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How new imaging techniques can aid in defining the cardiovascular profile of the high-risk patient

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SUMMARY: **How new imaging techniques can aid in defining the cardiovascular profile of the high-risk patient.**

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Cardiovascular prevention has been developed in the last eight years producing an ever increasing amount of data requiring frequent updating. Studies using angiography to determine change in coronary obstruction have indicated progression, stabilization, or regression of coronary lesions associated with changes in plasma lipids and lipoproteins. Moreover, the guidelines on arterial hypertension published in 2007 listed the risk factors affecting prognosis but even by 2009 an update modified not only the list of risks, but even the philosophy behind the thought process which introduced as essential element in the prognosis of hypertension the ascertained existence of a damaged organ. Thus, the documentation of atherosclerotic vascular disease (plaques) and the quantification of its extension in the arterial tree became a determinant in the definition of cardiovascular risk. Magnetic Resonance (MRI) and coronary computed tomography (coro CT) applied to the heart and large vessels are the most promising methods.

KEY WORDS: Cardiovascular diseases prevention - Risk factors - Lipid lowering treatment
Coronary artery disease - MRI - Coronary CT scan.

Background

Assessing the risk in severe inherited hyperlipidemia

The possible precocious occurrence of a coronary event in patients affected by severe forms of genetically inherited hyperlipidemia such as familial hypercholesterolemia (FH) homozygote (HozFH), double heterozygote "compound" (DhFH), heterozygote (HtzFH), autosomal recessive hypercholesterolemia (ARH), and HyperLp(a) lipidemia [HyperLp(a)], imposes an effective, continuous and personalized therapeutic approach. Pharmacological therapy on its own does not obtain adequate results in HozFH or DhFH, and in approximately 20% of cases affected by HtzFH, perhaps because of a genetically-determined variable response to statins, or intolerance. The natural history of HozFH and DhFH predicts, in the absence of treatment, a fatal event (sudden death and myocardial infarction) in the first or second decade of life. They have xanthomatosis (tuberous and tendineous) and atherosclerosis of coronary arteries and aortic root stenosis. Only 20% of HtzFH reaches the age of 70 years. A precocious, intensive treatment, carried out with rigorous attention to LDL-Cholesterol (LDLC) targets for individuals at high risk such as the above mentioned patients, suggested by international guidelines, enabled LDL-apheresis experts to observe the stabilization and, in some cases, angiographically documented regression of coronary atherosclerotic lesions. The Italian Multicenter Study on LDL-apheresis Working Group (2009) reported differences concerning the diagnostic modality of evaluating the cardiovascular system, both in the assessment of the pre-existing Coronary Artery Disease (CAD), and in the follow up of cardiovascular disease (1,2). While recourse to echocardiography, echodoppler of the carotid and vertebral arteries, standard and stress- electrocardiography (ECG) is relatively common. Centers where patients undergo coronary catheterization and other non-invasive cardiovascular techniques result as being only a little less inferior. Moreover, aorto-coronary angiography is prescribed to paediatric patients with some reluctance. This evidence may represent a limit in the prospective evaluation on

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the impact of lipid lowering treatment on the progression and stabilization–regression of pre-existing arteriosclerotic lesions. Even the possibility of confirming the effectiveness of LDL-apheresis reported in literature, in preventing the relapse of cardiac events or of obstruction of grafts after aorto-coronary by-pass operations, or of stents introduced during Percutaneous Transluminal Coronary Angioplasty (PTCA), is significantly limited from the lack of programming of diagnostic cardiovascular exams of a serial type. Repetition over time of any general cardiovascular exam is more frequent in highly specialized and clinical research oriented centers. Nevertheless, a precocious diagnosis of subclinical, silent forms is crucial, whether fatal and non fatal cardiovascular events are to be prevented (3,4). More recently novel imaging techniques, each one with its own strength and drawbacks, have been reported. Supposedly the new diagnostic techniques can help in the evaluation and quantification of atherosclerosis. Particularly when repetition over time, and the evaluation of the impact of existing lipid-lowering tools and emerging new pharmacological approach is necessary. This is not philosophically different from serial investigation of cardiovascular system in subjects affected by arterial hypertension.

