Twenty-years History of the Department of Cardiovascular Medicine,
Juntendo University Graduate School of Medicine

HIROYUKI DAIDA*

*Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

Cardiovascular disease is the leading cause of death and has been the major health care issue worldwide. Tremendous effort has been continuously made against cardiovascular disease from the bench, bed side and population science. In the clinical cardiology field, new development of technology continuously improved the patient outcome resulting marked improvement of prognosis during recent several decades. In this period, the Department of Cardiovascular Medicine (Department of Cardiology), Juntendo University has been actively working in the clinical practice, research and education especially in the field of coronary artery disease and atherosclerosis. In this article, I will review the twenty-years progress of this department especially in the field of catheter intervention, clinical trials and porcine model research as well as cardiac rehabilitation.

Key words: coronary artery disease (CAD), percutaneous coronary intervention (PCI), angiographic trial, IVUS trial, cardiac rehabilitation

Cardiovascular disease is the leading cause of death and has been the major health care issue worldwide. Tremendous effort has been continuously made against cardiovascular disease from the bench, bed side and population science. In the clinical cardiology field, from the development of open-heart surgery to genomewide analysis for the onset of myocardial infarction, new development of technology continuously improved the patient outcome resulting marked improvement of prognosis (Figure-1). For example, the mortality of ST elevation myocardial infarction reduced by one fifth over 50 years. During this era, one of the most rapidly advanced area in cardiology field is the area of coronary artery disease in which invention of coronary angiogram, coronary bypass surgery, percutaneous catheter intervention and new drug such as statin were developed. Advance of cardiac rehabilitation is also important from the stand point of preventive cardiology. The Department of Cardiovascular Medicine (Department of Cardiology), Juntendo University has been a leading institution of the coronary artery disease practice in Japan. In this article, I will review the twenty-years progress of cardiology especially in the field of atherosclerosis and coronary artery disease in the Juntendo University Graduate School of Medicine.

Trend of PCI in Juntendo University Hospital (JUH) (Figure-2)

With regard to percutaneous coronary intervention (PCI), the first percutaneous transluminal coronary angioplasty was performed in Juntendo University in February 1, 1984. Since then, number of catheter intervention gradually increased with advance of technology and expansion of indication. In early 1990, several new catheter technologies so
called new devices had introduced including rotational ablation catheter, directional coronary atherectomy catheter and bare metal stent. In 1994, the first case of coronary stent was performed in July 18. Between the era of PTCA (Percutaneous Balloon Angioplasty) and Stent, the issue of restenosis after balloon injury was one of the major research interest of cardiology community. In the Juntendo University, two multicenter trials were conducted targeting the prevention of restenosis after PTCA. The LDL Angioplasty Restenosis Trial (LART) was designed to test the hypothesis that...
high plasma lipoprotein (a) (Lp [a]) levels are associated with an increase incidence of restenosis after angioplasty. Using low-density lipoprotein (LDL) apheresis with a dextran sulfate cellulose column as an Lp (a) absorbent, this study indicated that reducing Lp (a) levels could prevent restenosis after angioplasty in high Lp (a) patients, particularly when combined with lipid-lowering drugs. The Probucol Angioplasty Restenosis Trial (PART) was a prospective, randomized, controlled study that investigated the effectiveness of probucol in reducing the rate of restenosis after PTCA. Probucol administered beginning 4 weeks before PTCA appears to reduce restenosis rates. After the introduction of stent, restenosis was halved and ten years later, drug eluting stent was developed with the advance of drug eluting system which almost eliminate the concern of restenosis. Meanwhile in the catheter laboratory, the technical advance stimulated the indication and increased the number of peripheral artery intervention in 2000-2010. In 2016, first TAVI (Transcatheter Aortic Valve Implantation) was performed in JUH which rapidly increased and structural heart intervention became one major area of practice in the Department of Cardiovascular Medicine. In 2018, the first Mitra Clip was performed which is still a challenge of structural heart disease field. Regarding to the clinical research activity, the Juntendo Catheterization Registry which was initiated to investigate the long-term outcome after PCI, established in the Catheterization Laboratory, publishing more than 100 papers between 2000 and 2019.

