound or cardiovascular MRI
  - Ankle-brachial index

Concomitant diabetes mellitus: type 1 or type 2

Lipid parameters
- Total, HDL and LDL cholesterol, triglycerides (values tested within 8 hours of symptom start)
- Blood collection time and time since last meal

Optional:
- Apo A-1, apo B, Lp(a)
- Last values available before discharge from unit
- Prior fasting lipid profile (separated from the event if not available at hospital admission for the acute coronary event)

Other test parameters (values available within 8 hours of symptom start)
- Fasting blood glucose
- Cardiac enzymes

Optional:
- HbA1c
- CRP
- Hyperuricemia
- Albuminuria, microalbuminuria
- Blood creatinine and urea (GFR will be calculated using the MDRD formula)

Drug treatment (full list of treatments)
- Drugs usually taken by the patient just before admission
- Received by the patient as initial treatment for the coronary heart disease event before hospital admission (e.g. heparin treatment)
- Prescribed at discharge from the involved unit.

Patient course after discharge
In patients for whom follow-up is not available, subsequent vascular events will be recorded and last patient data (dead or alive) will be noted if available
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