Serial cardiovascular diagnostic evaluation in Homozygous Familial Hypercholesterolemia

According to the available body of evidence all patients with HozFH must be submitted to:

Cardiovascular examination and ECG: must be performed before submitting patients to LDL-apheresis, and later at least once a year (follow-up) to highlight patients clinical condition;

Cardiac echocolorDoppler: must be performed before submitting patients to LDL-apheresis, and later every 1-2 years (follow-up). In case of documented lesions - left ventricule insufficiency, aortic supravalvular stenosis, and valvular insufficiency - the examination can be repeated more frequently;

Exercise ECG test: to highlight the possible presence of objective findings suggestive of myocardial ischemia that is not associated with angina or anginal equivalent. To be performed before submitting patients to LDL-apheresis and later once a year (follow-up). Where indicated it can be substituted with *stress myocardial scintigraphy*, or *pharmacologically stress-induced test*, or *stress echocardiography*;

Investigations are under way to characterize atherosclerotic lesions by imaging, particularly in coronary artery disease, not only including conventional angiography, but also B-mode ultrasound (B-mode US), Intravascular ultrasound (IVUS) , CT, and MR imaging.

Assessing the global cardiovascular risk

For a while now global cardiovascular risk as explained well by the Interheart Study states that multiple risk factors are more important than a single parameter. Interestingly, with regard to this matter, one study demonstrated how only a minority of patients hospitalized for an acute coronary syndrome showed LDLC levels at above risk level (5,6). Therefore, many patients who develop coronary artery disease have LDLC levels considered to be acceptable. In addition, the severity of the clinical profile only occasionally is provoked by the breakage of large plaques (> 70%) which strengthens the concept that plaques not considered critical can be responsible for coronary events (7). And finally a coronary angiography performed after an acute myocardial attack not often documents multiple noncritical lesions besides the lesion responsible (8). Due to the fact that these plaques do not hinder the flow of blood, common tests performed are not able to prove their existence. From this emerges a methodology which can evidence even those plaques deemed small. Common coronary angiography did not accomplish this assignment since during the early years in this century only 13% of symptomatic patients were tested with an even lower level of revascularization.

Magnetic Resonance and coronary computed tomography

Among modern technology, MRI and coro CT offer anatomic images and very detailed functions which are intuitive for cardiologists. They are precise images which are easily obtained within a reasonable timeframe and with little or no exposure to radiation and with modest use of contrasts. MRI is capable of great well-defined anatomical images of the heart which are superior to the echocardiogram and which provides information as to the texture of the structure itself (Fig. 1). With certain pharmacological tests it is even possible to obtain functional images which alert to the presence of myocardial ischaemia or contractile reserves. The coro CT instead represents the emerging method of primary prevention. It permits a coronary visualization that, if obtained at an acceptable cardiac frequency (< 70/min), provides good quality and definition. It is excellent at negative predictors while less talented at positive prediction due to difficulty in defining surfaces of plaques when calcification or coronary stents are present. It is, however, excellent at highlighting and evaluating arterial or venous bypasses (Fig. 2 a, b). The taking in of raw data and its successive analyzing allow for the multidisciplinary orthogonal reconstruction of curves and, in a sense, enable a qualitative and quantitative interpretation of the lesions. The information gained from the coro CT is multiple: the first consists in a simple calculation of the amount of coronary calcium present. This calculation correlates in a satisfactory manner to the coronary lesions (Fig. 3). The absence of calcium excludes any coronary artery disease with great precision (9). An anatomical image which proves the presence of coronary lesions allows for greater risk satisfac-

