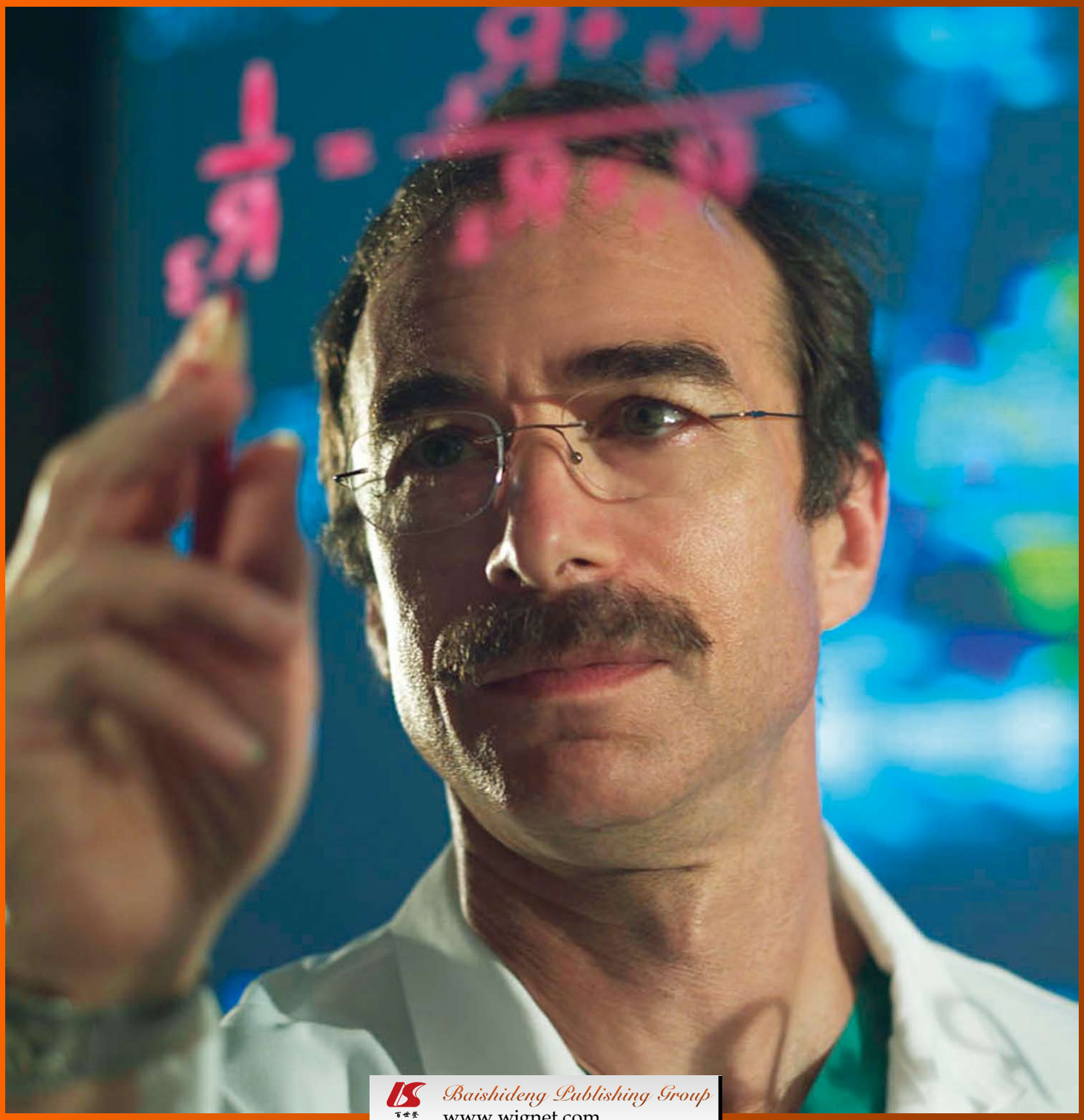
**ISSN** 1949-8462 (online)

# World Journal of *Cardiology*

*World J Cardiol* 2012 August 26; 4(8): 242-266



Baishideng Publishing Group
www.wjgnet.com

World Journal of Cardiology

*A peer-reviewed, online, open-access journal of Cardiology*

# Editorial Board

2009-2013

The *World Journal of Cardiology* Editorial Board consists of 362 members, representing a team of worldwide experts in cardiology. They are from 43 countries, including Argentina (4), Australia (9), Belgium (2), Brazil (5), Canada (24), Chile (1), China (18), Colombia (1), Czech (1), Denmark (4), France (3), Germany (32), Greece (14), Hungary (2), India (8), Iran (2), Ireland (1), Israel (2), Italy (44), Japan (24), Kosovo (1), Lebanon(1), Malaysia (1), Mexico (1), Morocco (1), Netherlands (9), Nigeria (1), Oman (1), Pakistan (1), Poland (3), Portugal (1), Russia (1), Singapore (1), Slovenia (2), South Africa (2), South Korea (6), Spain (10), Switzerland (1), Thailand (1), Turkey (8), United Kingdom (14), United States (93), and Uruguay (1).

**Denmark**

Morten Grunnet, *Ballerup*
Won Yong Kim, *Aarhus*
Ole Dyg Pedersen, *Copenhagen*
Jacob Tfelt-Hansen, *Copenhagen*

**France**

Philippe Commeau, *Ollioules*
Yves D Durandy, *Massy*
Thierry Lefèvre, *Massy*

**Germany**

Ferruh Artunc, *Tübingen*
Muhammet A Aydin, *Hamburg*
Alexander Bauer, *Heidelberg*
Peter Bernhardt, *Ulm*
Torsten Bossert, *Jena*
Marcus Dörr, *Greifswald*
Holger Eggebrecht, *Essen*
Tommaso Gori, *Mainz*
Dariusch Haghi, *Mannheim*
Stefan E Hardt, *Heidelberg*
Klaus Hertting, *Hamburg*
Thomas Jax, *Neuss*
Thorsten Kälsch, *Mannheim*
Klaus Kettering, *Frankfurt*
Grigorios Korosoglou, *Heidelberg*
Horst J Kuhn, *Planegg*
Lorenz H Lehmann, *Heidelberg*
Huige Li, *Mainz*
Veselin Mitrovic, *Bad Nauheim*
Ulrich Nellessen, *Stendal*
Guenter Pilz, *Hausham*
Peter W Radke, *Lübeck*
Obaida Rana, *Aachen*
Tienush Rassaf, *Düsseldorf*
Oliver Ritter, *Wuerzburg*
Erol Saygili, *Aachen*
Dirk Skowasch, *Bonn*
Tim Süselbeck, *Mannheim*
Dirk Taubert, *Cologne*
Theodor Tirilomis, *Goettingen*
Stephen Wildhirt, *Ulm*
Thomas Zeller, *Bad Krozingen*

**Greece**

Yiannis S Chatzizisis, *Thessaloniki*
Moses S Elisaf, *Ioannina*
Gerasimos Filippatos, *Athens*
Panagiotis Korantzopoulos, *Ioannina*
Nicholas G Kounis, *Patras*
Antigone Lazou, *Thessaloniki*
Konstantinos P Letsas, *Athens*
Athanassios N Manginas, *Athens*
Lampros Michalis, *Ioannian*
Serafim Nanas, *Athens*
Loukianos S Rallidis, *Athens*
Georgios I Tagarakis, *Thessaloniki*
Dimitrios Tziakas, *Alexandroupolis*
Theodoros Xanthos, *Athens*

**Hungary**

Gergely Feher, *Pecs*
Albert Varga, *Szeged*

**India**

MPS Chawla, *Roorkee*
S Dwivedi, *Delhi*
Rajeev Gupta, *Jaipur*
Deepak Kaul, *Chandigarh*
Prabhakaran Prabhakaran, *New Delhi*
KV Pugalendi, *Tamilnadu*
Rajesh Vijayvergiya, *Chandigarh*

**Iran**

VR Dabbagh Kakhki, *Mashhad*
Roya Kelishadi, *Isfahan*

**Ireland**

Jonathan D Dodd, *Dublin*

**Israel**

Jacob George, *Tel Aviv*
E Goldhammer, *Haifa*

**Italy**

Maria Grazia Andreassi, *Massa*
Giuseppe Barbaro, *Rome*
Riccardo Bigi, *Milan*
Tonino Bombardini, *Pisa*
Filippo Cademartiri, *Parma*
Alessandro Capucci, *Piacenza*
Sergio Coccheri, *Bologna*
Antonio Colombo, *Milan*
Alberto Cuocolo, *Napoli*
Roberto De Ponti, *Varese*
Gianluca Di Bella, *Messina*
Giovanni Fazio, *Palermo*
Vittorio Fineschi, *Foggia*
Antonio F Folino, *Padova*
Gabriele Fragasso, *Milano*
Carmine Gazzaruso, *Vigevano*
Massimo Imazio, *Torino*
Federico Lombardi, *Milan*
Roberto Marchioli, *Santa Maria Imbaro*
Giovan Giuseppe Mattera, *Pomezia*
Germano Melissano, *Milano*
Pietro A Modesti, *Florence*
Eraldo Occhetta, *Novara*
Pasquale Pagliaro, *Orbassano*
Emilio Maria G Pasanisi, *Pisa*
Vincenzo Pasceri, *Rome*
Salvatore Patanè, *Messina*
Nunzia Rosa Petix, *Florence*
Eugenio Picano, *Pisa*
Rita Rezzani, *Brescia*
Manfredi Rizzo, *Palermo*
Gian Paolo Rossi, *Padua*
Speranza Rubattu, *Rome*
Andrea Rubboli, *Bologna*
Rosa Sicari, *Pisa*
Giuseppe Tarantini, *Padua*
Luigi Tavazzi, *Cotignola*
Luca Testa, *Milan*
Maurizio Turiel, *Milan*
Cristina Vassalle, *Pisa*
Massimo Volpe, *Rome*

**Japan**

Yoshifusa Aizawa, *Niigata*
Junichiro Hashimoto, *Sendai*
Hajime Kataoka, *Oita*
Akinori Kimura, *Tokyo*
Sei Komatsu, *Amagasaki*
Ikuo Fukuda, *Hirosaki*
Satoshi Kurisu, *Hiroshima*
Yoshihiro Matsumoto, *Shizuoka*
Tetsuo Minamino, *Osaka*
Yoko Miyasaka, *Osaka*
Kenichi Nakajima, *Kanazawa*
Mashio Nakamura, *Tsu*
Kazuaki Nishio, *Tokyo*
Koichi Sakabe, *Kagawa*
Masataka Sata, *Tokushima*
Shinji Satoh, *Fukuoka*
Yoshihide Takahashi, *Kanagawa*
Masamichi Takano, *Chiba*
Kengo Tanabe, *Tokyo*
Hiroki Teragawa, *Hiroshima*
Hiroyasu Ueda, *Osaka*
Takanori Yasu, *Okinawa*
Hiroshi Yoshida, *Chiba*

**Kosovo**

Gani Bajraktari, *Prishtina*

**Lebanon**

Habib A Dakik, *Beirut*

**Malaysia**

Eric Tien Siang Lim, *Johor*

**Mexico**

Enrique Vallejo, *Mexico*

**Morocco**

Abdenasser Drighil, *Casablanca*

**Netherlands**

Folkert Wouter Asselbergs, *Groningen*
Jeroen J Bax, *Leiden*
JJ Brugts, *Rotterdam*
Peter W de Leeuw, *AZ Maastricht*
Corstiaan A Den Uil, *Rotterdam*
PA Doevendans, *Utrecht*
D Poldermans, *Rotterdam*
PW Serruys, *Rotterdam*

**Nigeria**

OS Ogah, *Ibadan*

**Pakistan**

Fahim H Jafary, *Karachi*

**Poland**

Pawel Buszman, *Katowice*
Maciej Kurpisz, *Poznan*
Sebastian Szmit, *Warsaw*

**Russia**

Nadezda Bylova, *Moscow*

**Singapore**

Jinsong Bian, *Singapore*

**Slovenia**

Mitja Lainscak, *Golnik*
Matej Podbregar, *Ljublajna*

**South Africa**

Benjamin Longo-Mbenza, *Pretoria*
JP Smedema, *Capetown*

**South Korea**

Jang-Ho Bae, *Daejeon*
Young-Guk Ko, *Seoul*
Sang-Hak Lee, *Seoul*
Pil-Ki Min, *Seoul*
Seung-Jung Park, *Seoul*

**Spain**

Miguel A Arias, *Toledo*
Antoni Bayés-Genís, *Barcelona*
Alberto Dominguez-Rodriguez, *Tenerife*
Lorenzo Facila, *Castellon*
José Luis Pérez-Castrillon, *Valladolid*
Jesus Peteiro, *Coruña*
Pedro L Sánchez, *Madrid*
José L Zamorano, *Madrid*

