The importance of basic science in clinical cardiology

Many innovations start in basic science and ensure that clinical practice continues to evolve

Basic science is essential for the development of new drugs, diagnostics, interventions, and devices. ‘Many innovations in clinical practice ultimately come from basic science’, says Prof. Ajay M. Shah (London, UK). ‘Without that sort of development clinical practice wouldn’t evolve’.

But, some clinicians may ask, how long does it take for a basic science advance to make a practical difference in the clinic? ‘Basic science discoveries have the potential of being translated into practice much more quickly than they used to be’, says Prof. Barbara Casadei (Oxford, UK), chairperson of the European Society of Cardiology (ESC) Council on Basic Cardiovascular Science. ‘If one looks at fields like microRNA, they have only been recently discovered and there are already clinical trials ongoing. So one can see how important it is to maintain a pipeline of discoveries’.

Drug-eluting stents are another good example of basic science influencing clinical practice in cardiology. The idea started in basic science when a researcher observed that the cancer drug paclitaxel could inhibit the proliferation of vascular smooth muscle cells. Shah says: ‘Someone then had the idea of putting it onto a stent, it was trialled and look where we are now’.

Exciting advances are also being made in molecular imaging, with new probes that can image biological processes in the whole animal or the whole patient. Shah says: ‘None of us would be surprised if in a few years’ time we are sending our patients to have a particular scan to identify a vulnerable plaque. None of that could happen without basic science’.

While basic science is vital, equally important is that it be well connected to clinical questions and to patients. Cardiology needs people who are comfortable with a foot in both camps and can do translational studies. Good career paths are needed for bright young clinical academics. ‘It’s easy to lose those people [given] the way the current system is configured in many countries’, says Shah.

At King’s College London, Ajay M. Shah works with a whole spectrum of people including basic, translational, and clinician scientists. It is an environment that fosters new developments and recognizes that the pathway to discovery is rarely predictable.

‘What’s much more common is that it’s serendipity’, says Shah. ‘Someone’s interested in a biological process for some other reason, possibly for the sake of developing new knowledge, and then a discovery is made. Someone then makes a connection that this might be useful for a particular condition’.

It illustrates how environment and interactions are crucial for identifying fundamental basic science discoveries that could be used in the clinical arena. Scientific journals like European Heart Journal can also encourage that interaction and exchange between basic and clinical scientists. Coming back to microRNAs, their discovery had nothing to do with clinical medicine. But once the finding was made, others spotted the relevance to diagnostics and treatment.

Shah says that maintaining a thriving relationship between basic science and clinical cardiology is more challenging today than it has been in the past. One reason is financial, since investments are increasingly directed at specific goals. He says: ‘The general health economy and research economy drives people in such a way that sometimes it is difficult to identify the funding for the interaction areas, and to find good ways of having basic science and clinical science communicate’.

A second reason comes back to the issue of careers and people. Shah says: ‘In many places around the world it is more difficult to identify good clinical academics, those people who understand basic science and clinical practice and are well placed to work on the translation’.

Clinical cardiology is becoming more specialized, as is research, and one of the consequences is that clinicians and scientists start to focus on one thing. It is’ easy to end up with an environment where there are a lot of specialists but poor communication between them. ‘Unless you have an environment that facilitates communication across all of those specialties then it’s going to be difficult to translate basic science discoveries into clinical practice’, says Shah.

Governments and universities around the world are taking renewed interest in the idea of academic health science centres. These centres have a common strategy across a hospital and a university or medical school, and the shared ambitions are the delivery of high-quality patient care, education and training, and developing new treatments. Achieving those aims requires interactions between people with different skill sets, and the institution clears the way by getting rid of artificial boundaries and barriers.
Shah says: ‘The clinical service is not just driven by the idea of delivering very good clinical care and making a profit, but there is also a very strong academic research ethos through the institution. If you get it right then the whole environment can be very fertile’.

The Cardiostars Project: inspiring the next generation of cardiologists

Internationally renowned cardiologists discuss their thoughts and opinions with the younger generation, to help them maximize their potential

During the European Society of Cardiology (ESC) Congress 2011 the ‘CardioStars’ project was born, a series of TV interviews with world famous cardiologists. Eugene Braunwald, Pedro Brugada, Valentin Fuster, and many others were invited to discuss their achievements, share personal and professional stories, offer suggestions to inspire young cardiologists to follow successful careers, and, finally, to give their views about the future of cardiology.

All interviews are available on YouTube: http://www.youtube.com/watch?v=WfqfR1eXPko&list=PL78B58E6E886BF1CC.