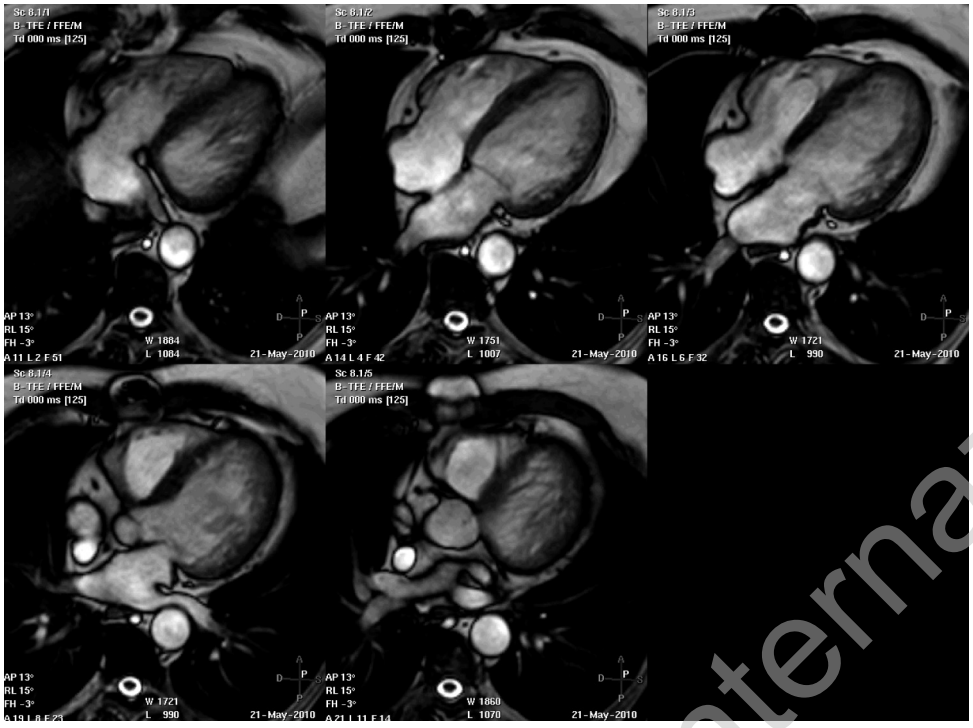
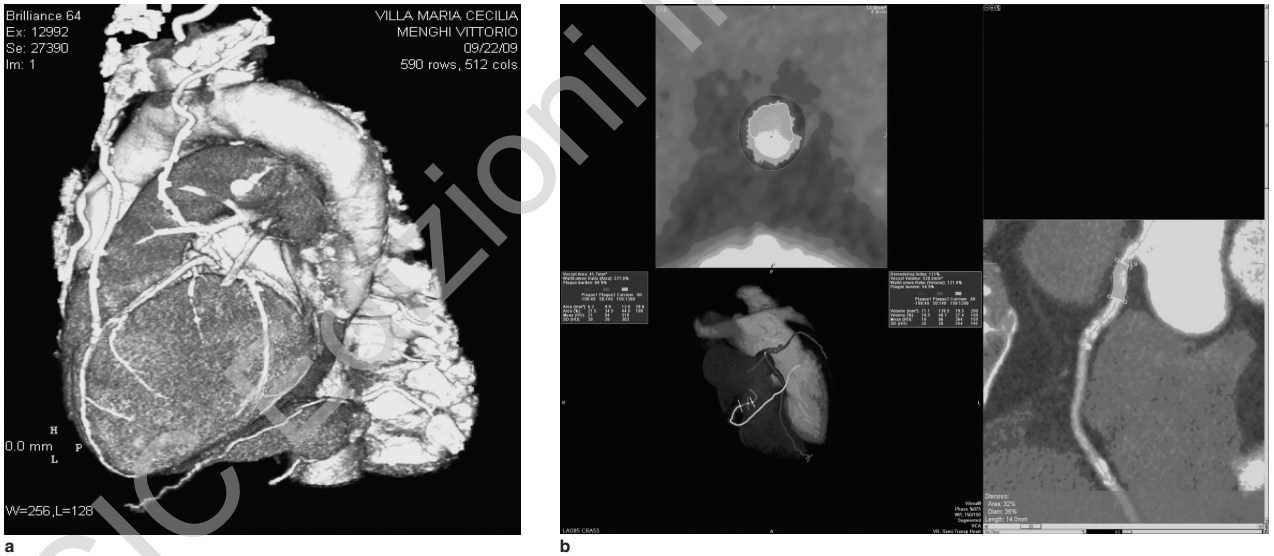


Fig. 1 - Cardiac and coronary arteries assessed by MRI.