**Switzerland**

Paul Erne, *Luzern*

**Thailand**

Nipon Chattipakorn, *Chiang Mai*

**Turkey**

Turgay Çelik, *Etlik-Ankara*
Yengi U Celikyurt, *Kocaeli*
Hamza Duygu, *Yesilyurt*
Cemil Gürgün, *İzmir*
T Fikret Ilgenli, *Kocaeli*
Ergün Barış Kaya, *Ankara*
Mehmet Ozaydin, *Isparta*
Mustafa Yildiz, *Istanbul*

**United Kingdom**

AD Blann, *Birmingham*
Geoffrey Burnstock, *London*
John GF Cleland, *Kingston upon Hull*
Armen Yuri Gasparyan, *Dudley*
Derek J Hausenloy, *London*
Farhad Kamali, *Newcastle upon Tyne*
Juan Carlos Kaski, *London*
Rajesh G Katare, *Bristol*
Sohail Q Khan, *Manchester*
Khalid Rahman, *Liverpool*
Alexander M Seifalian, *London*
Mark Slevin, *Manchester*
Anastasis Stephanou, *London*

**United States**

Kamran Akram, *Omaha*
Arshad Ali, *Ashland*
Mouaz Al-Mallah, *Detroit*
Naser M Ammash, *Rochester*
Vignendra Ariyarajah, *Philadelphia*
Wilbert S Aronow, *Valhalla*
S Serge Barold, *Tampa*
Gregory W Barsness, *Rochester*
Daniel S Berman, *Los Angeles*
John F Beshai, *Chicago*
William E Boden, *Buffalo*
Somjot S Brar, *Los Angeles*
David W Brown, *Decatur*
Lu Cai, *Louisville*
Christopher Paul Cannon, *Boston*
Ricardo Castillo, *Brooklyn*
Jun R Chiong, *Loma Linda*
Steven G Chrysant, *Oklahoma*
Timm Dickfeld, *Baltimore*
Dayue Darrel Duan, *Reno*
Rosemary B Duda, *Boston*
Michael E Farkouh, *New York*
Arthur Michael Feldman, *Philadelphia*
Ronald Freudenberger, *Allentown*
Jalal K Ghali, *Detroit*
Lev G Goldfarb, *Bethesda*
Samuel Z Goldhaber, *Boston*
Hitinder S Gurm, *Ann Arbor*
Julia H Indik, *Tucson*
Antony Leslie Innasimuthu, *Pittsburgh*
Ami E Iskandrian, *Birmingham*
Rovshan M Ismailov, *Pittsburgh*
Diwakar Jain, *Philadelphia*
Shahrokh Javaheri, *Mason*
Jacob Joseph, *West Roxbury*
Bobby V Khan, *Atlanta*
Christopher M Kramer, *Charlottesville*
Rakesh C Kukreja, *Richmond*
Roberto M Lang, *Chicago*
Marzia Leacche, *Nashville*
Jingping Lin, *Bethesda*
Yi-Hwa Liu, *New Haven*
Angel López-Candales, *Pittsburgh*
Frank Marcus, *Tucson*
Malek G Massad, *Chicago*
Jawahar L Mehta, *Little Rock*
Robert M Mentzer Jr, *Detroit*
J Gary Meszaros, *Rootstown*
Michael Miller, *Baltimore*
Emile R Mohler III, *Philadelphia*
Patrick M Moriarty, *Kansas City*
Jeffrey W Moses, *New York*
Mohammad-Reza Movahed, *Tucson*
Gerald V Naccarelli, *Hershey*
Andrea Natale, *Austin*
Tien MH Ng, *Los Angeles*
Steven Nissen, *Cleveland*
Gian M Novaro, *Weston*
Brian Olshansky, *Iowa*
Robert Lee Page II, *Aurora*
Weihong Pan, *Baton Rouge*
Linda Pauliks, *Hershey*
Philip Jack Podrid, *Boston*
Vikas K Rathi, *Midlothian*
Jun Ren, *Laramie*
Harmony R Reynolds, *New York*
Clive Rosendorff, *Bronx*
Samir Saba, *Pittsburgh*
Rajesh Sachdeva, *Little Rock*
Sandeep A Saha, *Spokane*
Tiziano M Scarabelli, *Detroit*
Robert H Schneider, *Maharishi Vedic*
Frank W Sellke, *Providence*
Samin K Sharma, *New York*
Jamshid Shirani, *Danville*
Boris Z Simkhovich, *Los Angeles*
Krishna Singh, *Johnson City*
Laurence S Sperling, *Atlanta*
Jonathan S Steinberg, *New York*
Ernst R von Schwarz, *Los Angeles*
Richard Gary Trohman, *Chicago*
Tong Tang, *San Diego*
Qing Kenneth Wang, *Cleveland*
Yi Wang, *Wilmington*
Adam Whaley-Connell, *Columbia*
Bruce L Wilkoff, *Cleveland*
Qinglin Yang, *Birmingham*
Xing Sheng Yang, *Atlanta*
Yucheng Yao, *Los Angeles*
Midori A Yenari, *San Francisco*
Cuihua Zhang, *Columbia*

**Uruguay**

Juan C Grignola, *Montevideo*

WJC

World Journal of Cardiology

Contents

Monthly Volume 4 Number 8 August 26, 2012

**REVIEW**

242 Changes in the safety paradigm with percutaneous coronary interventions in the modern era: Lessons learned from the ASCERT registry

*Rodríguez AE, Fernández-Pereira C, Rodríguez-Granillo AM*

**BRIEF ARTICLE**

250 Evaluation of the prevalence and severity of pain in patients with stable chronic heart failure

*Udeoji DU, Shah AB, Bharadwaj P, Katsiyiannis P, Schwarz ER*

256 Effect of eicosapentaenoic acid on regional arterial stiffness: Assessment by tissue Doppler imaging

*Haiden M, Miyasaka Y, Kimura Y, Tsujimoto S, Maeba H, Suwa Y, Iwasaka T, Shiojima I*

**CASE REPORT**

260 MRI-guided ablation of wide complex tachycardia in a univentricular heart

*Reiter T, Ritter O, Nordbeck P, Beer M, Bauer WR*

264 Acute coronary syndrome in a patient with a single coronary artery arising from the right sinus of Valsalva

*Liesting C, Brugts JJ, Kofflard MJM, Dirkali A*

*World Journal of Cardiology*
**Volume 4 Number 8 August 26, 2012**

## Contents


| | | |
|---|---|---|
| **ACKNOWLEDGMENTS** | I | Acknowledgments to reviewers of *World Journal of Cardiology* |
| **APPENDIX** | I | Meetings |
| | I-V | Instructions to authors |
| **ABOUT COVER** | | Editorial Board Member of *World Journal of Cardiology*, Brian Olshansky, MD, Professor of Medicine, Cardiac Electrophysiology, University of Iowa Hospitals, 200 Hawkins Drive, Room 4426a JCP, Iowa City, IA 52242, United States |
| **AIM AND SCOPE** | | *World Journal of Cardiology* (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a monthly peer-reviewed, online, open-access, journal supported by an editorial board consisting of 362 experts in cardiology from 43 countries.<br>The major task of *WJC* is to rapidly report the most recent developments in the research by the cardiologists. *WJC* accepts papers on the following aspects related to cardiology: arrhythmias, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, paediatrics, nursing, and health promotion. We also encourage papers that cover all other areas of cardiology as well as basic research. |
| **FLYLEAF** | I-III | Editorial Board |




NAME OF JOURNAL
*World Journal of Cardiology*

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITING
Editorial Board of *World Journal of Cardiology*,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: wjc@wjgnet.com
http://www.wjgnet.com

EDITOR-IN-CHIEF
**Raúl Moreno, MD, Director** of Interventional Cardiology, Interventional Cardiology, Hospital La Paz, Paseo La Castellana, 261, 28041 Madrid, Spain

**Victor L Serebruany, MD, PhD, Associate Professor,** Johns Hopkins University School of Medicine, President, HeartDrug™ Research Laboratories, Osler Medical Center, 7600 Osler Drive, Suite 307, Towson, MD 21204, United States

EDITORIAL OFFICE
Jian-Xia Cheng, Director
*World Journal of Cardiology*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: wjc@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai, Hong Kong, China
Telephone: +852-58042046
Fax: +852-31158812
E-mail: bpg@baishideng.com
http://www.wjgnet.com

PUBLICATION DATE
August 26, 2012



INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1949-8462/g_info_20100316161927.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
wjc@wjgnet.com
doi:10.4330/wjc.v4.i8.242

*World J Cardiol* 2012 August 26; 4(8): 242-249
ISSN 1949-8462 (online)


REVIEW

# Changes in the safety paradigm with percutaneous coronary interventions in the modern era: Lessons learned from the ASCERT registry

Alfredo E Rodríguez, Carlos Fernández-Pereira, Alfredo M Rodríguez-Granillo

Alfredo E Rodríguez, Carlos Fernández-Pereira, Alfredo M Rodríguez-Granillo, Cardiovascular Research Center, Cardiac Unit Otamendi Hospital, Azcuenga 870, 1072 Buenos Aires, Argentina
Author contributions: All authors were involved in the preparation and in manuscript processing.
Correspondence to: Alfredo E Rodriguez, MD, PhD, FACC, FSCAI, Cardiovascular Research Center, Cardiac Unit Otamendi Hospital, Azcuenga 870, 1072 Buenos Aires, Argentina. arodriguez@centroceci.com.ar
Telephone: +54-11-49648721 Fax: +54-11-49629012
Received: June 21, 2012 Revised: July 17, 2012
Accepted: July 24, 2012
Published online: August 26, 2012

## Abstract

In the past, comparative effectiveness trials evaluating percutaneous coronary interventions (PCI), using either balloon angioplasty or bare metal stent (BMS) implantation, *versus* coronary artery bypass surgery (CABG) found similar survival rates at long-term follow-up with both revascularization strategies. Two major meta-analyses of these trials reported 5- and 6-year comparative effectiveness between PCI and CABG: one included only four trials that compared PCI with BMS implantation *versus* CABG whereas the largest one also included trials using balloon angioplasty. In these studies, the authors observed no survival differences between groups although a significant survival advantage was seen in diabetics treated with CABG and this benefit was also perceived in elderly patients. In both reports, number of involved vessels, presence of left anterior descending artery stenosis or poor left ventricular ejection fraction were no predictors of poor survival with PCI. Therefore, extent of the coronary artery disease (CAD) was not associated with poor outcome after PCI in the pre-drug eluting stent (DES) era. Recently, the ASCERT (Database Collaboration on the Comparative Effectiveness of Revascularization Strategies) registry found higher mortality rate with PCI in patients ⩾ 65 years old in comparison with CABG, and advantages of surgery were seen in all subgroups including those at low risk. In this registry, PCI was accomplished by implantation of the first type of DES designs in 78% of cases. The intriguing observation of high mortality rate with PCI, including for non-diabetics and patients with two-vessel CAD, meaning a lack of clinical benefit with DES implantation, had not been seen previously. The study was not randomized, although its results are largely strengthened by its sample size. In this manuscript, the authors describe other registries and randomized trials reporting similar results supporting the findings of the aforementioned study and explore the reasons for these results, while also searching for potential solutions.



**Key words:** Percutaneous coronary interventions; Coronary artery bypass surgery; Drug eluting stents; Coronary artery disease; Elderly patients

**Peer reviewers:** Paul Erne, MD, Professor, Head, Department of Cardiology, Luzerner Kantonsspital, CH-6000 Luzern 16, Switzerland; Masamichi Takano, MD, PhD, Cardiovascular Center, Chiba-Hokusoh Hospital, Nippon Medical School, 1715 Kamakari, Imba, Chiba 270-1694, Japan; Hiroki Teragawa, MD, PhD, Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Rodríguez AE, Fernández-Pereira C, Rodríguez-Granillo AM. Changes in the safety paradigm with percutaneous coronary interventions in the modern era: Lessons learned from the ASCERT registry. *World J Cardiol* 2012; 4(8): 242-249 Available from: URL: http://www.wjgnet.com/1949-8462/full/v4/i8/242.htm DOI: http://dx.doi.org/10.4330/wjc.v4.i8.242

## COMPARATIVE EFFECTIVENESS BETWEEN PERCUTANEOUS INTERVENTIONS AND CORONARY BYPASS SURGERY IN THE PRE-DRUG ELUTING STENT ERA

In the past, comparative effectiveness trials evaluating percutaneous coronary interventions (PCI), either using balloon angioplasty or bare metal stent (BMS) implantation, *vs* coronary artery bypass surgery (CABG) found similar survival at long-term follow-up with both revascularization strategies[1]. However, in three of these trials some outcome differences between PCI and CABG were found: firstly, the bypass angioplasty revascularization investigation (BARI) trial[2] reported higher mortality in diabetic patients with PCI; secondly, the stent or surgery (SoS) trial[3] observed higher non-cardiac mortality with PCI; and finally, the estudio randomizado argentino angioplastia *vs* cirugia de bypass coronario Ⅱ (ERACI) trial[4] had higher mortality and myocardial infarction (MI) with CABG in the first 30 days and at one year after the procedure, advantages for PCI that were present but diminished at five years[5]. Accordingly, two major meta-analyses from those trials reported 5-year comparative effectiveness between PCI and CABG: one included only four trials that compared PCI with BMS implantation *versus* CABG[6], whereas the largest one also included trials using balloon angioplasty[1]. In the first meta-analysis[6], in patients with multiple vessel disease randomized either to BMS or CABG, 5-year follow-up outcome showed similar incidence of death, MI or cerebrovascular accident (CVA). In this analysis, patients with diabetes had no safety advantage with CABG. Hlatky *et al*[1] in the other meta-analysis, which included 10 trials, observed no survival differences between groups although a significant survival advantage was seen in diabetics treated with CABG. In this study, a survival benefit with CABG was also perceived in elderly patients (> 65 years). In both reports[1,6], number of vessels, presence of left anterior descending artery stenosis or poor left ventricular ejection fraction were not predictors of poor survival with PCI. Therefore, extent of the coronary artery disease (CAD) was not associated with poor outcome for PCI in the pre- drug eluting stent (DES) era[1,6].