In this report, we select some of the many important messages we received from several of these interviews.

Eugene Braunwald MD

At http://www.youtube.com/watch?v=jRj7bdu22a8

Widely considered as a father of cardiology, Dr Eugene Braunwald kindly agreed to share his inspiring memories on ESC TV during the ESC Congress in Amsterdam.

Dr Braunwald remembered that while writing the first edition of Braunwald’s Heart Disease he was working a 16 h day, 6½ days a week. In 1979, he took a sabbatical from Brigham and Women’s Hospital in Boston and had a limited amount of time in which to complete the book. He was interested in producing a book that would be a continuity and not a series of disconnected chapters. He authored and co-authored more than half of the book and it was a tremendous experience for him. He confessed that, during that very hard and stressful time, he probably learned more cardiology than ever before.

During his life Dr Braunwald has worked with many renowned specialists in cardiology. At the end of the discussion, replying to the question who he respected most and who was the most important mentor for him, he replied, ‘it was the surgeon Dr Glenn Morrow who influenced me most. We worked together in my 30’s at the National Institute of Health where Glenn taught me how to think and he changed the way I looked at patients. He also taught me how to write scientific papers. Over the course of 13 years we published together more that 100 papers and I owe him much for clarity of expression’.

Dr Braunwald emphasized that to succeed, young scientists need to have passion—a ‘fire in the belly’. There is no formula to become a renowned and famous specialist in cardiology, but he emphasized the need to have curiosity. ‘Enthusiasm in what you are doing, chase after something and finally, the idea of discovery, are the most important driving elements’, he said.

Pedro Brugada MD

At http://www.youtube.com/watch?v=a8jXXvK7JT0

Dr Pedro Brugada, an ESC Gold Medallist in 2012, has dedicated a career looking beyond the ECG. Together with his two brothers he described the sudden death syndrome that is named after the family, the Brugada Syndrome.

He highlighted the good fortune of having learnt different languages during childhood, which gave him an important advantage for a successful career outside his home country.

Speaking of the future, he said that progress during the last years has been fascinating.

We are able to treat conditions with interventional cardiology, such as ablation of arrhythmias, that were thought to be impossible 30 years ago. Now is a beautiful time to be a doctor he said, ‘we are going to face a doubling of the prevalence of cardiac diseases, and we don’t have enough human resources to face this epidemic. Our patients live longer, they become more complex and healthcare budgets are diminishing, so we have a real challenge ahead’, for which he did not see a solution. He stated that we need an immense change in how we practice medicine and how we use our financial resources.

Speaking of travel abroad during training, he quoted a Spanish saying ‘to have good fruits the plant needs to be transplanted’. He said that he forced his trainees to see a different world and different ways of doing things. ‘During training you should go abroad, it is a great experience that should be obligatory’.

His advice to young cardiologists is to apply the Latin motto ‘Nihil sine nixu’, that is, nothing without effort.
He was worried about the future of healthcare professionals in finding employment in spite of the great efforts to achieve their qualification. He recommended ‘just go on and keep fighting; there is only one thing that rewards you at the end of your life and it is hard work. Never expect anybody to do anything for you just do it yourself because nobody loves you more than yourself’.

Valentin Fuster MD

At http://www.youtube.com/watch?v=6FvQ2rvXgDc

Dr Valentin Fuster is an extremely well-known cardiologist on both sides of the Atlantic Ocean. A former AHA president and new chief editor-to-be of JACC (July 2014), Dr Fuster is really eager to stimulate and inspire the young at the beginning of their careers. He was interviewed during the ESC Congress 2011 in Paris.

He pointed out the importance of having a mentor, whom he defined ‘as somebody who will jump into the ocean for you and that the best mentor is the one who is critical of you not the one that says you are doing fantastic, you need somebody that tells you what you should not do’. In 2011 he highlighted three items for the future that are true nowadays: the movement from disease to prevention, from the heart to the brain and technology (imaging, genetics and tissue regeneration).

Speaking of projects involving the young, he stated, ‘if you don’t focus on the young generation you are completely off road’. The advice he gives to the young generations is quite clear; to find balance in life and on the young generation you are completely off road’. The advice he gave to the young generations is quite clear; to find balance in life through the 4 T’s: time to think, find your talent, and transmit positivity and tutoring. He told the young, ‘your life has to be more than your profession, you have to give back to society. Whatever you do, there is nothing more satisfactory than the feeling you are doing something worthy for society, even if it is very small’.