a **b**

Fig. 2 a, b - a) Heart and coronary artery tree imaging by coro CT. b) Heart and coronary artery tree imaging by coro CT.

tion and renders more precise the definition of the extent of the stenosis (9). This definition is not affected by the statin therapy, seemingly (10). Recently studies have appeared demonstrating a great correlation between survival and presence or absence of coronary artery disease with subcritical and critical lesions. The methodology is even able to discriminate between patients with only a single chamber involved with respect to multiple chambers. The more advanced technology allows for excellent visualization of the coronary branches with reduced radiation exposure as compared with the past (between 1.5-3.0 mSv compared with 1.0 mSv of a chest X-ray and 10-20 mSv of a scintigraphy). In our opinion the new frontier of diagnosis with coro CT is represented by the evaluation of non-calcified plaques (Fig. 4) (11). The criticism directed at the determination of coronary calcium, in fact, consisted in the fact that it is an indicator of the extent of coronary plaques but not of how dangerous they

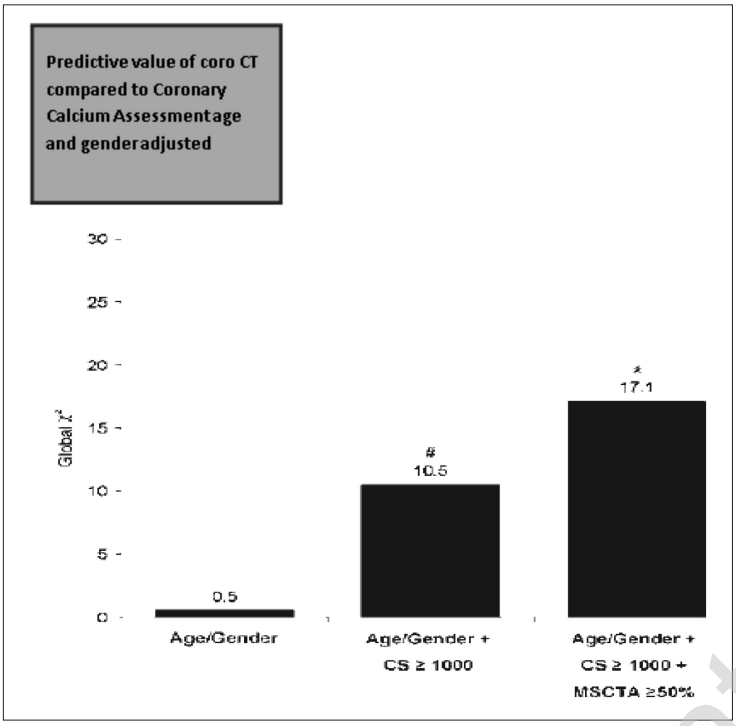


Fig. 3 - Adapted from: van Werkhoven JM, Schuijf JD, Gaemperli O, Jukema JW, Kroft LJ, Boersma E, Pazhenkottil A, Valenta I, Pundziute G, de Roos A, van der Wall EE, Kaufmann PA, Bax JJ. Incremental prognostic value of multi-slice computed tomography coronary angiography over coronary artery calcium scoring in patients with suspected coronary artery disease. Eur Heart J. 2009 Nov;30(21):2622-9.