The introduction of different DES designs during PCI compared to BMS significantly reduced the incidence of angiographic restenosis and target lesion and vessel revascularization (TLR and TVR, respectively). It is important to mention that these efficacy advantages were sustained at 5 years of follow-up[7-10]. However, increased frequency of very late stent thrombosis and requirements for a long-term period of dual antiplatelet therapy, mandatory for at least one year after implantation with the first DES designs, could decrease this advantage[11-14].

## LESSONS FROM ASCERT (DATABASE COLLABORATION ON THE COMPARATIVE EFFECTIVENESS OF REVASCULARIZATION STRATEGIES) REGISTRY

Recently, a large registry[15] found a higher mortality rate with PCI in patients ⩾ 65 years old in comparison with CABG and advantages of surgery were seen in all subgroups, including those at low risk[15]. In this registry, PCI was accomplished by implantation of the first DES designs in 78% of cases. The observation of higher mortality rates with PCI[15], including for non-diabetics and patients with two-vessel CAD, were not seen in previous studies in the non-DES era[1,6]. The study was not randomized, although its results are largely strengthened by its sample size. The study included two prospective registries from 64 centers in the USA over the years 2004 to 2008. Almost 190 000 patients were included in both groups and, despite the nature of the study, differences in favor of CABG still remained after a matched comparison in 86 300 patients.

The lack of clinical improvement with DES in this subgroup has been a surprise for our interventional cardiology community and concerns have been raised in an accompanying editorial about the non-randomized nature of the study[15,16] which could be related to these unexpected results.

It is true that randomized clinical trials are the gold standard to assess results of different clinical and surgical therapies, although it is also well known that they have a limitation driven by patient selection; therefore, large prospective registries which allow us to include more complex and real world populations are also an important tool to assess these clinical results. Therefore, both randomized trials and registries should be taken into account to evaluate revascularization outcomes.

In the study carried out by Weintraub *et al*[15], the authors recognized that "....a single unmeasured confounder could produce survival differences only if it increased the long-term risk of death by a factor of approximately two or if the long-term risk of death was three to five times as high in the PCI group as in the CABG group"; therefore, unmeasured confounder factors can be linked with different survival outcomes reported by such a study. However, survival advantages with CABG remained after the authors adjusted for clinical and angiographic variables (Figure 1). Furthermore, results were still in favor of CABG after propensity-matched comparisons and these results agree with other contemporary studies such as the New York database[17] for PCI and CABG and the ERACI Ⅲ registry[18-20].

In the New York registry, they also found a survival advantage with CABG and this advantage also included subgroups defined as low risk.

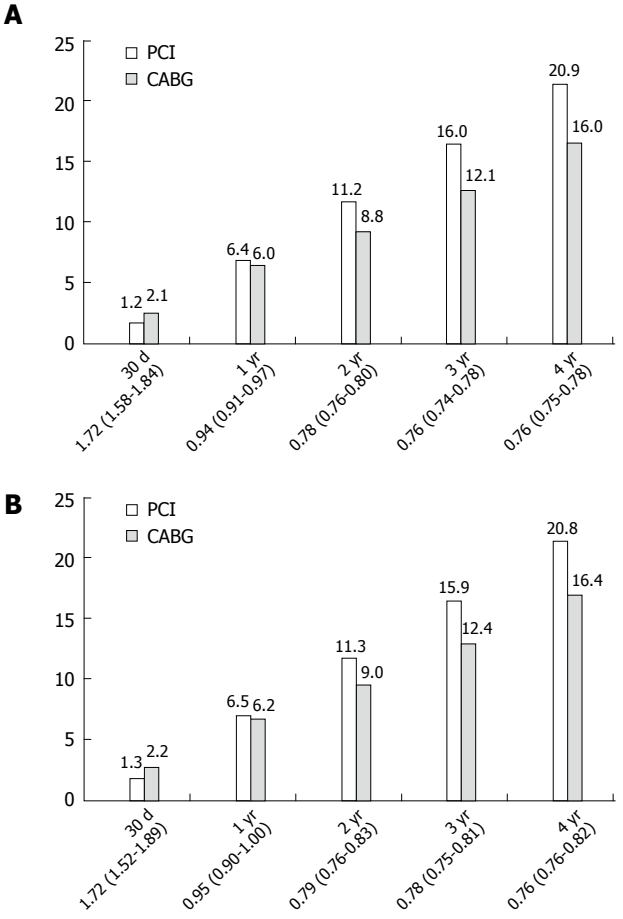



**Figure 1 Mortality rate in ASCERT registry by year in adjusted and unadjusted groups.** A: Unadjusted analysis (relative risk with CABG); B: Adjusted analysis by inverse probability weighting (relative risk with CABG). Modified from Weintraub *et al*[15]. Comparative Effectiveness of Revascularization Strategies[15]. CABG: Coronary artery bypass surgery; PCI: Percutaneous coronary interventions.

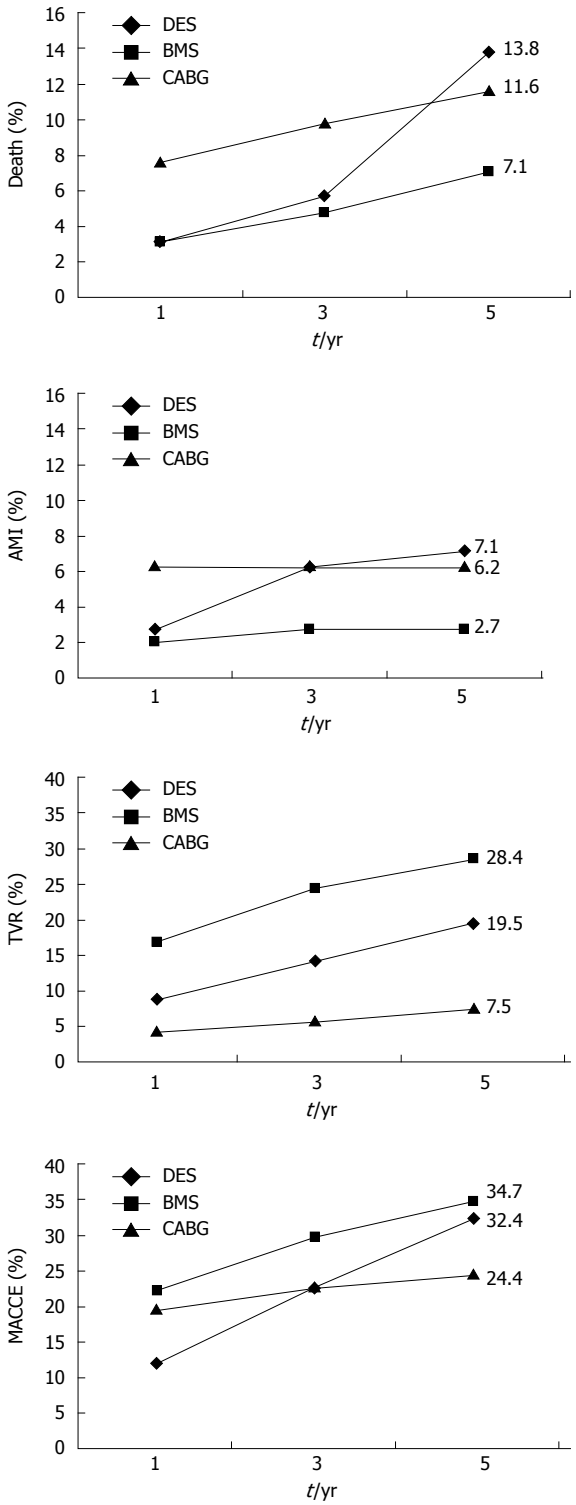



**Figure 2 ERACI Ⅲ results by year.** Death, acute myocardial infarction (AMI), major adverse cardiovascular events (MACCE) and target vessel revascularization (TVR) increase over time[20].

In the ERACI Ⅲ registry, there was an increased incidence of death and MI with DES beyond the first year in comparison with BMS or CABG groups, differences still significant at 5 years of follow-up; as we can see in Figure 2, at one year in ERACI Ⅲ, the DES group had a significantly lower incidence of any death, MI, stroke and TVR (major adverse cardiovascular events: MACCE) compared with either BMS or CABG groups. Death and MI were similar between BMS and DES groups but significantly lower than the CABG group. On the other hand, at 3 years, MACCE rate became similar in these three groups by an increased rate of cardiac events in the DES group, and additionally at 5 years significantly higher rates of death and MI in the ERACI Ⅲ DES group of patients compared with the BMS group were seen, meaning a significantly late loss of their initial advantage (Figure 2). In conclusion, in the ERACI Ⅲ registry, patients treated with DES had higher than expected risk of serious cardiac events over the subsequent five years compared with patients treated with a BMS, despite a substantial reduction in the rate of repeat coronary revascularization procedures. These differences do not appear to be explained by different adverse risk profiles among DES-treated patients, as multivariable statistical adjustment for baseline factors did not materially affect the results in this study[20] (Table 1).

However, as we discussed previously, all registries have a common limitation of non-randomized nature;

**Table 1 Drug eluting stent:Bare metal stent hazard ratios (95% confidence limits) in multivariable Cox models adjusted for baseline characteristics from ERACI Ⅲ at five-year follow-up[20]**

| Endpoint | All patients ($n$ = 450) | $P$ values | Propensity score matched points ($n$ = 242) | $P$ values |
|---|---|---|---|---|
| MACCE | 0.75 (0.51-12) | 0.1562 | 1.20 (0.75-0.90) | 0.45 |
| Death | 1.84 (0.92-0.68) | 0.0864 | 2.53 (1.10-0.83) | 0.03 |
| Death, MI or stroke | 1.66 (0.95-0.88) | 0.0744 | 3.31 (1.62-0.76) | 0.001 |
| Repeat revascularization | 0.52 (0.31-0.85) | 0.0096 | 0.84 (0.48-0.47) | 0.37 |

MI: Myocardial infarction; MACCE: Major adverse cardiovascular events.

consequently we need to find randomized studies sharing similar results.

## COMPARATIVE EFFECTIVENESS BETWEEN PERCUTANEOUS INTERVENTIONS AND BYPASS SURGERY IN THE DES ERA: LESSONS FROM RANDOMIZED CLINICAL TRIALS

The SYNergy between PCI with TAXUS and Cardiac Surgery[21,22] (SYNTAX) trial, which is nowadays the largest randomized study comparing PCI with DES implantation (Taxus, Boston Scientific Corp, Natrick, Massachusetts) *vs* CABG in the modern era, has already reported one-, three- and four-year follow-up results. This study included patients with unprotected left main stenosis and three-vessel CAD.

If we discard from this trial the subgroup of left main patients, inclusion and exclusion criteria from ASCERT[16] and SYNTAX[21] are quite similar. Both studies included only patients with multiple vessel disease, whereas in both patients were excluded with cardiogenic shock, MI in the previous 7 d, single-vessel CAD, and previous CABG.

If we analyze SYNTAX trial data at one year of follow-up, patients treated with PCI or CABG had similar incidence of death, MI and the composite of death/MI and CVA, although CVA was significantly higher in the CABG group; repeat revascularization procedures (TVR) were higher in PCI (Figure 3), and this was the only disadvantage in the PCI group during the first year of follow-up[21].

However, these numbers change at the third[22] and fourth year[23] of follow-up (Figure 3); death, MI and the composite of death/MI/CVA are all significantly higher in the PCI group of patients. Additionally, these results were also seen in the subgroup of patients with three-vessel disease, which is a comparative population to the ASCERT registry. In this cohort at 3 years of follow-up, death (5.7% *vs* 9.5%, $P = 0.048$), MI (3.3% *vs* 7.1%, $P = 0.005$), death/MI/CVA (10.6% *vs* 14.8%, $P < 0.04$) and MACCE (18.8% *vs* 28.8%, $P < 0.001$) were all significantly higher with PCI[22].

