Atherosclerosis is a chronic degenerative disease, with a significant inflammatory component, characterized by phases of rapid activation leading to important clinical events, such as myocardial infarction. One of the major challenges of modern cardiology is limiting the progression of atherosclerotic disease and anticipating the phases of instability as to limit its consequences. In this contest modern techniques of intra-coronary imaging, such as optical coherence tomography, could have a pivotal role in identifying patients at higher risk of acute events in the short term. The purpose of the CLIMA study is to identify and map the vulnerability criteria of atherosclerotic coronary plaques in the individual patient, and provide a personalized risk score for coronary events.
atherosclerosis, with the use of behavioural and/or pharmacologic measure. While the behavioural measure could, and should, be implemented for the population in general, the extensive use of drugs in primary prevention settings is neither recommended by the guidelines, nor is economically sustainable. Hence the importance of identifying patients at higher cardiovascular risk, by accurately staging the atherosclerotic disease, also during its clinically silent phase.5

Intra-coronary imaging with optical coherence tomography in the assessment of atherosclerosis

Optical coherence tomography (OCT) is an imaging technique employing retro-reflection of light at near infrared frequency from the optical interface of the tissue to generate high resolution images (10–15 μm).6,7 Coronary application of OCT allows for atherosclerotic plaque visualization and its functional characterization8–10 with high degree of specificity and sensibility. In particular, as compared to other imaging techniques (e.g. intravascular ultrasound), OCT allows for identification of the cellular components of the plaque10,11: it is possible to measure the density of inflammatory cells utilizing algorithms exploiting tissues acoustic properties12; it is reliable enough as to measure the small vascular structures feeding the coronary lesions (vasa vasorum)13; it is the sole presently available technology able to quantify the component of the atherosclerotic plaque, among which the extension of the lipid pool and the thickness of the fibrous cap in vivo.7,14 The major shortcoming of this technique is its limited tissue penetration, such that an optimal plaque definition is possible only in its superficial layer, not deeper than 500 μm. This limitation is the reason why OCT doesn’t have the same accuracy for all the various vascular districts. Optical coherence tomography is then the imaging technique with the highest potential for identification of vulnerable plaques, regardless their extension/severity (e.g. angiographically non-critical lesions) (Figure 1). Post-mortem studies revealed that vulnerable plaques are rich in inflammatory cells (mostly macrophages and lymphocytes, and lesser amount of mastocytes), producing lytic enzymes (metalloprotease) able to breakdown the collagen of the fibrous cap, which then becomes vulnerable to the haemodynamic stress. The density of the neo-formed vessels has also been considered a factor in the progression/instability of the plaque, in that it provide for the influx of monocytes/macrophages in the lesions, as well as the intra-plaque haemorrhage, originating from the rupture of the neo-formed vessels. Furthermore, OCT offers a better visualization of intra-plaque calcifications, which according to some researchers, illustrate the stage of the atheroma, and represent a point of less resistance to the mechanical solicitations.15

Rationale for a novel use of intra-coronary optical coherence tomography

During the last decade several groups utilized intracoronary OCT with the purpose to validate, in vivo, the findings of post-mortem studies, and to understand new pathophyslogic scenarios. Serial studies from our group outlined that the evolution/healing mechanisms of the culprit plaques, responsible for ACS, are heterogeneous and not always predictable.16 The opportunity to employ OCT, in vivo, in serial studies, is of significant advantage over the post-mortem studies.17,18 It is, in fact possible to evaluate
the evolution of vulnerable plaques both from the morphologic and functional aspect (variation of the thickness of the fibrous cap, and reduction of the inflammatory component), as well as the efficacy of the lipid lowering therapy on the progression/regression of coronary atherosclerosis.

The CLIMA study

The CLIMA study (clinical trial.gov NCT02883088) was conceived as a prospective observational registry to investigate the correlation between the morphology of atherosclerotic plaques, as assessed by OCT analysis, and the risk of future cardiovascular events in the mid (months), and long-term follow-up (years). This is a multicentre study, involving high volume units with significant experience in intravascular imaging, aiming at collecting data on all patients who underwent OCT evaluation of the left anterior descending coronary artery in its mid-proximal portion (at least 30 mm), which was not revascularized (percutaneous and/or surgical approach). The enrolled patients will be regularly followed both with telephone and office visits, for a 10 years period. During the follow-up all new cardiovascular events and cardiology related hospitalizations will be recorded; the clinical documentation will be carefully collected and transferred in a dedicated database which will be evaluated by a specific committee. The comprehensiveness and the accuracy of the data in the registry will be constantly verified, in an effort to limit incomplete data (<5% for each variable recorded).

Study endpoints

Primary endpoint of the study is the correlation between OCT criteria of plaque vulnerability (derived from post-mortem studies), and the actual incidence of cardiac events attributable to the atherosclerotic plaques. A map of the coronary lesions will be constructed for each single patient, and the tendency toward instability over time will be assessed, according to the presence of OCT vulnerability criteria. In detail, will be evaluated the effectiveness of a risk scoring system based on several OCT instability criteria present concurrently in the same plaque. For the study, only patients with non-critical atherosclerotic plaques in the mid-proximal portion of the left anterior descending coronary artery will be enrolled, and only major cardiac events (cardiac death and anterior myocardial infarction [STEMI/NSTEMI]) immediately attributable to such plaques will be considered.

Optical coherence tomography criteria for vulnerability

Based on post-mortem studies and the present pathophysiological understanding the following OCT criteria were selected for the definition of vulnerable atherosclerotic plaque:

- Presence of calcific nodules
- Presence of neo-vascularization (vasa-vasorum) and/or intra-plaque haemorrhage
- Presence of cholesterol crystals (within the lipid pool)
- Presence of calcific nodules
- Presence of neo-vascularization (vasa-vasorum) and/or intra-plaque haemorrhage
- Presence of cholesterol crystals (within the lipid pool)
- Presence of macrophage inflammatory infiltrate

Optical coherence tomography images will be evaluated by two independent specialists.

Study population and preliminary results

After a first initial phase which included 500 patients, necessary to test the research hypothesis and to calculated the necessary statistical sample, a total of 1003 patients (1776 lipid plaques) have been enrolled after OCT evaluation in the setting of ACS or stable ischaemic cardiomyopathy. The enrolment process started in January 2013 and was concluded in December 2016, and presently all the enrolled patients reached, at least, the minimum follow-up of 1 year; the rate of major cardiac events has been 4%. The ability of OCT to study plaque morphological features with unprecedented detail, including the accurate assessment of fibrous cap thickness and signs of local inflammation enabled the identification of a population subgroup with a high risk of developing hard events. Indeed, the CLIMA registry applied for the first time in a prospective study a novel OCT grading based on the simultaneous presence of four adopted vulnerability criteria including the presence of macrophages.

Conflict of interest: none declared.

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