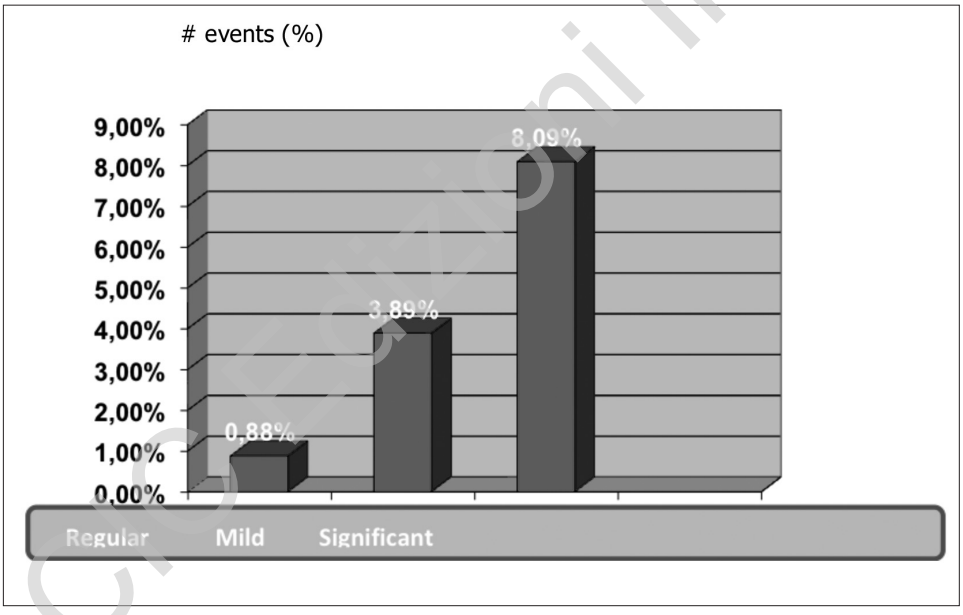


Fig. 4 - Severity of coronary artery disease assessed by coro CT.

might be. In a famous discussion of this very argument, Narula confirmed that "the necessity of identifying vulnerable plaques represents one of the most anticipated and important events in the war against heart disease" (12). In recent years in fact coronary plaques have begun to be analyzed distinguishing between the calcified lesions and the fibro-adipose lesions which as a known fact represent those of greater risk (13). The presence of coronary calcium and the absence of soft plaques as well as the presence of a remodeling indicator of <1 allow for the distinction between plaques on stable surfaces from those characteristic of acute coronary syndromes (14). This fact is of great interest because it would allow for the identification of vulnerable plaques and also allow for the evaluation of therapy in stabilizing such plaques. With this increase in knowledge new ways of predicting risk have

emerged among which is the actual amount of plaque. This expresses the cumulative extension of the plaques in a predetermined vascular path or in all areas analyzed and plays an important role in predicting a survival free of events or the appearance of cardiovascular events (15,16). McPherson confirmed this fact and identified factors of plaque which justify the increasing danger such as 1) the amount of plaque 2) the softened fibrous cap 3) an elevated amount of lipid core and 4) a larger amount of calcium (17). Revisiting an acclaimed editorial by Braunwald one can conclude that one fourth of the population consists of people at low risk (<0.5%/year) and within this group the average risk is modest; the issue is quite different if a larger group of population is taken into account (18). This of course cannot be ignored. At this point we cannot face the expense/cost ratio of preventive treatment in the identification of those patients who will eventually face a coronary event. For them a new diagnostic method is necessary. Then there is the moderate risk group (0.5-2%/year), another approximate 40% of the population. For this group ulterior diagnostic measures must be taken such as the ABI (ankle-brachial index) and high sensitivity C protein to determine those at higher risk (19). Those whose test is positive to any of the above mentioned tests, should be placed into the high risk group (2-15%/year) and subjected to more refined evaluation. The high risk group represents approximately 15% of the population and only they are studied with imaging techniques among which is the highly acclaimed coro CT. The highest risk group (>15%/year), those who have lesions when analyzed by coro CT, need to be evaluated by more invasive means such as coronary angiography and finally MRI to evaluate the need for revascularization and, in any case, to determine the best treatment strategy.

Conclusion

The determination of risk factors as suggested by Framingham is a cornerstone in cardiac risk evaluation. In moderate to high-risk patients it is advisable to use other methodologies that better allow individuation of higher risk patients. In light of this, MRI and especially coro CT with its ability to point out the extent of the plaques is taking an ever-increasing role in primary prevention of coronary heart disease, and in secondary prevention of its ischemic complications. The methods used in atherosclerosis imaging, have its own advantages and disadvantages. Notwithstanding significant efforts are aimed at improving the existing techniques diagnostic capability. Coro CT is highly effective when used by well-trained technicians. On the other hand, when used by unskilled technicians it presents a health hazard to the patient as well as an increased healthcare cost. This methodology which in itself is very helpful in identifying the presence of coronary heart disease cannot for now be compared with coronary angiography which documents and quantifies the severity of every single stenosis. However, improving promising technologies and intensive investigations are on the way. The final challenge will be not only aimed at assessing cardiovascular system safely and effectively by means of novel imaging techniques, but also to offer the clinicians a reliable and accurate diagnostic opportunity to evaluate the impact of usual medical care and upcoming pharmacological and non pharmacological novel therapeutic approaches on existing atherosclerotic lesions and to follow up them serially, meanwhile preventing the development of new plaques in the native arteries.