The PCI policy of this study which was non-ischemia guided stent implantation leading to an excess of DES per patient/lesion implanted would be one of the reasons of these findings[24].

Therefore, increased serious cardiac events beyond one year with PCI appear to be a common finding in both ASCERT and SYNTAX.

Reasons of these findings are unclear, although the observation of high mortality rate in elderly patients after PCI raises the question whether this subgroup is at high risk if they are treated with PCI.

However, the ASCERT statement that high mortality was noted in all subgroups, including in patients whose clinical and angiographic criteria were more consistent with selection for PCI, should be taken with caution. In fact, we do not know if results in some of the trials mentioned previously are also related to poor late outcome in an elderly population; indeed we do not know the outcome of elderly patients in the SYNTAX trial.

Consequently, we do not know what the clinical reasons for these findings are; however, we will try to explore some hypotheses and also find potential solutions.

After introduction of the first DES designs together with the reduction of angiographic restenosis, a high rate of late and very late stent thrombosis was described and became a concern for some investigators[11-14]. In spite of this, several randomized studies did not shown major safety concerns with DES implantation, while other studies reported a high rate of cardiac events at late follow-up together with the increased incidence of very late stent thrombosis in complex patient/lesion subsets such as diabetics, stent restenosis, ST elevation MI, bifurcations, etc., most of them classified as off-label indications by the Food and Drug Administration[25-27].

Therefore, at the end of the last decade concerns about the safety of the first DES designs were reduced but the debate did not disappear and persists nowadays[28].

There was a requirement for dual antiplatelet therapy to be prescribed with the first DES designs during the first six months post-procedure although clopidogrel therapy was recommended in most patients beyond one year. How this necessity for dual antiplatelet therapy can be linked with poor outcome in the elderly patients is unknown. However, some recent data from a small randomized study add limited, but valued, information and strengthen the ASCERT results.

The Oral Rapamycin in Argentina Ⅲ (ORAR) trial was a cost-effectiveness randomized comparison between DES *versus* BMS plus 14 d of oral rapamycin (OR)[29,30]; in the DES arm, first DES designs were used in 96.8% of cases. At 4 years of follow-up, patients included in the

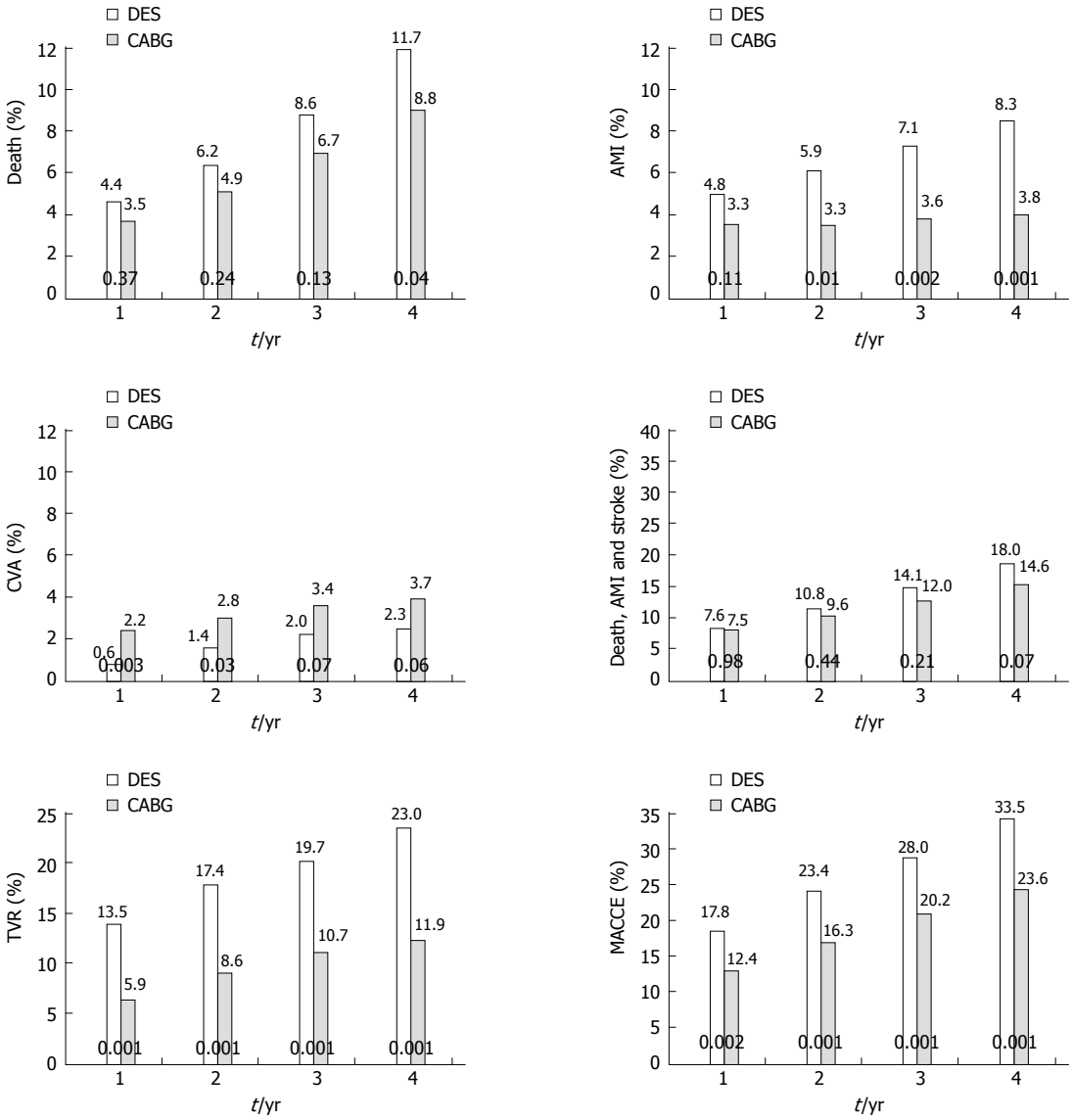



**Figure 3 Increased rate of cardiac events at one, two, three and four years of follow-up in the syntax trial in both groups: drug eluting stent and coronary artery bypass surgery[21-23].** AMI: Acute myocardial infarction; CVA: Cerebrovascular accident; TVR: Target vessel revascularization; MACCE: Major adverse cardiovascular events; DES: Drug eluting stent; CABG: Coronary artery bypass surgery.

OR group were at lower risk of death from any cause (DES: OR hazard risk 2.84, CI: 1.12-7.34, $P = 0.024$) and the composite of death + MI + CVA (DES: OR hazard risk 2.18, CI: 1.09-4.34, $P = 0.018$) without differences in TVF ($P = 0.091$) or TVR ($P = 0.162$) compared to the DES group.

However, as we can see in Table 2, in the group of patients who were less than 65 years of age, incidence of death ($P = 0.32$), cardiac death ($P = 0.41$), MI ($P = 0.56$) and composite of death + MI + CVA were similar ($P = 0.56$). Requirements for new hospital admissions during follow-up were also similar in both groups (45% *vs* 35% in OR and DES, respectively, $P = 0.26$. Conversely, in the elderly group (≥ 65 years) there were significant differences in incidence of MI ($P = 0.05$), death + MI + CVA ($P = 0.03$) and TVF ($P = 0.02$). Of note, at 4 years, elderly patients treated with DES had new hospital admittances more frequently during follow-up than those treated in the OR plus BMS group ( 64.6% *vs* 37.5%, respectively, $P = 0.011$). In both groups, DES patients were more frequently taking clopidogrel therapy (Table 2).

The main results of this randomized study suggested that safety advantages in favor of an OR plus BMS strategy observed in ORAR Ⅲ were driven by the poor outcome in patients ≥ 65 years treated with DES.

Results from ORAR Ⅲ agree with those reported by the ASCERT[15] registry, although clinical reasons for these findings cannot be determined due to the sample size of such a small population.

## RESULTS WITH THE LATEST DES DESIGNS

Altogether the above-mentioned studies share a common finding: the first DES platforms with durable and non-biocompatible polymers were used with requirements for

**Table 2 Comparison of oral rapamycin *vs* drug eluting stent treatment in patients under 65 years old and equal to or older than 65 years old at 5.1 years (4.2-5.8) of follow-up**

| | < 65 yr | | | ⩾ 65 yr | | |
|---|---|---|---|---|---|---|
| | OR ($n$ = 60) | DES ($n$ = 52) | $P$ value | OR ($n$ = 40) | DES ($n$ = 48) | $P$ value |
| Death | 3.3% (2) | 9.6% (5) | 0.32 | 7.5% (3) | 20.8% (10) | 0.07 |
| Cardiac death | 0.0% (0) | 5.8% (3) | 0.19 | 5.0% (2) | 12.5% (6) | 0.22 |
| MI | 10% (6) | 13.5% (7) | 0.56 | 0.0% (0) | 12.5% (6) | 0.05 |
| Death + MI + CVA | 10.0% (6) | 13.5% (7) | 0.56 | 7.5% (3) | 25.0% (12) | 0.03 |
| TVF | 26.7% (16) | 28.8% (15) | 0.79 | 22.5% (9) | 45.8% (22) | 0.02 |
| TLR | 9.3% (9/97) | 14.6% (12/82) | 0.26 | 11.5% (7/61) | 20.5% (18/88) | 0.14 |
| TVR | 14.8% (12/81) | 17.4% (12/69) | 0.66 | 14.0% (7/50) | 21.9% (16/75) | 0.26 |
| New hospital admissions[1] | 45.0% (27) | 34.6% (18) | 0.26 | 37.5% (15) | 64.6% (31) | 0.01 |
| Continue clopidogrel therapy[2] | 15.5% (9/58) | 44.7% (21/47) | 0.002 | 24.3% (9/37) | 52.6% (20/38) | 0.05 |

[1]Patients with at least one cardiovascular or not cardiovascular hospital readmissions; [2]Of surviving patients. OR: Oral rapamycin therapy and bare metal stent; DES: Drug eluting stent; MI: Myocardial Infarction; CVA: Cerebrovascular accident; TVF: Target vessel failure; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

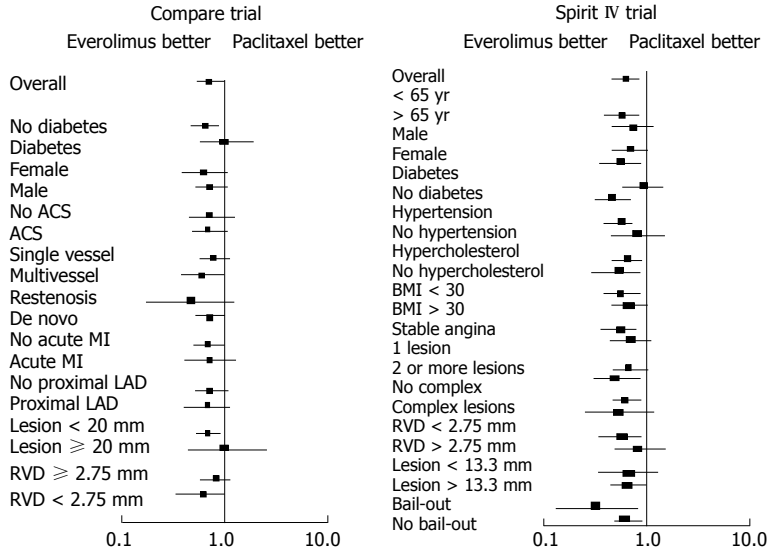



**Figure 4 Reduction of cardiac events in all subgroups from COMPARE and SPIRIT Ⅳ trials with the use of everolimus-eluting stents[34,35].** ACS: Acute coronary syndrome; MI: Myocardial infarction; LAD: Left anterior descending artery; RVD: Reference vessel diameter; BMI: Body mass index.

long periods of clopidogrel therapy which were greater than needed for the latest ones currently used and recommended[28,31]. Therefore, worries about the first DES designs which were largely described and debated a decade ago with the paradigm of more efficacy but perhaps less safety[11,32,33] could explain the controversial PCI results of these studies[15,17,21,22] observed today but with a patient recruitment period in 2004-2008.

However, nowadays newer DES designs either with biocompatible or biodegradable[28,31,34-36] polymers demonstrate in randomized clinical trials a significantly lower incidence of adverse events including death, cardiac death and MI compared to the first ones[33] (Figure 4). In addition, necessity for long-term clopidogrel therapy appears to be no longer than 6 mo, consequently we have new tools today to improve outcome in our patients who undergo PCI with DES implantation; as we can see in Figure 4, benefits apply to several subgroups of patient/lesion characteristics.