Eugenio Picano MD

At http://www.youtube.com/watch?v=VVQxQiXplbk

Dr Eugenio Picano is the father of stress echocardiography in Europe and an expert who supports cardiac imaging. He highlighted the tremendous technological advances of recent years and the potential danger of a change in the cultural attitude to cardiac imaging. In the past everything was clinically driven; now, due to early specialization and high technological impact, imaging specialists risk being image-driven and sometimes are more interested in obtaining beautiful images than in solving clinical problems.

He said that economic restraints are changing how we manage health. Previously it was thought that the more one spent on healthcare, the better; now, one needs to perform imaging with a wise strategy. He recommended choosing the cost-effective and less risky option for patients as sometimes ‘less is more in imaging’. He said that young cardiologists are experiencing an exciting period in the middle of economic crises and technological growth that will completely change the landscape of cardiac imaging.

This is a unique opportunity for the younger generation to make a breakthrough constructive contribution, both in the scientific field and on the academic side. Prof. Picano pointed out in a jovial mood that ‘in the academic field it is important to choose a good scientific professional father (mentor), to mature quickly, and then you should scientifically kill your mentor’.

In the near future cardiac imaging will change very rapidly and he summarized these changes with ‘symbolic’ words: portability (pocket size machines, to scan everywhere), connectivity (remote connections), sustainability (to wisely use the resources devoted to cardiac imaging, to get the best with the least expense and the least risk. If one is short of money, one has to think more and this is not necessarily bad).

His take-home message for the young: ‘you are in a very favourable position, in the middle of a crisis, crisis means danger, but it also means opportunities. Five years from now the cardiac imaging practice and science will be totally different from what you learnt from your masters, so the future is your talent and your ability to work’.

Panos Vardas MD

http://www.youtube.com/watch?v=KFPQClJtOeg

To our great pleasure, Prof. Panos Vardas, the current ESC president, agreed to an interview and to share his inspiring vision with us physicians of the younger generation.

‘I chose medicine to serve a mission’, he stated. The reason why he continued with cardiology was that he considers it to be a ‘marvellous specialty’. It deals with patients across many age groups, has a wide variety of conditions, and has effective treatments.

Asked about his vision, he first mentioned research. ‘I was thinking and dreaming how to find solutions for important pending issues in cardiovascular medicine’, he stated. As an example, he proudly mentioned one of his experiments performed in the late 1980s, where he created a small leadless pacemaker and applied it in dogs. ‘In general, I am a person with enthusiasm’, he continued, emphasizing his will to pass this spirit on to the younger generation.

For him, passion, courage, tenacity, and devotion to the needed work are the main and essential qualities for a successful career, with which, ‘you can afford to do anything’, said Prof. Vardas. According to him, being a good cardiologist is different from being a leader. While a good cardiologist is devoted to his/her individual patient, a leader acts more horizontally, trying to coordinate and to lead a number of persons and groups. His main advice to the generation of young cardiologists is to continue working for human beings, to be proud about the specialty they had chosen to serve, and to work very hard to discover radically new options for the treatment of cardiovascular diseases. Regarding his dedication to his job as ESC president, he stated, ‘I try to always be at the bridge and to steer the vessel properly. This is my mission’.

Rafael Vidal-Pérez, Ricardo Fonts-Cardvalho, Luna Gargani, Ewa Jankowska, Michal Pazdernik, Janine Pöss, Markus Wallner, and Stéphane Zuily
50th Anniversary of angioplasty

Angioplasty turned 50 in January 2014

Fifty years ago, on 16 January 1964 a medical revolution occurred with the world’s first percutaneous transluminal angioplasty, when a stenotic femoral artery was successfully dilated. This remarkable feat paved the way for minimally invasive vascular surgery and made angioplasty a cornerstone for current treatments of cardiovascular and peripheral arterial disease.

On 16 January 1964, Dr Charles Theodore Dotter, an interventional radiologist at the University of Oregon Hospital, Portland, OR, USA, performed the first-ever angioplasty. The patient, Laura Shaw, aged 82 years, had ischaemic leg pain and gangrene of her left foot. She refused the initial surgical advice of foot amputation and Dr Dotter was consulted. Using increasing diameter coaxial Teflon catheters inserted percutaneously, he dilated a localized tight stenosis of the superficial femoral artery. The first-ever transluminal angioplasty successfully restored blood flow to her foot and remained patent until her death from pneumonia two and a half years later.