### Angiographic and IVUS trials for prevention of atherosclerosis progression

Between 1990–2000, there were numerous angiographic trials conducted around the world using diet modification, exercise and a combination of lipid lowering drugs and later using statins to investigate whether risk modification could reduce the progression of atherosclerosis. In the Department of Cardiovascular Medicine, Juntendo University, several trials were conducted using pravastatin and LDL apheresis in this decade. Overall results of these angiographic trials indicated that aggressive modification of lipids could inhibit atherosclerotic plaque progression and induce regression to some extent. Intravascular Ultrasound (IVUS) was developed as an intra-coronary imaging device which enabled to measure the plaque volume with high reproducibility. In the field of atherosclerosis progression research, substantial numbers of trials using IVUS were conducted since then.

The ESTABLISH trial, JAPAN-ACS and COSMOS study are the three early major coronary plaque regression studies conducted in Japan (Table-1). These three studies are designed to clarify the mechanism of the statin efficacy in secondary coronary artery disease (CAD) prevention and to investigate whether early aggressive lipid-lowering therapy could induce a significant reduction in plaque volume (Table-2, 3).

The ESTABLISH study investigated the efficacy of early aggressive statin therapy in acute coronary syndrome. Early LDL-C lowering by 20 mg of atorvastatin for 6 months significantly reduced the plaque volume in patients with ACS.

The JAPAN-ACS study was designed to evaluate

---

**Table 1** Multi-center Coronary Angiographic Trials conducted in the Department of Cardiovascular Medicine

| Trial name | Intervention | Subjects | Publication |
|------------|--------------|----------|-------------|
| L-ART      | LDL-apheresis| Post PTCA| Am J Cardiol, 1994 |
| PART       | Probucol     | Post PTCA| J Am Coll Cardiol, 1997 |
| Regression trial | | | |
| Coronary Atherosclerosis and Lipid Study | Pravastatin | Chronic CAD | J Atheroscler Thromb, 2003 |
| PCAB | Pravastatin | Post CABG | Circ J, 2005 |
| LCAPS | LDL-apheresis | FH | Atherosclerosis, 1999 |

---
whether the effects of aggressive lipid-lowering therapy with atorvastatin on coronary plaque volume in patients with ACS are generalized for other statins in multicenter setting. This study proved non-inferiority of pitavastatin to atorvastatin in terms of plaque regression. Overall, LDL-C was reduced by 36% down to 84 mg/dl and the plaque volume was significantly decreased by 17.5% during 10 months after ACS. The COSMOS study examined the effect of rosuvastatin on plaque volume in Japanese patients with stable CAD, including those receiving prior lipid-lowering therapy. A 76-week open-label trial was performed at 37 centers in Japan. The change in the serum low-density lipoprotein-cholesterol level from baseline to end of follow-up was −38.6%. The plaque volume, the primary endpoint, was significantly reduced by 5.1%.

Although the regression of atherosclerotic plaque is a surrogate marker of clinical outcome, these IVUS trials suggested the clinical efficacy of aggressive LDL-C lowering in Japanese patients with coronary artery disease. Whether plaque volume changes could predict the future events has been a matter of discussion. Dohi et al found significant lower incidence of cardiovascular event in the patients with plaque regression than patients with progression in Extended ESTABLISH trial in

| Study          | ESTABLISH 2004 | JAPAN-ACS 2008 | COSMOS 2009 |
|----------------|----------------|----------------|-------------|
| Intervention   | Atorvastatin 20 mg vs. Control (n=24/24) | Atorvastatin 20 mg vs. Pitavastatin 4 mg (n=127/125) | Rosuvastatin 2.5 - 20 mg (n=126) |
| Subjects       | ACS Emergent PCI | ACS, HL Emergent PCI | Stable ASHD Scheduled PCI |
| LDL-C levels (% change) | 125 ➔ 70 (41.7%) | 132 ➔ 84 (36.0%) | 140 ➔ 83 (38.6%) |
| % plaque regression | 13.1%         | 17.5%          | 5.1%       |

Table 3 Intravascular ultrasound trials conducted or participated by the Department of Cardiovascular Medicine with two representative cases from ESTABLISH and ESPECIAL-ACS trial

| Trial name | Intervention | Subjects | Publication |
|------------|--------------|----------|-------------|
| ESTABLISH | Statin       | ACS      | Circulation, 2004 11) |
| ALPS-J     | CCB          | CAD      | Cir J, 2011 15) |
| ZEUS       | Ezetimibe    | ACS      | IJC Meth Endocr, 2014 16) |
| ESPECIAL-ACS | DPP-4 inhibitor | ACS | J Cardiol, 2016 17) |
| Rehabilitation | Cardiac Rehabilitation | ACS | Int Heart J, 2015 18), Circ J, 2018 19) |
| Multicenter trial |               |          |             |
| JAPAN-ACS  | Statin       | ACS      | J Am Coll Cardiol, 2009 12) |
| COSMOS     | Statin       | CAD      | Circ J, 2009 13) |

ESTABLISH
Baseline statin
Follow-up statin

ESPECIAL-ACS IB-IVUS
Baseline DPP-4
Follow-up DPP-4
4 years follow-up\(^{14}\).