## CONCLUSION

PCI is the most common myocardial revascularization strategy in the current era. However, revascularization guidelines for PCI and CABG in multiple vessel CAD, established some years ago in the pre-DES era, should be refocused according to the latest data from randomized studies and large registries. The ASCERT study was, to our knowledge, the largest registry comparing current PCI strategies *vs* CABG in patients with multiple vessel disease who were older than 64 years. In spite of study limitations mainly driven by the non-randomized nature, its sample size largely supported results. Furthermore, these outcomes were also observed in some randomized studies sharing similar clinical and angiographic findings.

We are unable to find clinical reasons for these results, although we cannot discard the concept that side effects linked with the first DES designs, including mandatory requirements for long-term dual antiplatelet therapy,

could be associated with this poor all-comers outcome in an elderly PCI population.

Whether new DES designs would modify these intriguing results should be determined by prospective studies.

## REFERENCES


1 **Hlatky MA**, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrié D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kähler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009; **373**: 1190-1197

2 Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med* 1996; **335**: 217-225

3 **Booth J**, Clayton T, Pepper J, Nugara F, Flather M, Sigwart U, Stables RH. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). *Circulation* 2008; **118**: 381-388

4 **Rodriguez A**, Bernardi V, Navia J, Baldi J, Grinfeld L, Martinez J, Vogel D, Grinfeld R, Delacasa A, Garrido M, Oliveri R, Mele E, Palacios I, O'Neill W. Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators. *J Am Coll Cardiol* 2001; **37**: 51-58

5 **Rodriguez AE**, Baldi J, Fernández Pereira C, Navia J, Rodriguez Alemparte M, Delacasa A, Vigo F, Vogel D, O'Neill W, Palacios IF. Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol* 2005; **46**: 582-588

6 **Daemen J**, Boersma E, Flather M, Booth J, Stables R, Rodriguez A, Rodriguez-Granillo G, Hueb WA, Lemos PA, Serruys PW. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 2008; **118**: 1146-1154

7 **Moses JW**, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349**: 1315-1323

8 **Stone GW**, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; **356**: 998-1008

9 **Stettler C**, Wandel S, Allemann S, Kastrati A, Morice MC, Schömig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabaté M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Jüni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007; **370**: 937-948

10 **Grube E**, Dawkins K, Guagliumi G, Banning A, Zmudka K, Colombo A, Thuesen L, Hauptman K, Marco J, Wijns W, Joshi A, Mascioli S. TAXUS VI final 5-year results: a multicentre, randomised trial comparing polymer-based moderate-release paclitaxel-eluting stent with a bare metal stent for treatment of long, complex coronary artery lesions. *EuroIntervention* 2009; **4**: 572-577

11 **Camenzind E**, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation* 2007; **115**: 1440-155; discussion 1455

12 **Lagerqvist B**, James SK, Stenestrand U, Lindbäck J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007; **356**: 1009-1019

13 **Rodriguez AE**, Mieres J, Fernandez-Pereira C, Vigo CF, Rodriguez-Alemparte M, Berrocal D, Grinfeld L, Palacios I. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. *J Am Coll Cardiol* 2006; **47**: 205-207

14 **Brunner-La Rocca HP**, Kaiser C, Bernheim A, Zellweger MJ, Jeger R, Buser PT, Osswald S, Pfisterer M. Cost-effectiveness of drug-eluting stents in patients at high or low risk of major cardiac events in the Basel Stent KostenEffektivitäts Trial (BASKET): an 18-month analysis. *Lancet* 2007; **370**: 1552-1559

15 **Weintraub WS**, Grau-Sepulveda MV, Weiss JM, O'Brien SM, Peterson ED, Kolm P, Zhang Z, Klein LW, Shaw RE, McKay C, Ritzenthaler LL, Popma JJ, Messenger JC, Shahian DM, Grover FL, Mayer JE, Shewan CM, Garratt KN, Moussa ID, Dangas GD, Edwards FH. Comparative effectiveness of revascularization strategies. *N Engl J Med* 2012; **366**: 1467-1476

16 **Mauri L**. Why we still need randomized trials to compare effectiveness. *N Engl J Med* 2012; **366**: 1538-1540

17 **Hannan EL**, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, Higgins RS, Carlson RE, Jones RH. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med* 2008; **358**: 331-341

18 **Rodriguez AE**, Grinfeld L, Fernandez-Pereira C, Mieres J, Rodriguez Alemparte M, Berrocal D, Rodriguez-Granillo AM, Vigo CF, Russo Felsen M, O'Neill W, Palacios I. Revascularization strategies of coronary multiple vessel disease in the Drug Eluting Stent Era: one year follow-up results of the ERACI III Trial. *EuroIntervention* 2006; **2**: 53-60

19 **Rodriguez AE**, Maree AO, Mieres J, Berrocal D, Grinfeld L, Fernandez-Pereira C, Curotto V, Rodriguez-Granillo A, O' Neill W, Palacios IF. Late loss of early benefit from drug-eluting stents when compared with bare-metal stents and coronary artery bypass surgery: 3 years follow-up of the ERACI III registry. *Eur Heart J* 2007; **28**: 2118-2125

20 **Rodriguez A**, Hlatky M, Grinfeld L, Mieres J, Rodriguez-Granillo AM, Berrocal D, Boothroy D, Fernandez-Pereira C, Palacios P, Oneill W.Results in long-term outcome of patients with multiple vessel disease treated with drug eluting, bare metal stents and coronary bypass surgery: insights from five years follow up of ERACI III study. *Eur Heart J* 2010; 31suppl 1: 1-296

21 **Serruys PW**, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360**: 961-972

22 **Kappetein AP**, Feldman TE, Mack MJ, Morice MC, Holmes DR, Ståhle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 2011; **32**: 2125-2134

23 **Serruys PW**. The Syntax Trial at 4 years. 2011 Annual EACTS Meeting; Lisbon, Portugal

24 **Abbate A**, Biondi-Zoccai GG, Appleton DL, Erne P, Schoenenberger AW, Lipinski MJ, Agostoni P, Sheiban I,

Vetrovec GW. Survival and cardiac remodeling benefits in patients undergoing late percutaneous coronary intervention of the infarct-related artery: evidence from a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2008; **51**: 956-964

25 **Beohar N**, Davidson CJ, Kip KE, Goodreau L, Vlachos HA, Meyers SN, Benzuly KH, Flaherty JD, Ricciardi MJ, Bennett CL, Williams DO. Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 2007; **297**: 1992-2000

26 **Win HK**, Caldera AE, Maresh K, Lopez J, Rihal CS, Parikh MA, Granada JF, Marulkar S, Nassif D, Cohen DJ, Kleiman NS. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 2007; **297**: 2001-2009

27 **Ho PM**, Peterson ED, Wang L, Magid DJ, Fihn SD, Larsen GC, Jesse RA, Rumsfeld JS. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA* 2008; **299**: 532-539

28 **Claessen BE**, Stone GW, Smits PC, Kedhi E, Kikkert WJ, Piek JJ, Henriques JP. Would SYNTAX have been a positive trial if XIENCE V had been used instead of TAXUS?: A meta-analysis of a first-generation vs. a second-generation drug-eluting stent system. *Neth Heart J* 2010; **18**: 451-453

29 **Rodriguez AE**, Maree A, Tarragona S, Fernandez-Pereira C, Santaera O, Rodriguez Granillo AM, Rodriguez-Granillo GA, Russo-Felssen M, Kukreja N, Antoniucci D, Palacios IF, Serruys PW. Percutaneous coronary intervention with oral sirolimus and bare metal stents has comparable safety and efficacy to treatment with drug eluting stents, but with significant cost saving: long-term follow-up results from the randomised, controlled ORAR III (Oral Rapamycin in ARgentina) study. *EuroIntervention* 2009; **5**: 255-264

30 **Rodriguez AE**, Rodriguez-Granillo AM, Antoniucci D, Mieres J, Fernandez-Pereira C, Rodriguez-Granillo GA, Santaera O, Rubilar B, Palacios IF, Serruys PW; on behalf of ORAR III Investigators. Randomized comparison of cost-saving and effectiveness of oral rapamycin plus bare-metal stents with drug-eluting stents: Three-year outcome from the randomized oral rapamycin in Argentina (ORAR) III trial. *Catheter Cardiovasc Interv* 2011; Epub ahead of print

31 **Caixeta A**, Lansky AJ, Serruys PW, Hermiller JB, Ruygrok P, Onuma Y, Gordon P, Yaqub M, Miquel-Hebert K, Veldhof S, Sood P, Su X, Jonnavithula L, Sudhir K, Stone GW. Clinical follow-up 3 years after everolimus- and paclitaxel-eluting stents: a pooled analysis from the SPIRIT II (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions) and SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) randomized trials. *JACC Cardiovasc Interv* 2010; **3**: 1220-1228

32 **Rodriguez AE**, Rodriguez-Granillo GA, Palacios IF. Late stent thrombosis: the Damocle's sword of drug eluting stents? *EuroIntervention* 2007; **2**: 512-517

33 **Rodriguez AE**. Emerging drugs for coronary restenosis: the role of systemic oral agents the in stent era. *Expert Opin Emerg Drugs* 2009; **14**: 561-576

34 **Claessen BE**, Smits PC, Kereiakes DJ, Parise H, Fahy M, Kedhi E, Serruys PW, Lansky AJ, Cristea E, Sudhir K, Sood P, Simonton CA, Stone GW. Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents pooled analysis from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) Randomized Trials. *JACC Cardiovasc Interv* 2011; **4**: 1209-1215

35 **Hermiller JB**, Sudhir K, Applegate RJ, Rizvi A, Wang J, Gordon PC, Yaqub M, Cao S, Ferguson JM, Smith RS, Sood P, Stone GW. Impact of age on clinical outcomes after everolimus-eluting and paclitaxel-eluting stent implantation: pooled analysis from the SPIRIT III and SPIRIT IV clinical trials. *EuroIntervention* 2012; **8**: 87-93

36 **Byrne RA**, Kastrati A. No country for old stents? Improving long-term patient outcomes with biodegradable polymer drug-eluting stents. *Expert Rev Cardiovasc Ther* 2012; **10**: 429-432

**S- Editor** Cheng JX **L- Editor** Logan S **E- Editor** Zhang DN

World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
wjc@wjgnet.com
doi:10.4330/wjc.v4.i8.250

*World J Cardiol* 2012 August 26; 4(8): 250-255
ISSN 1949-8462 (online)


BRIEF ARTICLE

# Evaluation of the prevalence and severity of pain in patients with stable chronic heart failure

Dioma U Udeoji, Ankit B Shah, Parag Bharadwaj, Peter Katsiyiannis, Ernst R Schwarz

Dioma U Udeoji, Peter Katsiyianis, Ernst R Schwarz, Heart Institute of Southern California, Temecula, CA 92592, United State
Dioma U Udeoji, Ankit B Shah, Parag Bharadwaj, Ernst R Schwarz, Cedars-Sinai Medical Center, Los Angeles, CA 90048, United States
Parag Bharadwaj, Ernst R Schwarz, University of California Los Angeles, Los Angeles, CA 90095, United States
Author contributions: Udeoji DU designed the study, acquired data, statistically analyzed, and interpreted data, drafted the article, wrote the manuscript and critically revised the manuscript; Shah AB supported the work and made contributions, analyzed data, interpreted data and reviewed the manuscript; Bharadwaj P was a co-investigator and part of the administration, gave supportive contributions, technology and material support, participated in the study design and manuscript review; Katsiyiannis P was part of the administration, gave supportive contributions, technology and material support; Schwarz ER was the principal Investigator and part of the administration, gave supportive work/contributions, technology and material support, participated in the study design, manuscript writing, critical revision of the manuscript and general supervision of the work.
Correspondence to: Ernst R Schwarz, MD, PHD, FACC, FSCAI, FESC, Heart Institute of Southern California, 31720 Temecula Parkway, Ste. 200, Temecula, CA 92592, United States. ernst.schwarz@cshs.org
Telephone: 1-951-3020606 Fax: +1-951-2497277
Received: July 5, 2012 Revised: August 20, 2012
Accepted: August 24, 2012
Published online: August 26, 2012

## Abstract

**AIM:** To evaluate the prevalence and severity of pain in patients with chronic stable heart failure (HF) in an outpatient clinic setting.

**METHODS:** This is a cross-sectional study evaluating symptoms of generalized or specific pain in patients with chronic stable heart failure. A standardized questionnaire (Edmonton Symptom Assessment System) was administered during a routine outpatient clinic visit. The severity of pain and other symptoms were assessed on a 10 point scale with 10 being the worst and 0 representing no symptoms.