Dr Dotter used one of the first commercially produced catheters to carry out the procedure after having met the manufacturer, Bill Cook, at a medical trade show the previous year. Cook had recently started his own medical equipment company and was displaying how Teflon tubing could be shaped using a blowtorch to create a catheter that could enter a blood vessel through a needle puncture.

Together, Dr Dotter and Cook visualized and designed the starting blocks for the future of minimally invasive treatments, an achievement that led to Dotter being nominated for the Nobel Prize in Medicine in 1978.

Dotter’s techniques were embraced and expanded by investigators in Europe, notably Dr Eberhard Zeitler in Germany, who introduced Andreas Grünzig to the technique. Dr Grünzig performed the first coronary angioplasty on an awake patient in September 1977.

It is estimated that >60 million vascular angioplasties have been performed worldwide since Dotter introduced the procedure.1 Today, >75 000 coronary angioplasties are carried out annually in the UK2 alone.

Charles Dotter has been called the ‘Father of Interventional Radiology’.

Andros Tofield

References

1. Kaufman J. In historic 2014, future of image-guided interventions to be discussed in Portland. Intervent News, http://www.cxvascular.com/in-features/interventional-news—features/in-historic-2014-future-of-image-guided-interventions-to-be-discussed-in-portland (accessed January 2014).
2. NHS Choices. Coronary angioplasty and stent insertion. http://www.nhs.uk/conditions/coronary-angioplasty/Pages/Introduction.aspx (accessed January 2014).
The past two decades have seen an ever-increasing number of biomarkers proposed for the assessment and management of patients with cardiovascular diseases. Some of the biomarkers such as cardiac troponin, the natriuretic peptides, or low-density lipoproteins have successfully been transitioned from bench to bedside and are invaluable in daily clinical practice. An even larger group of biomarkers have been linked to underlying disease processes such as inflammation, thrombosis, and increased oxidative stress, and have shown an incremental value for risk stratification, but have not made the transition into clinical practice yet.

The book ‘Biomarkers in Cardiovascular Diseases’ by Tousoulis and Stefanadis nicely summarizes the most promising biomarkers intended for use in patients with cardiovascular diseases. In a first part labelled ‘classical biomarkers’, the authors cover the full spectrum of cardiovascular disorders in 12 chapters dedicated to specific diseases, including traditional biomarker topics such as acute coronary syndromes, heart failure, or dyslipidaemias, but also addressing topics such as pulmonary hypertension, coronary artery bypass grafting, or cardiac arrhythmias. The second part of the book focuses on ‘novel biomarkers’.

Every chapter ends with a concise conclusion section summarizing the chapter’s key points. The breakdown into the parts ‘classical’ and ‘novel’ biomarkers is not particularly intuitive in the sense that most of the biomarkers discussed in the ‘classical’ part chapters have not yet arrived into clinical practice and that many of the biomarkers discussed in the ‘novel’ part chapters have already been discussed in the ‘classical’ part chapters.

In summary, ‘Biomarkers in Cardiovascular Diseases’ offers a comprehensive review of well-selected promising biomarkers for (potential) use in the entire spectrum of cardiovascular diseases. In doing so, the book is of interest for basic and clinical cardiovascular scientists as well as for clinicians with an interest in biomarker research.
Cardiac resynchronization therapy (CRT) has evolved enormously since its beginnings as a treatment for patients with advanced heart failure and cardiac systolic dysfunction. This has become possible, firstly, because of its continuous technical development, and the improved training and specialization of the professionals responsible for the implant and monitoring of the devices. Secondly, multiple randomized clinical trials have been carried out in recent years, allowing the identification of patients who would benefit most from this therapy.

The first European guidelines for CRT published in 2007, supported the use of CRT in patients with characteristics similar to those enrolled in previous studies, setting a class I level of recommendation for patients in sinus rhythm with advanced heart-failure symptoms [New York Heart Association (NYHA) functional class III or IV], ejection fraction of 35% or less, QRS widening of 120 ms or more, and left ventricular dilatation. Implantation in patients with the same characteristics but in atrial fibrillation had a much lower indication (Class IIb, level of evidence C).

However, as already revealed in the European CRT Survey in 2010, the CRT indications used in daily practice went far beyond those recommended in the guidelines. They included patients with QRS less than 120 ms with or without left bundle branch block (LBBB), asymptomatic patients or those with NYHA Class I–II/IV symptoms, and subjects with atrial fibrillation, who were underrepresented in the randomized controlled trials published at that time.

