Austin Journal of Clinical Cardiology

Austin Publishing Group

Open Access Full Text Article

Editorial

What do we need to seek in the next step in Clinical Cardiology for Better Treatment of Patients with Cardiovascular Diseases?

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Received: January 23, 2014; Accepted: January 25, 2014; Published: January 27, 2014

With the marked development of catheterization techniques and medical instruments together with that of underlying supportive biological, physiological, pharmacological research, and metallurgical engineering, percutaneous vascular intervention has grown to be able to treat patients not only by dilatation with simple ballooning, but also by debulking atheromatous plaques or scaffolding stenotic lesions with metal stents with more ease [1]. Imaging devices provide more accurate assessment of lesion characteristics and severity than an angiogram, and often help interventionists decide how and how much they should dilate lesions. Stents have enabled much better procedural success in both coronary and peripheral artery disease, and excellent long-term patency has been achieved by using drug-eluting stents (DES). However, there are still issues to be solved for better management of these patients, especially those with severely tight or calcified lesions, seriously depressed left ventricular (LV) function, or renal insufficiency.

In percutaneous coronary intervention (PCI), DES have been reported to reduce the restenosis rate, target lesion or vessel revascularization (TLR or TVR) rate, and thereby major adverse cardiac events (MACE), compared to uncoated bare metal stents (BMS) [2-5]. However, it is also reported that neoatherosclerosis, developing in the stented segment with new lipid-laden atherogenic change over the stent struts, is slowly created and limits blood flow and hence, the advantages over BMS years after the procedure [6-8]. Is this true of second-generation DES, showing comparable or even better long-term outcomes with less frequent stent thrombosis (ST) than former DES [9-15], in which polymers, antiproliferative agents, and stent structure are believed to be improved? It is unknown whether such stenotic changes should also be expected with newer DES after a much longer interval as "very late catch-up", because we have just started to obtain 5-year follow-up data [16].

In patients with acute myocardial infarction (AMI), emergency primary angioplasty to recanalize the occluded infarct-related artery is currently regarded as standard therapy for reducing cardiac mortality. In the balloon-only era, rapid closure of the infarcted lesion often took place after balloon dilatation [17]. Stent implantation, by blocking lesion recoil, proved to be quite beneficial to overcome this phenomenon, avoiding time-consuming repetitive balloon inflations until restoration of vessel patency. However, restenosis is still reported to be fairly frequent within a year with BMS use, especially at the time of implantation in the proximal left anterior descending artery compared with stenting in other coronary segments [18,19]. Currently, DES is used with more satisfactory TLR or TVR results during a 1- to 3-year follow-up period, although no significant difference is often observed between these two stent types in terms of the incidence of death or recurrent AMI [20-24]. However, accumulated data have begun to show a higher risk of ST in those treated with DES over a 1-year follow-up period [23-26]. Kalesan et al. [27] demonstrated in a meta-analysis that 1 year after AMI treatment, very late ST is significantly more likely to occur in patients receiving DES than in those with BMS placement. The large amount of intracoronary thrombus in patients with AMI may predispose them to stent malapposition because of stent undersizing or thrombus resolution. This may elevate the incidence of later ST, unless appropriate intimal coverage of the stent adluminal surface is achieved. This means that longer close management with steady antiplatelet treatment may be needed once patients with AMI are treated with DES. Longer follow-up studies of DES placement, particularly second-generation DES in AMI, are awaited.

As regards the treatment of unprotected left main coronary artery (LMCA) disease, PCI, in contrast to coronary bypass surgery (CABG), has been demonstrated to provide comparable long-term outcomes in terms of mortality and MACE, although a higher frequency of TVR must be expected [28-33]. However, ST in LMCA is highly likely to cause extremely dangerous hemodynamic deterioration, and even mortality, whereas occlusion of one graft conduit is not usually as harmful in patients undergoing CABG due to its smaller supply of the myocardial area than LMCA [34]. Therefore, considering the treatment of LMCA using DES, prevention of very late ST is of significant long-term importance. ST can occur unexpectedly a long time after stent implantation when insufficient attention is paid by both cardiologists and patients themselves. Once DES is implanted, even if ST is a low probability, cautious and close management and occasional follow-up examinations must be continued for a long period of time. Prolonged medication with antiplatelet agents may not be reduced as a result of symptomatic stability, which is obviously accompanied by more financial cost. When considered from the standpoint of patients, stenting to LMCA may involve extremely high mental stress from the fear of sudden death. Therefore, PCI and CABG in an unprotected LMCA lesion should be compared because of the considerably long follow-up period, not only from the view of the clinical outcome but also from the viewpoint of patients' mental

Citation: Shirotani M, Togi K, Uemori N. What do we need to seek in the next step in Clinical Cardiology for Better Treatment of Patients with Cardiovascular Diseases?. Austin J Clin Cardiolog. 2014;1(1): 1006.

strain and financial costs associated with clinical care, which must be secured in patients receiving DES.

Other new PCI devices are becoming available. Treatment of both *de novo* lesions and in-stent restenosis by drug-eluting balloons can be useful [35-37] as it does not add more metal foreign bodies to the lesion that could promote further inflammatory reactions or clot formation. Bioresorbable vessel scaffolding (BVS) may also be substituted for stents and possibly requires a shorter period of antiplatelet therapy [38,39]. It is of interest how BVS acts at a bifurcating lesion when it is positioned over the side branch. Development of these new devices may also change the utilization of modalities assisting in the judgment of the indication, lesion characteristics, and procedural endpoint among intravascular ultrasound, optical coherence tomography, or a pressure guidewire to measure fractional flow reserve.