**RESULTS:** Sixty-two patients [age 56 ± 13 years, 51 males, 11 females, mean ejection fraction (EF) 33% ± 17%] completed the assessment. Thirty-two patients (52%) reported any pain of various character and location such as chest, back, abdomen or the extremities, with a mean pain score of 2.5 ± 3.1. Patients with an EF less than 40% ($n$ = 45, 73%) reported higher pain scores than patients with an EF greater than 40% ($n$ = 17, 27%), scores were 3.1 ± 3.3 *vs* 1.2 ± 1.9, $P$ < 0.001. Most frequent symptoms were tiredness (in 75% of patients), decreased wellbeing (84%), shortness of breath (SOB, 76%), and drowsiness (70%). The most severe symptom was tiredness with a score of 4.0 ± 2.8, followed by decreased wellbeing (3.7 ± 2.7), SOB (3.6 ± 2.8), and drowsiness (2.8 ± 2.8).

**CONCLUSION:** Pain appears to be prevalent and significantly affects quality of life in HF patients. Adequate pain assessment and management should be an integral part of chronic heart failure management.



**Key words:** Heart failure; Pain; Symptoms; Therapy; Palliative care

**Peer reviewer:** Dr. Shinro Matsuo, Kanazawa University, 13-1 Takaramachi, Kanazawa 920-8641, Japan

Udeoji DU, Shah AB, Bharadwaj P, Katsiyiannis P, Schwarz ER. Evaluation of the prevalence and severity of pain in patients with stable chronic heart failure. *World J Cardiol* 2012; 4(8): 250-255 Available from: URL: http://www.wjgnet.com/1949-8462/full/v4/i8/250.htm DOI: http://dx.doi.org/10.4330/wjc.v4.i8.250

## INTRODUCTION

Heart failure is one of the major health problems worldwide especially for people over the age of 65 years[1,2]. In the United States, more than 38 million people suffer from heart diseases. Almost six million patients are diagnosed with heart failure (HF) with more than 550 000 newly diagnosed cases each year[1,3,4]. HF accounts for 12-15 million office visits per year and over six million hospital admissions in the United States[1,4]. HF usually is a chronic illness that might involve multiple organs systems over time leading to a variety of non-organ-specific symptomatology.

The burden of pain is under-recognized by clinicians as a symptom among heart failure patients. Only few studies have demonstrated an association between pain and heart failure. Evidence demonstrated that HF is a gradual disease process, which is initiated with risk factors, often triggered by an acute event, and progresses to changes in cardiac structure to loss of function that subsequently results in clinically overt HF with functional decline, and death[5-10].

The present study was designed to evaluate the prevalence and severity of generalized symptoms and pain in adult patients with stable chronic HF.

## MATERIALS AND METHODS

This is a cross-sectional study of symptom assessment in patients with an established diagnosis of chronic HF. Patients were recruited to participate in the study during a routine outpatient clinic visit between May and December of 2011. The study was approved by the institutional review board. Patients were enrolled after obtaining informed consent.

Inclusion criteria were as follows: (1) age 18 years or older; (2) a primary diagnosis of chronic HF since at least three months; (3) systolic dysfunction; (4) on a stable medication and treatment regimen; and (5) ability to read and understand the English language and respond properly.

Exclusion criteria were (1) unstable patients in new york heart association (NYHA) class Ⅳ; (2) patients with concomitant diagnoses that might cause pain or significantly affect quality of life and other symptomatic conditions such as severe chronic obstructive pulmonary disease, diabetes mellitus with end-organ damage, severe liver or kidney failure, active myocardial ischemia, angina pectoris, active or recent malignancies, recent or debilitating strokes, fibromyalgia or other debilitating acute or chronic illnesses; (3) chronic/daily analgesic use for any specific or non- specific non HF-related reasons; and (4) patients with past medical history of cerebral infarction.

All patients were evaluated using a brief cognitive screening test, the "Mini cog"[11-14]. This test is a 5-point cognitive screening which consists of a three different word recall (score 0-3) and a clock drawing with the hand pointing at a specific time (score 0, or 2). Patients with a Mini-cog score of more than three, which rules out dementia were included into the study[11-14]. The study was conducted by a healthcare professional who was not directly involved in the patients' care. A standardized questionnaire, the Edmonton Symptom Assessment System (ESAS)[15-17] was used to evaluate for symptoms and severity by using a scoring system. The ESAS scoring scale ranges from 0 to 10 with 0 representing no symptoms and 10 representing worst possible symptoms. The presence and severity of the following nine subjective complaints were assessed: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing, and shortness of breath. A diagram of the human body enabled the patient to mark the site of existing pain sensations. The functional status of HF was assessed using both history and physical examination and only patients in NYHA classes Ⅱ and Ⅲ were enrolled in the study. Ejection fraction (EF) was measured by 2-D transthoracic echocardiography using the Simpson method either at the time of the visit or echocardiographic data from former visits was used as long as the echo study was performed within six months prior to the beginning of the study. The patients were on a standard regimen containing the following medications: beta blockers (82% of the patients), ACE-inhibitors (44%), angiotensin Ⅱ receptor blocker (29%), aldosterone antagonists (40%), other diuretics (66%) and digoxin (29%). All patients were on a stable medication regimen without major medication changes except dose adjustments within the last three months. For further analysis, the patients were then divided into two groups: group 1 represented patients with an EF of more than 40%, group 2 represented patients with an EF of less than or equal to 40%. Data between the groups were compared using a student *t*-test. A $P$ value of less than 0.05 was considered statistically significant.

## RESULTS

Sixty-two patients were enrolled in the study, 51 men, 11 women, age 56 ± 13 years (range 28-77 years). The EF was 33% ± 17% (range 10%-76%). The total pain score was 2.5% ± 3.1. 32% reported pain in more than one anatomical site, 15% reported pain either in the chest, back, neck, abdominal or in the extremities. Four patients (7%) did not indicate the site of pain but reported generalized body pain. Patients suffered different co-morbidities irrespective of the EF. The most common co-morbidities were hypertension ($n$ = 38, 61%), hyperlipidemia ($n$ = 29, 47%), end stage renal disease ($n$ = 20, 32%), and diabetes ($n$ = 17, 27%). Other common conditions were atrial fibrillation (28%), depression (18%), obesity (16%), osteoarthritis (15%), COPD (8%), gout (8%), thyroid diseases (7%), anemia (7%) and peripheral artery disease (PAD, 3%). Patients reported pain regardless of the EF and co-morbidities. Patients with degenerative joint diseases reported higher pain scores.

Most frequently reported symptoms were tiredness ($n$ = 47, 76%), decreased wellbeing ($n$ = 52, 84%), shortness of breath (SOB, $n$ = 47, 76%), and drowsiness ($n$ = 43, 69%). The most severe symptoms based on the score were tiredness (score 4.0 ± 2.8), decreased wellbeing (3.7 ± 2.7), SOB (3.6 ± 2.8), and drowsiness (2.8 ± 2.8).

Seventeen patients had an EF > 40% (group 1), 11 (65%) males and 6 (35%) females, age 54 ± 14 years (range 32-74 years), forty-five patients had an EF ≤ 40% (group 2), 40 (89%) males and 5 (11%) females, age 57 ± 13 (range 30-77) years. EFs were 56% ± 11% (range 43%-76%) in group 1 and 24% ± 10% (range 10%-40%) in group 2. Pain score in group 1 was 1.2 ± 1.9, pain score in group 2 was 3.1 ± 3.3 ($P$ < 0.001 between the groups, Table 1).

Pain was present in both groups regardless of co-morbidities. Thirty-two patients (52%) reported pain of various intensities at various locations with pain scores of 2.5 ± 3.1.

**Table 1 Patients symptoms**

| Patients symptoms | All patients | EF > 40% | EF ≤ 40% | *P* value |
|---|---|---|---|---|
| Pain | 2.5 ± 3.1 | 1.2 ± 1.9 | 3.1 ± 3.3 | 0.001 |
| Tiredness | 4.0 ± 2.8 | 3.7 ± 2.8 | 4.2 ± 2.9 | 0.276 |
| Nausea | 1.2 ± 2.3 | 1.2 ± 2.4 | 1.2 ± 2.3 | 0.497 |
| Depression | 2.5 ± 3.0 | 1.8 ± 2.6 | 2.7 ± 3.2 | 0.126 |
| Anxiety | 2.2 ± 2.5 | 1.7 ± 2.3 | 2.4 ± 2.6 | 0.143 |
| Drowsiness | 2.8 ± 2.8 | 2.1 ± 2.6 | 3.0 ± 2.9 | 0.116 |
| Appetite | 2.7 ± 3.0 | 2.5 ± 3.1 | 2.7 ± 2.9 | 0.396 |
| Wellbeing | 3.7 ± 2.7 | 2.7 ± 2.5 | 4.1 ± 2.6 | 0.025 |
| Shortness of breath | 3.6 ± 2.8 | 2.7 ± 2.9 | 4.1 ± 2.7 | 0.052 |
| Other problems from co morbidities | 2.1 ± 3.1 | 1.7 ± 2.8 | 2.3 ± 3.3 | 0.296 |

Using Edmonton Symptom Assessment System questionnaire; each symptom has scale of 0-10, with 0 = no symptoms and 10 = worst possible symptoms. *P* values compares group 1 [ejection fraction (EF) > 40] and group 2 (EF ≤ 40).

## DISCUSSION

We evaluated the prevalence and severity of pain in patients with chronic stable heart failure. Fifty-two percent ($n$ = 32) of the patients reported presence of pain of various characters and intensities ranging from a scale of 1-10 at different anatomical sites, or generalized pain. Patients reported pain regardless of the EF and co-morbidities. Patients with degenerative joint diseases reported higher pain scores. The prevalence and severity of pain were higher in patients with a lower EF (≤ 40%).

Pain in HF can be secondary to physical, spiritual, psychological and social factors[4]. Physical pain experienced by patients can be caused by multiple co-morbidities[4,18]. The International Association for the Study of Pain defines pain as an unpleasant sensory or emotional feeling that is associated with potential or actual tissue damage[19]. Pain is present in many medical conditions and it is the most common reason for clinician's consultation in the United States[20,21].

Pain that is transient, lasting only until the stimulus is removed or the pathology is healed is regarded as acute while pain that persist for years in conditions like cancer, rheumatoid arthritis, peripheral neuropathy and idiopathic type of pain is regarded as chronic. Some authors define acute pain as pain lasting less than one month while others define acute pain as pain that is less than three months from the time of onset. Chronic pain is defined by some as pain lasting up to six months from the onset or a subjective feeling that extends beyond the expected period of healing. Pain lasting between the intervals of 1 mo to 6 mo is regarded to be subacute.

The presence or absence of psychological and social factors can affect the intensity of pain feeling. Some studies showed that patients with psychological issues, anxiety and/or depression reported higher pain score[4,22-25]. Patients who experience severe symptoms such as SOB and fatigue that interfere with daily activities often also complain of pain, which easily can lead to more suffering and even social isolation[4,19].

According to Woolf, there are three classes of pain: nociceptive pain, pathological pain and inflammatory pain[26]. Others types of pain are phantom, incident, psychogenic and breakthrough pain.

Nociceptive pain is caused by noxious stimulation of sensory receptors that responds to potentially damaging stimuli. The stimuli can be from thermal, mechanical or chemical injury. Nociceptive pain can be superficial, somatic or visceral. Superficial pain is caused by activation of nociceptors in the skin or other superficial tissue. It is sharp and well-defined e.g., first degree burns and minor wounds. Somatic pain is initiated by stimulation of nociceptors in body surface or musculoskeletal tissues such as the tendons, ligaments, bones, muscles, fasciae, and blood vessels. Such pain is aching, dull and poorly localized pain. It is aggravated by exertion and relieved by rest. Examples include post surgical pain from surgical incisions, broken bones and sprains. Visceral pain is pain (from the visceral organs) due to stretch, ischemia and inflammation. It is diffuse, vague and difficult to locate. It is described as deep squeezing, pressure like, dull or diffuse type of pain which can be associated with malaise, nausea, vomiting or fever.

Pathological pain is a disease state caused by damage to the nervous system e.g., neuropathic pain or by its abnormal function e.g., fibromyalgia, tension headache and irritable bowel syndrome[26].

Neuropathic pain is caused by disease, injury or malfunction to any part of the nervous system- the central and the peripheral[27]. It may be associated with abnormal sensations (dysesthesia) or pain from normal non-painful stimuli (allodynia). Neuropathic pain is typically burning, shooting, cutting, drilling, stabbing, piercing, itching, stinging, tingling or it may be felt like a coldness, numbness, "pins and needles" or "electric shock" like type of sensation[28]. The pain occur at the level or below the level of injury within days, weeks, or months of the injury.

Neuropathic pain can be episodic and/or continuous in nature. It is divided into three types: (1) the central neuropathic pain involving the brain and spinal cord; (2) the peripheral neuropathic pain involving the peripheral nervous system and (3) the mixed neuropathic pain involving both the central and the peripheral nervous system.

Inflammatory pain is a type of pain that is associated with infiltration of immune cells due to cellular or tissue damage[26].

Psychogenic pain or somatoform pain is pain caused by or increased by a mental, an emotional, or a behavioral factor(s). Such pain can manifest as headache, stomach pain and back pain *etc*.