**Coronary atherosclerosis experimental research; Porcine model (Table-4)**

In the atherosclerosis research, animal experimental model is essential to further understand the mechanism of development of atherosclerosis and to investigate the effectiveness of treatment and/or development of new treatment option. Among the several animal models in the atherosclerosis research, porcine model is the closest animal to human atherosclerosis. The department of Cardiovascular medicine Juntendo University, started the porcine model research in 2000. In this laboratory, protective effect of pharmacological intervention to vascular injury was intensively investigated. Agents investigated were probucol\(^{20}\), Pitavastatin\(^{21}\), Fenofibrate\(^{22}\), Pioglitazone\(^{23}\), etc. We also have tried to develop a statin eluting stent\(^{27}\) and new porcine atherosclerosis model with LDL-R knockout swine recently\(^{28}\).

**Development of Cardiac Rehabilitation program (Figure-3)**

Cardiac rehabilitation program was started in 1993 in JUH which is gradually developed and became one of the leading institutions in Japan now. Currently more than 12,000 sessions were provided annually in the Cardiovascular Fitness and Cardiac Rehabilitation Center in the JUH. We conducted the one of the earliest randomized trial, J-CARP (Juntendo Cardiac Rehabilitation Program) study in 1997 which investigated the efficacy of phase III cardiac rehabilitation in elderly patients with chronic coronary artery disease\(^{29}\). Since then, we have studied and reported the efficacy of cardiac rehabilitation in the coronary risk factor profile, exercise capacity, muscle power, QOL and long-term prognosis in elderly patients, and post CABG patients with diabetes mellitus or metabolic syndrome\(^{30-32}\). More recently, we conducted IVUS trial to investigate the efficacy of cardiac rehabilitation on coronary artery plaque volume and characteristics and found significant correlation between plaque volume or fat content and daily physical activity\(^{18}\)\(^{19}\). A new project is now on going regarding to remote cardiac rehabilitation in which...

### Table-4 Porcine experimental studies for atherosclerosis research with histological presentations from statin-eluting stent study and LDL K/O pig model

| Treatment                  | Reference                        |
|----------------------------|----------------------------------|
| Probucol                   | Jpn Heart J. 2004\(^{20}\)       |
| Pitavastatin               | Atherosclerosis, 2004\(^{21}\)   |
| Fenofibrate                | Atherosclerosis, 2006\(^{22}\)   |
| Pioglitazone               | Atherosclerosis, 2008\(^{23}\)   |
| CCB and ARB                | Circ J. 2016\(^{24}\)           |
| ARB + Pioglitazone         | Circ J. 2011\(^{25}\)           |
| LIPOPHILIC ANTIOXIDANT, BO-653 | J Medical Res and Science, 2012\(^{26}\) |
| Statin Eluting–Stent       | Circ J. 2008\(^{27}\)           |
| Nobel model LDL-R Knock-Out Swine | PLoS One, 2016\(^{28}\) |
home-based rehabilitation under the remote monitoring using IoT.

Establishment of Clinical Research and Trial Center (Figure-4)

Department of Cardiovascular Medicine has been actively contributing to the development of clinical research environment in Juntendo University. The Juntendo Clinical Research Center was founded in November 2008 when SPIRITS-J\(^3\), a very first large scale registration study was initiated involving Juntendo Alumni Association. In April 2014, the Clinical Research Center renamed to Clinical Research Support Center and started the preparation for application of the Core Research Hospital of Japanese Ministry of Health, Welfare and Labor. In April 2017, the Innovative Medical Technology Research and Development Center was founded followed by the establishment of Juntendo Clinical Research and Trial Center in 2018. In terms of large scale clinical study, after the SPRITS-J completed,
we started the RAFFINE, a registration of atrial fibrillation patients among the Juntendo University hospitals and related institutions in 2013 which was completed in 2019\textsuperscript{31}. In 2017, Star-ACS was initiated which is a registration for ACS with atrial fibrillation is still on going. In terms of clinical trial, RESPACT EPA, multi-center interventional trial with EPA is ongoing with 120 institutions on Japan supported by Juntendo Clinical Research and Trial Center which will be completed in 2022.