Despite the high expense and the significant non-responder rates, the off-label use of CRT in daily practice and the inclusion of patients for subsequent clinical trials conducted to date showed a tendency to expand the use of these devices to most patients with systolic dysfunction.

Following the encouraging results in improvement of functional class and ventricular volumes of the MIRACLE-ICD II, the attention of researchers focused on the efficacy of CRT in less symptomatic patients. The REVERSE and MADIT-CRT studies recruited a total of 2430 patients with CF I–II, LVEF \leq 30–40% and QRS \geq 120–130 m. While in the MADIT-CRT the primary endpoint (defined as hospitalization for heart failure or death from all causes) reached statistical significance (17.2% in the CRT-D group vs. 25.3 in the ICD only), this did not occur in REVERSE, where the entire population studied showed a favourable clinical response and a decrease in ventricular volume. Neither study was able to show a benefit for mortality and this was attributed to the relatively short follow-up period in patients with a better prognosis, because they presented at an earlier stage of the disease. Although the subgroup with CF I/IV was underrepresented in these studies and there was no demonstration of a reduction in events, there was a favourable effect of CRT on ventricular remodelling, which entails the need for further clinical trials. Perhaps, these can be carried out with a larger number of patients followed for longer period of time to prove the reduction of events in these patients.

The clinical practice guidelines soon echoed these results. As a result, an update on current guidelines was published in 2010, establishing as class I CRT in CF II and QRS \geq 150 ms. The publication of RAFT in 2010, conducted on 1798 patients in FC II–III, increased the evidence for use of CRT in patients with FC II, placing all symptomatic patients on the same level (NYHA class II–IV) in the guidelines published in August 2013.

Despite the huge number of patients with both permanent AF and heart failure, representing >20% of CRT recipients in Europe, this group was barely included in the large randomized clinical trials.

The studies published, in which the efficacy of CRT in patients in sinus rhythm (SR) was compared to those with atrial fibrillation, showed a lower clinical efficacy and a higher rate of non-responders in the AF group, and this is partly explained by the difficulty in achieving an acceptable biventricular stimulation. Therefore, it was expected that, in the APAF and PAVE studies conducted on patients with atrial fibrillation and AV node ablation, CRT decreased both mortality and the number of hospitalizations due to heart failure, slightly increasing the recommendation level in the latest guidelines, which then became class IIa, level of evidence B.

Following this line of work, in the recently published CERTIFY study, a prospective observational design conducted on 7384 patients, mortality was compared after CRT in a group of patients in sinus rhythm compared with another group with atrial fibrillation and heart rate control with node ablation or medical treatment. Unlike previous studies, cardiac and total mortality were higher in the cohort with atrial fibrillation treated with drugs, with no significant differences between patients in sinus rhythm and those with AF and AV node ablation, probably setting a path to be followed for new randomized clinical trials to demonstrate the efficacy of CRT in patients with atrial fibrillation.

Finally, just 4 months ago the BLOCK-HF came to light, which is another example of the continuous search for new indications for
CRT. Six hundred and ninety-one (691) patients with AV conduction disorders of different severity and CF I–III and LVEF ≤50% were implanted with pacemakers, where the left ventricle electrode was active in 50% of the cases. For a long follow-up, patients assigned to CRT-OFF showed a significantly higher incidence of the primary end-point (defined as the time to death from any cause, decompensated CHF requiring i.v. treatment or 15% increase in LV end-systolic volume). Despite the limitations of the study, which lacks a control...
group (with an expected lower rate of complications related to the implant), it suggests that CRT may be beneficial in patients with a lower degree of systolic dysfunction and an indication for pacemaker avoiding the deleterious effect of stimulation from the right ventricle.

Recently, several studies were published that show no benefit in patients with narrow QRS despite having evidence of ventricular dys-synchrony22 or in those with QRS morphologies different from LBBB.23,24

Although, at present, the data of the aforementioned clinical trials and indications of the guidelines based on the QRS width and the morphology of the bundle branch block restrict our choice of patients, we believe that CRT is a very effective treatment that extends the life and quality of life of many of our patients and we hope that it can increasingly benefit a larger number of patients in the future (Figures 1 and 2).