Phantom pain is a type of pain that result from a part of the body that was surgically or accidentally removed or from which the brain no longer receives signals. This type of pain is mostly reported by amputees.

Breakthrough pain is pain that spontaneously comes on just for short periods of time in patients with a background level of pain and is usually not relieved by the patients' regular pain medication. The character of this breakthrough pain differs from person to person and according to the cause of the pain. This pain type is commonly seen in cancer patients.

Incident pain is type of pain that arises secondary to exertion e.g., stretching a wound, movement of an arthritic joint *etc*.

There is limited data on pain association with chronic heart failure. It has been a priority for physicians to manage pain in chronically ill patient but it is rare for physicians to assess or recognize pain as being a symptom in patients with HF. The presence of pain in chronic heart failure patients are insidious and unnoticed[7]. Few studies demonstrated the association of pain with heart failure. A case series using a retrospective review of fifty patients with chronic heart failure for a period of three and a half year indicated that pain was part of multiple symptoms addressed during their hospital visits[29]. A multicenter, cross-sectional studies of 60 patients with heart failure indicated that more than fifty percent of these patients reported pain, shortness of breath, tiredness, drowsiness or dry mouth[22]. Another study with 1786 chronic heart failure patient who completed questionnaires for symptom assessment of heart failure showed that even though pain is common, pain is not necessarily due to angina even in patients with coronary heart disease[30]. Data obtained from three-hundred patients with chronic HF indicated that sixty-seven percent of the patients reported pain with increment in the prevalence of pain as the functional class worsens[7]. In a study of ninety-six veterans with chronic HF, more than fifty percent reported pain with more than thirty-seven percent rating their pain as moderate to severe[4]. Our study demonstrated that pain was present in more than 50% of the patients which reinforces the evidence that pain is one of the symptoms of chronic HF. The pain sensation in patients with chronic HF might be inflammatory and neuropathic in origin or a combination of different types of pain, however, a concise classification of the pain character in these patients is outside the frame of the present study.

It is imperative for clinicians to recognize pain as part of expected symptoms in patients with HF. Adequate pain management that might involve palliative care providers and multidisciplinary teams might be effective in minimizing sufferings and improve quality of life[4,22,31-35].

This is a cross sectional subjective assessment of symptoms rather than an objective measure. Patients were randomly selected from an outpatient clinic cohort. No additional questionnaires were provided.

This study did not identify the causal mechanisms behind the association of pain and heart failure.

Pain and other non specific symptoms are usually not regarded as typical symptoms in patients with chronic heart failure[4,7]. Evidence supports that more than fifty percent of patients with chronic HF report pain of various characters and intensities. Our data suggest that among other symptoms, pain appears to be prevalent and significantly affects quality of life in heart failure patients. Adequate pain assessment and management should be an integral part of chronic heart failure management. Involving a multidisciplinary team in the management of heart failure can help to address the complex nature of pain and improve the quality of life. Further research to study the causal mechanism of pain association with heart failure is needed.

## COMMENTS

### Background

Pain is a debilitating symptom and a cause of significant burden in patients with chronic diseases. Despite anecdotal data, only few studies demonstrate the clinical relevance of pain in patients with chronic advanced heart failure.

### Research frontiers

Chronic heart failure is of growing incidence and prevalence and is now the main cause for hospital admission among the elderly and increasing expenditure in medicine. The evaluation and treatment of patients with chronic heart failure (HF) needs to go beyond cardiac dysfunction and requires a holistic approach of the multisystem involvement and non-specific symptomatology of the patients. The assessment and recognition of pain as a result of the involvement of the entire body system is of enormous clinical relevance.

### Innovations and breakthroughs

The data show that pain is a prevalent symptom in patients with chronic HF and can present either as localized or generalized pain. Pain significantly impairs quality of life and often is a leading symptom resulting in recurrent physician office visits, emergency department visits, and subsequent hospitalizations. Despite this, pain has never been considered a characteristic symptom of HF.

### Applications

Based on the data, a systematic evaluation of non specific, generalized symptoms including localized or generalized pain should be part of a routine assessment in patients with HF. Adequate pain management will help to (1) alleviate symptoms; (2) improve quality of life; (3) increase patient compliance; (4) reduce emergency visits and hospital admissions; (5) reduce overall morbidity; and (6) reduce costs. Even though pain management is not part of the present study, this aspect requires further investigation.

### Terminology

Heart failure is a condition that is usually caused by a reduction of the contractile function of the ventricular chambers or an impairment of the relaxation properties of the cardiac chambers.

### *Peer review*

This article retrospectively investigated the prevalence and severity of pain in patients with chronic heart failure. Chest pain is a clinical symptom suggesting myocardial ischemia. The research may include a potential important topic. There are some issues that need to be addressed precisely.

## REFERENCES


1 **Hunt SA**, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005; **112**: e154-e235

2 **Masoudi FA**, Havranek EP, Krumholz HM. The burden of chronic congestive heart failure in older persons: magnitude and implications for policy and research. *Heart Fail Rev* 2002; **7**: 9-16

3 **Lloyd-Jones D**, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Roger VL, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; **121**: e46-e215

4 **Goebel JR**, Doering LV, Shugarman LR, Asch SM, Sherbourne CD, Lanto AB, Evangelista LS, Nyamathi AM, Maliski SL, Lorenz KA. Heart failure: the hidden problem of pain. *J Pain Symptom Manage* 2009; **38**: 698-707

5 **Mitani H**, Hashimoto H, Isshiki T, Kurokawa S, Ogawa K, Matsumoto K, Miyake F, Yoshino H, Fukuhara S. Health-related quality of life of Japanese patients with chronic heart failure: assessment using the Medical Outcome Study Short Form 36. *Circ J* 2003; **67**: 215-220

6 **Cohn JN**. Structural basis for heart failure. Ventricular remodeling and its pharmacological inhibition. *Circulation* 1995; **91**: 2504-2507

7 **Evangelista LS**, Sackett E, Dracup K. Pain and heart failure: unrecognized and untreated. *Eur J Cardiovasc Nurs* 2009; **8**: 169-173

8 **Howlett JG**. Palliative care in heart failure: addressing the largest care gap. *Curr Opin Cardiol* 2011; **26**: 144-148

9 **Ammar KA**, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC, Rodeheffer RJ. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation* 2007; **115**: 1563-1570

10 **Mann DL**. Mechanisms and models in heart failure: A combinatorial approach. *Circulation* 1999; **100**: 999-1008

11 **Borson S**, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry* 2000; **15**: 1021-1027

12 **Costa D**, Severo M, Fraga S, Barros H. Mini-Cog and Mini-Mental State Examination: agreement in a cross-sectional study with an elderly sample. *Dement Geriatr Cogn Disord* 2012; **33**: 118-124

13 **Borson S**, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. *J Am Geriatr Soc* 2003; **51**: 1451-1454

14 **Milian M**, Leiherr AM, Straten G, Müller S, Leyhe T, Eschweiler GW. The Mini-Cog versus the Mini-Mental State Examination and the Clock Drawing Test in daily clinical practice: screening value in a German Memory Clinic. *Int Psychogeriatr* 2012; **24**: 766-774

15 **Bruera E**, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care* 1991; **7**: 6-9

16 **Moro C**, Brunelli C, Miccinesi G, Fallai M, Morino P, Piazza M, Labianca R, Ripamonti C. Edmonton symptom assessment scale: Italian validation in two palliative care settings. *Support Care Cancer* 2006; **14**: 30-37

17 **Chang VT**, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. *Cancer* 2000; **88**: 2164-2171

18 **Goebel JR**, Doering LV, Lorenz KA, Maliski SL, Nyamathi AM, Evangelista LS. Caring for special populations: total pain theory in advanced heart failure: applications to research and practice. *Nurs Forum* 2009; **44**: 175-185

19 **Bonica JJ**. The need of a taxonomy. *Pain* 1979; **6**: 247-248

20 **Turk DC**, Dworkin RH. What should be the core outcomes in chronic pain clinical trials? *Arthritis Res Ther* 2004; **6**: 151-154

21 **Breivik H**, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, Kvarstein G, Stubhaug A. Assessment of pain. *Br J Anaesth* 2008; **101**: 17-24

22 **Bekelman DB**, Havranek EP, Becker DM, Kutner JS, Peterson PN, Wittstein IS, Gottlieb SH, Yamashita TE, Fairclough DL, Dy SM. Symptoms, depression, and quality of life in patients with heart failure. *J Card Fail* 2007; **13**: 643-648

23 **Butler LD**, Koopman C, Cordova MJ, Garlan RW, DiMiceli S, Spiegel D. Psychological distress and pain significantly increase before death in metastatic breast cancer patients. *Psychosom Med* 2003; **65**: 416-426

24 **Carr EC**, Nicky Thomas V, Wilson-Barnet J. Patient experiences of anxiety, depression and acute pain after surgery: a longitudinal perspective. *Int J Nurs Stud* 2005; **42**: 521-530

25 **Carels RA**, Musher-Eizenman D, Cacciapaglia H, Pérez-Benítez CI, Christie S, O'Brien W. Psychosocial functioning and physical symptoms in heart failure patients: a within-individual approach. *J Psychosom Res* 2004; **56**: 95-101

26 **Woolf CJ**. What is this thing called pain? *J Clin Invest* 2010; **120**: 3742-3744

27 **Treede RD**, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008; **70**: 1630-1635

28 **Paice JA**. Mechanisms and management of neuropathic pain in cancer. *J Support Oncol* 2003; **1**: 107-120

29 **Bekelman DB**, Nowels CT, Allen LA, Shakar S, Kutner JS, Matlock DD. Outpatient palliative care for chronic heart failure: a case series. *J Palliat Med* 2011; **14**: 815-821

30 **Clark AL**, Goode KM. Do patients with chronic heart failure have chest pain? *Int J Cardiol* 2012; Epub ahead of print

31 **Bekelman DB**, Rumsfeld JS, Havranek EP, Yamashita TE, Hutt E, Gottlieb SH, Dy SM, Kutner JS. Symptom burden, depression, and spiritual well-being: a comparison of heart

failure and advanced cancer patients. *J Gen Intern Med* 2009; **24**: 592-598
32 **Zambroski CH**, Moser DK, Bhat G, Ziegler C. Impact of symptom prevalence and symptom burden on quality of life in patients with heart failure. *Eur J Cardiovasc Nurs* 2005; **4**: 198-206
33 **Goodlin SJ**. Palliative care in congestive heart failure. *J Am Coll Cardiol* 2009; **54**: 386-396
34 **Rustøen T**, Stubhaug A, Eidsmo I, Westheim A, Paul SM, Miaskowski C. Pain and quality of life in hospitalized patients with heart failure. *J Pain Symptom Manage* 2008; **36**: 497-504
35 **Goodlin SJ**, Wingate S, Pressler SJ, Teerlink JR, Storey CP. Investigating pain in heart failure patients: rationale and design of the Pain Assessment, Incidence & amp; Nature in Heart Failure (PAIN-HF) study. *J Card Fail* 2008; **14**: 276-282

**S- Editor** Cheng JX **L- Editor** A **E- Editor** Zhang DN

World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
wjc@wjgnet.com
doi:10.4330/wjc.v4.i8.256

*World J Cardiol* 2012 August 26; 4(8): 256-259
ISSN 1949-8462 (online)


BRIEF ARTICLE

# Effect of eicosapentaenoic acid on regional arterial stiffness: Assessment by tissue Doppler imaging

Mio Haiden, Yoko Miyasaka, Yutaka Kimura, Satoshi Tsujimoto, Hirofumi Maeba, Yoshinobu Suwa, Toshiji Iwasaka, Ichiro Shiojima

Mio Haiden, Yoko Miyasaka, Yutaka Kimura, Satoshi Tsujimoto, Hirofumi Maeba, Yoshinobu Suwa, Toshiji Iwasaka, Ichiro Shiojima, Division of Cardiology, Department of Medicine II, Kansai Medical University, Hirakata, Osaka 573-1191, Japan

Author contributions: Haiden M, Miyasaka Y, Kimura Y, and Iwasaka T designed the study concept; Haiden M, Miyasaka Y, Tsujimoto S, Maeba H, and Suwa Y collected the data; Haiden M, Miyasaka Y, and Shiojima I wrote the manuscript; Haiden M, Miyasaka Y, Kimura Y, Tsujimoto S, Maeba H, Suwa Y, Iwasaka T, and Shiojima I analyzed and interpreted the data, and gave the final approval for the manuscript.

Correspondence to: Yoko Miyasaka, MD, PhD, FACC, FAHA, Division of Cardiology, Department of Medicine II, Kansai Medical University, 2-3-1, Shin-machi, Hirakata, Osaka 573-1191, Japan. miyasaka@hirakata.kmu.ac.jp
Telephone: +81-72-8040101 Fax: +81-72-8042865
Received: June 21, 2012 Revised: August 10, 2012
Accepted: August 17, 2012
Published online: August 26, 2012

## Abstract

**AIM:** To evaluate the effects of eicosapentaenoic acid (EPA) on regional arterial stiffness assessed by strain rate using tissue Doppler imaging.