Summary

The 20 years history of the department of Cardiovascular Medicine, Juntendo University was reviewed from the standpoint of research and clinical practice regarding to atherosclerosis and coronary artery disease. During this two decades, significant advance in science and technology were observed in cardiovascular medicine from acute intervention to chronic patients care as well as disease prevention. Cardiovascular Medicine Team in Juntendo is continuously working to provide better practice and research in the past, present and future.

Acknowledgment

The author thanks all the staff and members of the Department of Cardiovascular Medicine, Juntendo University for their continuous support and Ms. Matsumoto for her secretarial assistance.

Reference

1) World Health Organization: The top 10 causes of death. http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death (Last Accessed Jan. 7, 2020)
2) Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A: Growing epidemic of coronary heart disease in low- and middle-income countries. Curr Probl Cardiol, 2010; 35: 72-115.
3) Mathers CD, Loncar D: Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med, 2006; 3: e442.
4) Nabel EG, Braunwald E: A Tale of Coronary Artery Disease and Myocardial Infarction. N Engl J Med, 2012; 366: 54–63.
5) Daida H, Lee YJ, Yokoi H, et al: Prevention of restenosis after percutaneous transluminal coronary angioplasty by reducing lipoprotein (a) levels with low-density lipoprotein apheresis. Low-density lipoprotein apheresis angioplasty restenosis trial (L–ART) group. Am J Cardiol, 1994; 73: 1037–1040.
6) Yokoi H, Daida H, Kuwabara Y, et al: Effectiveness of an antioxidant in preventing restenosis after percutaneous transluminal coronary angioplasty: The probucol angioplasty restenosis trial. J Am Coll Cardiol, 1997; 30: 855–862.
7) Daida H, Kuwabara Y, Yokoi H, et al: Effect of probucol on repeat revascularization rate after percutaneous transluminal coronary angioplasty (from the probucol angioplasty restenosis trial [PART]). Am J Cardiol, 2000: 86: 550–552. A9.
8) Daida H, Ouchi Y, Saito Y, et al: Coronary Atherosclerosis and Lipid Research Group: Preventing angiographic progression of coronary atherosclerosis with pravastatin. J Atheroscler Thromb, 2003; 10: 25–31.
9) Makuuchi H, Furuse A, Endo M, et al: Effect of pravastatin on progression of coronary atherosclerosis in patients after coronary artery bypass surgery. Circ J, 2005; 69: 636–643.
10) Nishimura S, Sekiguchi M, Kano T, et al: Effects of intensive lipid lowering by low-density lipoprotein apheresis on regression of coronary atherosclerosis in patients with familial hypercholesterolemia: Japan low–density lipoprotein apheresis coronary atherosclerosis prospective study (L–CAPS). Atherosclerosis, 1999: 144: 409–417.
11) Okazaki S, Yokoyama T, Miyauchi K, et al: Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation, 2004; 110: 1061–1068.
12) Hiro T, Kimura T, Morimoto T, et al: JAPAN–ACS Investigators: Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: A multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN–ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol, 2009; 54: 293–302.
13) Takayama T, Hiro T, Yamagishi M, et al: COSMOS Investigators: Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: Multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). Circ J, 2009; 73: 2110–2117.
14) Dohi T, Miyauchi K, Okazaki S, et al: Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended–ESTABLISH trial): a follow-up study. Atherosclerosis, 2010; 210: 497–502.
15) Kojima T, Miyauchi K, Yokoyama T, et al: Azelnidipine and amlodipine anti-atherosclerosis trial in hypertensive patients undergoing coronary intervention by serial volumetric intravascular ultrasound analysis in Juntendo University (ALPS-J). Circ J, 2011; 75: 1071–1079.
16) Nakajima N, Miyauchi K, Yokoyama T, et al: Effect of combination of ezetimibe and a statin on coronary plaque regression in patients with acute coronary syndrome ZEUS trial (eZETimibe Ultrasound Study). IJC Metab Endocr, 2014; 3: 8–13.
17) Kuramitsu S, Miyauchi K, Yokoi H, et al: Effect of
sitagliptin on plaque changes in coronary artery following acute coronary syndrome in diabetic patients: The ESPECIAL-ACS study. J Cardiol, 2017; 69: 369–376.