References

1. Stefanutti C. Italian Multicenter Study on Low-Density Lipoprotein Apheresis: retrospective analysis (2007). Italian Multicenter Study on Low-density Lipoprotein Apheresis Working Group. Ther Apher Dial 2010 Feb;14(1):79-86.
2. Stefanutti C. The 2009 2nd Italian Consensus Conference on LDL-apheresis. Nutr Metab Cardiovasc Dis 2010 Dec;20(10):761-2.
3. Stefanutti C, Vivenzio A, Di Giacomo S, Mazzarella B, Bosco G, Berni A. Aorta and coronary angiographic follow-up of children with severe hypercholesterolemia treated with low-density lipoprotein apheresis. Transfusion 2009 Jul;49(7):1461-70.
4. Koga N. Angiographic and pathological studies on regression of coronary atherosclerosis of FH patients who received LDL-apheresis treatment. Artif Organs 1992 Apr;16(2):171-6.
5. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): casecontrol study. Lancet 2004 Sep 11-17;364(9438):937-52.
6. Sachdeva A, Cannon CP, Deedwania PC, Labresh KA, Smith SC Jr, Dai D, Hernandez A, Fonarow GC. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. Am Heart J 2009 Jan;157(1):111-117.
7. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, Borrico S, Gorlin R, Fuster V. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12(1):56-62.
8. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000 Sep 28;343(13):915-22.
9. Villines TC, Hulten EA, Shaw LJ, Goyal M, Dunning A, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Cademartiri F, Cal-

lister TQ, Chang HJ, Cheng VY, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Lin FY, Maffei E, Raff GL, Min JK; CONFIRM Registry Investigators. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry. J Am Coll Cardiol 2011 Dec 6;58(24):2533-40.

10. Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. Arterioscler Thromb Vasc Biol 2004;24(7):1272-7.
11. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Maffei E, Raff G, Shaw LJ, Villines T, Berman DS; CONFIRM Investigators. Ageand sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol 2011 Aug 16;58(8):849-60.
12. Narula J, Finn AV, Demaria AN. Picking plaques that pop. J Am Coll Cardiol 2005 Jun 21;45(12):1970-3.
13. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, Inoue K, Okumura M, Ishii J, Anno H, Virmani R, Ozaki Y, Hishida H, Narula J. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol 2007;50(4):319-26.
14. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida, Wong ND, Virmani R, Kondo T, Ozaki Y, Narula J. Computed Tomographic Angiography Characteristics of Atherosclerotic Plaques Subsequently Resulting in Acute Coronary SyndromeFREE. J Am Coll Cardiol 2009;54(1):49-57.
15. Kristensen TS, Kofoed KF, Kühl JT, Nielsen WB, Nielsen MB, Kelbæk H. Prognostic implications of nonobstructive coronary plaques in patients with non-ST-segment elevation myocardial infarction: a multidetector computed tomography study. J Am Coll Cardiol 2011 Jul 26;58(5):502-9.
16. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364(3):226-35.
17. McPherson JA, Maehara A, Weisz G, Mintz GS, Cristea E, Mehran R, Foster M, Verheye S, Rabbani L, Xu K, Fahy M, Templin B, Zhang Z, Lansky AJ, de Bruyne B, Serruys PW, Stone GW. Residual plaque burden in patients with acute coronary syndromes after successful percutaneous coronary intervention. JACC Cardiovasc Imaging 2012;5:76-85.
18. Braunwald E. Epilogue: what do clinicians expect from imagers? J Am Coll Cardiol 2006;47:101-3.
19. Stefanutti C, Morozzi C, Petta A. Lipid and low-density-lipoprotein apheresis. Effects on plasma inflammatory profile and on cytokine pattern in patients with severe dyslipidemia. Cytokine 2011;56(3):842-9.