Subsequent to successful coronary recanalization in AMI patients, are beta-blockers additionally able to improve the long-term clinical course? This question remains to be further elucidated [40,41]. Beta-blockers are known to inhibit adverse arrhythmia [42] and are also known to improve LV contractility [43-45]. However, there are concerns about inducing coronary vasoconstriction as a result of their beta-blocking effect on coronary vascular smooth muscle cells (VSMC) [46,47]. Coronary vasospasm is reported to be commonly induced early after AMI onset. Racial differences in its frequency were demonstrated by Pristipino et al. [48], in which Japanese patients showed more provocative coronary vasospasm (80%) than Caucasians (still as high as 37% within 14 days of AMI onset). It was reported in a study of a small number of Japanese subjects that atenolol tended to increase provocative coronary vasospasm in both the infarct-related artery (IRA) and non-IRA, although it did not reach statistical significance (Figure 1) [49]. With reference to beta-blockers, their various cardiac effects should be taken into consideration. Moreover, their actions can vary depending upon the pharmacological characteristics (e. g. beta1-adrenoceptor selectivity, intrinsic sympathomimetic activity) of each beta-blocking agent used. Their short- and long-term influence on AMI patients should be evaluated in large-scale randomized trials, paying attention to the agent (s) used and the racial background of subjects.

Coronary vasospastic angina has been diagnosed by the spasm provocation test during coronary angiography. Intracoronary administration of acetylcholine (Ach) and ergonovine is commonly used. However, the pattern of provoked spasm is reported to be different between the two agents; more diffuse with the former and more focal with the latter [50]. Patients can show positive in a test performed using one agent, yet sometimes pseudo-negative in a test using another [50,51], although usually only one is used in the daily clinical setting. Back-up temporary pacing is necessary for the Ach provocation test because it frequently causes heart block. This test is sometimes complicated with dangerous ventricular arrhythmia together with ST elevation on the electrocardiogram. Considering the financial cost and safety, a less invasive diagnostic method is expected to be explored. A couple of reports have suggested the association with the elevation of plasma inflammatory or oxidative stress biomarkers [52-55]; however, they can also be influenced if other pathological conditions such as infection or collagen disease coexist. Sakata et al. [56] suggested the efficacy of assessing regional myocardial autonomic nerve activity by means of nuclear medicine imaging. The leukocyte Rho-kinase level has been shown to be elevated in patients with coronary vasospasm [57,58]. Rho/Rho-kinase has been demonstrated to play a pivotal role in promoting VSMC contraction by enhancing myosin light chain phosphorylation via suppression of the myosin-binding unit of myosin phosphatase [59,60]. Further studies are awaited to develop easier and more efficacious diagnosis of this disease and its variable vasomotor activities.

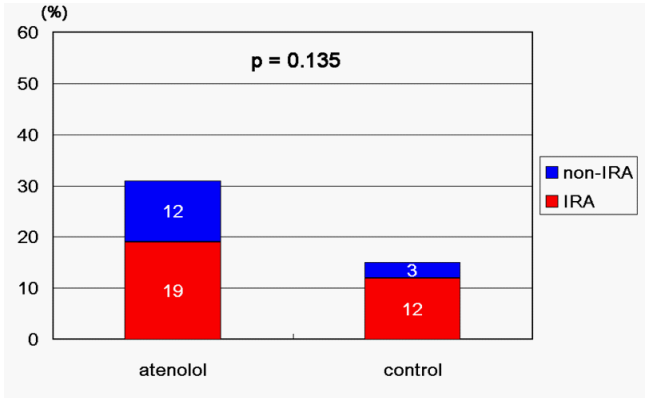

Figure 1: Frequency of inducible coronary vasospasm by ergonovine 4 weeks after AMI onset. IRA: infarct-related artery.

Cell therapy is now becoming an attractive field in the treatment of chronic heart failure or restoration of LV function after AMI. Many attempts using a variety of cell origins (e. g. autologous bone marrow cells, peripheral blood stem cells) have been reported; however, the long-term beneficial effects remain controversial, including concerns about promoting intimal hyperplasia following coronary intervention [61-71]. New technologies such as surgical coverage of the damaged LV with a myocardial sheet produced by autologous cell culture or transformation of induced pluripotent stem cells [72,73] may emerge as promising therapeutic options. Together with basic translational research, rapid but solid development in this field is awaited with great hope and expectation.

A number of other important issues remain to be solved in addition to the above issues. We hope that many exciting studies will be submitted to this journal to develop fresh diagnostic and therapeutic methods. Such advancements will surely contribute to more efficient clinical practice to refine the management of cardiovascular diseases.

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Austin J Clin Cardiolog - Volume 1 Issue 1 - 2014
ISSN : 2381-9111 | www.austinpublishinggroup.org

Citation: Shirotani M, Togi K, Uemori N. What do we need to seek in the next step in Clinical Cardiology for Better Treatment of Patients with Cardiovascular Diseases?. Austin J Clin Cardiolog. 2014;1(1): 1006.