References
1. Vandes PE, Aurichio A, Blanc J, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Ota A, Sutton R, Trusz-Gluzka M. European Society of Cardiology; European Heart Rhythm Association. Guidelines for cardiac pacing and cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. Eur Heart J 2007; 28: 959–998.
2. Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Arch Intern Med 2011; 171: 1454–1462.
3. Aurichio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, Bocker D, Block M, Kerkels JH, Kramer A, Huelle E. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. J Am Coll Cardiol 2003; 42: 2109–2116.
4. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009; 361: 1329–1338.
5. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Kirkels JH, DeMarco T, Foster E, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace 2013; 15: 1070–1118.
6. Hernández-Madrid A, Mata R, Mora C, Zamorano J, Almenar L, Sancho-Tello de Carranza M, Fernández-Lozano I. Análisis transversal de la resincronización cardíaca en España. Indicaciones. Técnicas de implante. Optimización y seguimiento. Rev Esp Cardiol 2012; 65: 826–834.
7. Wilton SB, Leung AA, Ghali WA, Farris P, Exner DV. Outcomes of cardiac resynchron-ization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm 2011; 8: 1088–1094.
8. Brignole M, Bitto G, Mont L, Iacopino S, De Marchi G, Oddone D, Luzi M, Tolosana JM, Navazio A, Menozzi C. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J 2011; 32: 4220–4229.
9. Gillenson DJ, Nava SS, Cohn JN, Colonna G, Missal MS, Schnyder P, Saccardi P, Guntner P, Cox A. Cardiac-resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Systolic Dysfunction (RESORD) study. J Cardiovasc Electrophysiol 2005; 16: 1160–1165.
10. Gasparini M, Leclercq C, Lunati M, Landolina A, Aurichio A, Santini M, Boriani G, Lamp B, Proclemer A, Cuprins A, Krebs C, Levasa F. Cardiac Resynchronization Therapy (MADIT-CRT). N Engl J Med 2011; 365: 1395–1398.
11. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Goresan JI, Gras D, Krum H, Sogard P, Holzmeister J, EchoCRT Study Group. Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Asymptomatic Differences. Circ J 2012; 76: 1585–1595.
12. Brignole M, Nava SS, Colonna G, Missal MS, Schnyder P, Cohn JN, Guntner P, Cox A. Cardiac-resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003; 42: 1454–1459.
13. Young JB, Abraham WT, Kocovic DZ, Foster E, Yang PG. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003; 42: 1454–1459.
14. Wilton SB, Leung AA, Ghali WA, Farris P, Exner DV. Outcomes of cardiac resynchron-ization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm 2011; 8: 1088–1094.
15. Brignole M, Bitto G, Mont L, Iacopino S, De Marchi G, Oddone D, Luzi M, Tolosana JM, Navazio A, Menozzi C. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J 2011; 32: 4220–4229.
16. Gillenson DJ, Nava SS, Cohn JN, Colonna G, Missal MS, Schnyder P, Saccardi P, Guntner P, Cox A. Cardiac-resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Systolic Dysfunction (RESORD) study. J Cardiovasc Electrophysiol 2005; 16: 1160–1165.
17. Gasparini M, Leclercq C, Lunati M, Landolina A, Aurichio A, Santini M, Boriani G, Lamp B, Proclemer A, Cuprins A, Krebs C, Levasa F. Cardiac Resynchronization Therapy (MADIT-CRT). N Engl J Med 2011; 365: 1395–1398.
18. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Goresan JI, Gras D, Krum H, Sogard P, Holzmeister J, EchoCRT Study Group. Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Asymptomatic Differences. Circ J 2012; 76: 1585–1595.
19. Brignole M, Nava SS, Colonna G, Missal MS, Schnyder P, Cohn JN, Guntner P, Cox A. Cardiac-resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003; 42: 1454–1459.
20. Wilton SB, Leung AA, Ghali WA, Farris P, Exner DV. Outcomes of cardiac resynchron-ization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm 2011; 8: 1088–1094.
21. Brignole M, Nava SS, Colonna G, Missal MS, Schnyder P, Cohn JN, Guntner P, Cox A. Cardiac-resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Systolic Dysfunction (RESORD) study. J Cardiovasc Electrophysiol 2005; 16: 1160–1165.
22. Gasparini M, Leclercq C, Lunati M, Landolina A, Aurichio A, Santini M, Boriani G, Lamp B, Proclemer A, Cuprins A, Krebs C, Levasa F. Cardiac Resynchronization Therapy (MADIT-CRT). N Engl J Med 2011; 365: 1395–1398.
23. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Goresan JI, Gras D, Krum H, Sogard P, Holzmeister J, EchoCRT Study Group. Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Asymptomatic Differences. Circ J 2012; 76: 1585–1595.
24. Wilton SB, Leung AA, Ghali WA, Farris P, Exner DV. Outcomes of cardiac resynchron-ization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm 2011; 8: 1088–1094.