18) Nishitani–Yokoyama M, Miyauchi K, Shimada K, et al: Effects of Phase II Comprehensive Cardiac Rehabilitation on Coronary Plaque Volume After Acute Coronary Syndrome. Int Heart J, 2015; 56: 597–604.

19) Nishitani–Yokoyama M, Miyauchi K, Shimada K, et al: Impact of Physical Activity on Coronary Plaque Volume and Components in Acute Coronary Syndrome Patients After Early Phase II Cardiac Rehabilitation. Circ J, 2018; 83: 101–109.

20) Yokoyama T, Miyauchi K, Kurata T, Sato H, Daida H: Effect of probucol on neointimal thickening in a stent porcine restenosis model. Jpn Heart J, 2004; 45: 305–313.

21) Yokoyama T, Miyauchi K, Kurata T, Satoh H, Daida H: Inhibitory efficacy of pitavastatin on the early inflammatory response and neointimal thickening in a porcine coronary after stenting. Atherosclerosis, 2004; 174: 253–259.

22) Kasai T, Miyauchi K, Yokoyama T, Aihara K, Daida H: Efficacy of peroxisome proliferative activated receptor (PPAR)-alpha ligands, fenofibrate, on intimal hyperplasia and constrictive remodeling after coronary angioplasty in porcine models. Atherosclerosis, 2006; 188: 274–280.

23) Kasai T, Miyauchi K, Yokoyama T, et al: Pioglitazone attenuates neointimal thickening via suppression of the early inflammatory response in a porcine coronary after stenting. Atherosclerosis, 2008; 197: 612–619.

24) Kubota N, Miyauchi K, Kasai T, et al: Synergistic effects of calcium-channel and angiotensin–receptor blockers on endothelial function and inflammatory responses in a porcine drug-eluting stent model. Circ J, 2010; 74: 1704–1710.

25) Dohi T, Miyauchi K, Iesaki T, et al: Candesartan with pioglitazone protects against endothelial dysfunction and inflammatory responses in porcine coronary arteries implanted with sirolimus-eluting. Circ J, 2011; 75: 1098–1106.

26) Inoue K, Cynshi O, Kawabe Y, et al: Effect of BO–653 and probucol on c–MYC and PDGF–A messenger RNA of the iliac artery after balloon denudation in cholesterol–fed rabbits. Atherosclerosis, 2002; 161: 353–363.

27) Miyauchi K, Kasai T, Yokoyama T, et al: Effectiveness of statin–eluting stent on early inflammatory response and neointimal thickness in a porcine coronary model. Circ J, 2008; 72: 832–838.

28) Ogita M, Miyauchi K, Onishi A, et al: Development of Accelerated Coronary Atherosclerosis Model Using Low Density Lipoprotein Receptor Knock–Out Swine with Balloon Injury. PLoS One, 2016; 11: e0163055.

29) Seki E, Watanabe Y, Sunayama S, et al: Effects of phase III cardiac rehabilitation programs on health–related quality of life in elderly patients with coronary artery disease: Juntendo cardiac rehabilitation program (J–CARP). Circ J, 2003; 67: 73–77.

30) Onishi T, Shimada K, Sunayama S, et al: Effects of cardiac rehabilitation in patients with metabolic syndrome after coronary artery bypass grafting. J Cardiol, 2009; 53: 381–387.

31) Nishitani M, Shimada K, Masaki M, et al: Effect of cardiac rehabilitation on muscle mass, muscle strength, and exercise tolerance in diabetic patients after coronary artery bypass grafting. J Cardiol, 2013; 61: 216–221.

32) Sumide T, Shimada K, Ohmura H, et al: Relationship between exercise tolerance and muscle strength following cardiac rehabilitation: Comparison of patients after cardiac surgery and patients with myocardial infarction. J Cardiol, 2009; 54: 273–281.

33) Ohmura H, Mita T, Taneda Y, et al: SPIRITS–J Study Investigators: Efficacy and safety of sitagliptin in Japanese patients with type 2 diabetes. J Clin Med Res, 2015; 7: 211–219.

34) Miyazaki S, Miyauchi K, Hayashi H, et al: Registry of Japanese patients with atrial fibrillation focused on anticoagulant therapy in the new era: The RAFFINE registry study design and baseline characteristics. J Cardiol, 2018; 71: 390–396.