**METHODS:** Nineteen eligible patients were prospectively studied (mean age 62 ± 8 years, 68% men). Subjects with large vessel complications and/or diabetes mellitus were excluded. The strain rate of the ascending aorta was measured by tissue Doppler imaging as an index of regional arterial stiffness, and brachial-ankle pulse wave velocity (baPWV) was measured as an index of degree of systemic arteriosclerosis. These indices were compared before and after administration of EPA at 1800 mg/d for one year.

**RESULTS:** The plasma concentration of EPA increased significantly after EPA administration (3.0% ± 1.1% to 8.5% ± 2.9%, $P < 0.001$). There were no significant changes in baPWV (1765 ± 335 cm/s to 1745 ± 374 cm/s), low-density lipoprotein cholesterol levels (114 ± 29 mg/dL to 108 ± 28 mg/dL), or systolic blood pressure (131 ± 16 mmHg to 130 ± 13 mmHg) before and after EPA administration. In contrast, the strain rate was significantly increased by administration of EPA (19.2 ± 5.6 $s^{-1}$, 23.0 ± 6.6 $s^{-1}$, $P < 0.05$).

**CONCLUSION:** One year of administration of EPA resulted in an improvement in regional arterial stiffness which was independent of blood pressure or serum cholesterol levels.



**Key words:** Echocardiography; Tissue Doppler imaging; Strain rate; Arterial stiffness; Eicosapentaenoic acid

**Peer reviewer:** Gani Bajraktari, Professor, Service of Cardiology, University Clinical Centre of Kosova, Prishtina 10000, Yugoslavia

Haiden M, Miyasaka Y, Kimura Y, Tsujimoto S, Maeba H, Suwa Y, Iwasaka T, Shiojima I. Effect of eicosapentaenoic acid on regional arterial stiffness: Assessment by tissue Doppler imaging. *World J Cardiol* 2012; 4(8): 256-259 Available from: URL: http://www.wjgnet.com/1949-8462/full/v4/i8/256.htm DOI: http://dx.doi.org/10.4330/wjc.v4.i8.256

## INTRODUCTION

Eicosapentaenoic acid (EPA) is derived from fish oil. It was previously reported that EPA administration reduces peripheral arterial stiffness measured by brachial-ankle pulse wave velocity (baPWV)[1]. It was also reported that EPA administration results in a reduction of the incidence of cardiovascular diseases[2]. However, whether

EPA has any effect on regional arterial stiffness has remained unclear.

We have previously reported that strain rate of the ascending aorta measured by tissue Doppler imaging is an accurate and blood pressure-independent index of regional arterial stiffness[3]. We therefore examined whether administration of EPA reduces regional arterial stiffness assessed by the strain rate of the ascending aorta.

## MATERIALS AND METHODS

### Study population

With approval from the Institutional Review Board, we prospectively enrolled 19 patients (mean age 62 ± 8 years, 68% men) who visited our outpatient clinic for the management of hypertension or dyslipidemia. We excluded patients with diabetes mellitus (HbA1c > 6.0%) and/or large vessel complications including ischemic heart disease, cerebrovascular disease, aortic aneurysm (diameter of aorta ⩾ 35 mm), and arteriosclerosis obliterans (ankle-brachial index < 0.8)[4,5], assessed by history taking, physical examination, electrocardiography, transthoracic echocardiography, blood tests, and computed tomography. Blood pressure was less than 140/90 mmHg in all patients, and low-density lipoprotein (LDL) cholesterol levels were less than 140 mg/dL for at least 2 years at the time of their enrollment.

### Measurement of strain rate and baPWV

To evaluate the effects of EPA on arterial stiffness, baPWV (as an index of degree of systemic arteriosclerosis[6]) and strain rate (as an index of regional arterial stiffness[3]) were measured simultaneously. Both indices were determined before administration and one year after administration of EPA at a daily dose of 1800 mg. After identifying the long axis of the ascending aortic wall by tissue Doppler imaging, the strain rate was calculated by establishing a region of interest on the ascending aortic wall using Vivid Five (GE, Yokogawa Medical Systems), and the velocity between two points was measured and divided by the distance between these two points[3] (Figure 1). The movement velocity between any two points can be quantitatively assessed by this index, which is known to be unaffected by tissue swing or tethering[7-9]. The same point was assessed before and after EPA administration and the average of three heart beats was evaluated. Comprehensive echocardiography was also performed before and after EPA administration. Blood pressure and baPWV were simultaneously measured using an automatic waveform analyzer (BP-203RPE; AT Company, Colin Medical Technology). Both tests were conducted in a room with calming background music where the temperature was maintained at 20 ℃. Each subject was instructed to rest in the supine position for 15 min. Then, blood pressure and baPWV were simultaneously measured, and tissue Doppler imaging was subsequently performed. Written informed consent to participate in the study was obtained from all patients.

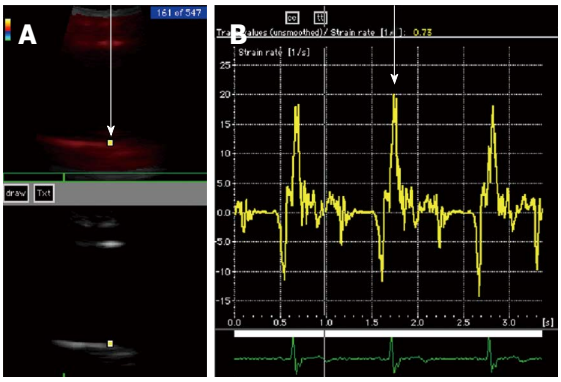



**Figure 1 Measurement of the strain rate of the ascending aorta by tissue Doppler echocardiography.** A: A region of interest (arrow) was identified on the ascending aortic wall; B: Strain rate (arrow) was recorded and the peak value during initial contraction was measured by averaging the systolic peak of three heart beats.

### Normal values in healthy subjects and intra- and inter-observer variability

The strain rate of the ascending aorta was measured in 10 healthy subjects (mean age 36 ± 19 years, 50% men) to obtain the normal range of the index. Inter-observer variability was assessed from 10 randomly selected images by 2 independent observers, each blinded to the results obtained by the other. Intra-observer variability was assessed by repeated measurements from 10 images by the same observer one week after the first analysis. Inter- and intra-observer variability was calculated as the absolute difference between repeated measurements in percentage of their mean.

### Statistical analysis

The results represent the mean ± SD. The significance of differences between variables was determined by analysis of variance. Student's *t* test was used for statistical comparisons and a *P* value of < 0.05 was considered to be statistically significant.

## RESULTS

### Effects of EPA on lipid profile and blood pressure

There was no difference in the proportion of patients with hypertension or dyslipidemia before and after administration of EPA. No appreciable difference was noted in the details of the use of concurrent drugs. There was no significant difference before and after EPA administration in LDL cholesterol levels (114 ± 29 mg/dL to 108 ± 28 mg/dL), triglyceride levels (107 ± 52 mg/dL to 99 ± 24 mg/dL), or systolic blood pressure (131 ± 16 mmHg to 130 ± 13 mmHg). The mean plasma concentration of EPA increased from 3.0% ± 1.1% to 8.5% ± 2.9% at one year after EPA administration (*P* < 0.001) (Table 1). None of the patients experienced any particular adverse reactions.

### Effects of EPA on baPWV and the strain rate of the aorta

Echocardiographic left ventricular systolic or diastolic

**Table 1 Clinical data before and after eicosapentaenoic acid administration ($n$ = 19)**

| Variables | Pre-administration | After-administration | *P* value |
|---|---|---|---|
| Systemic hypertension | 17 (89%) | 17 (89%) | NS |
| Dyslipidemia | 14 (74%) | 14 (74%) | NS |
| Body mass index (kg/m$^2$) | 23.9 ± 2.3 | 23.9 ± 2.5 | NS |
| Systolic BP (mmHg) | 131 ± 16 | 130 ± 13 | NS |
| Diastolic BP (mmHg) | 83 ± 9 | 80 ± 7 | NS |
| Triglyceride (mg/dL) | 107 ± 52 | 99 ± 24 | NS |
| LDL cholesterol (mg/dL) | 114 ± 29 | 108 ± 28 | NS |
| EPA (%) | 3.0 ± 1.1 | 8.5 ± 2.9 | < 0.001 |

Values are given as mean ± SD or number (percentage). BP: Blood pressure; LDL: Low-density-lipoprotein; NS: Not significant.

**Table 2 Echocardiographic data before and after eicosapentaenoic acid administration ($n$ = 19, mean ± SD)**

| Variables | Pre-administration | After-administration | *P* value |
|---|---|---|---|
| LA dimension (mm) | 38 ± 5 | 39 ± 4 | NS |
| LVDd (mm) | 48 ± 3 | 48 ± 4 | NS |
| LVDs (mm) | 29 ± 4 | 30 ± 5 | NS |
| Mitral E/A | 0.96 ± 0.28 | 1.01 ± 0.56 | NS |
| Mitral DT (ms) | 218 ± 44 | 232 ± 60 | NS |
| LV ejection fraction (%) | 76 ± 8 | 76 ± 9 | NS |
| Strain rate of aorta (s$^{-1}$) | 19.2 ± 5.6 | 23.0 ± 6.6 | < 0.05 |

LA: Left atrial; LVDd: Left ventricular end-diastolic dimension; LVDs: Left ventricular end-systolic dimension; DT: Deceleration time; NS: Not significant.

parameters were not significantly different before and after administration of EPA (Table 2). baPWV was 1765 ± 335 cm/s before EPA administration and 1745 ± 374 cm/s at one year after EPA administration. The difference was not statistically significant. In contrast, the strain rate of the ascending aorta was significantly increased from 19.2 ± 5.6 s$^{-1}$ to 23.0 ± 6.6 s$^{-1}$ by EPA administration ($P$ < 0.05) (Figure 2), indicating that EPA administration for one year improved the regional stiffness of the ascending aorta.

### *Normal values and reproducibility of the strain rate of the aorta*

The mean value of the strain rate of the ascending aorta in 10 healthy subjects was 31.9 ± 5.0 s$^{-1}$. Inter-observer and intra-observer variability for strain rate were 12% ± 5% and 11% ± 4%, respectively.

## DISCUSSION

Our data show that administration of EPA for one year resulted in an improvement in regional arterial stiffness as indicated by increased strain rate of the ascending aorta, and that this effect of EPA on regional arterial stiffness is independent of blood pressure or serum cholesterol levels.

The degree of arteriosclerosis represents an important predictive factor for cardiovascular outcome[10-13]. Appropriate management of arteriosclerosis is clinically important, especially in the early stage of cardiovascular diseases. EPA is taken up by vascular smooth muscle cells and considered to maintain the elasticity of arteries. It was previously reported that administration of EPA reduces peripheral arterial stiffness measured by baPWV, and the incidence of cardiovascular disease[2,14,15].

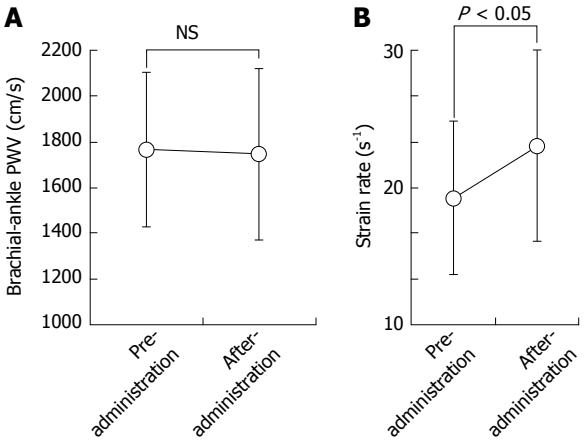



**Figure 2 Effect of eicosapentaenoic acid on brachial-ankle pulse wave velocity and the strain rate of the ascending aorta.** A: No difference was noted in baPWV before and after eicosapentaenoic acid (EPA) administration; B: In contrast, a statistically significant increase in the strain rate of the ascending aorta was observed after one year of EPA administration. PWV: Pulse wave velocity; NS: Not significant.

To date, baPWV has been used as a noninvasive index of arterial stiffness or arterial distensibility[6,16]. There are, however, several limitations concerning the evaluation of arterial stiffness by baPWV. Firstly, the actual length of an artery used for measuring PWV is estimated based on an anatomical correction value. Secondly, baPWV is affected by systolic blood pressure and overestimated in hypertensive subjects[17,18]. In contrast, the strain rate measured by tissue Doppler imaging accurately reflects the velocity of tissue movements[7-9], and thus can be used to noninvasively assess regional arterial stiffness. Our previous study demonstrated that the strain rate of the ascending aorta is an accurate and blood pressure-independent index of regional atrial stiffness[3]. Positive results validating tissue Doppler imaging assessment of arterial wall properties have also been reported in the evaluation of abdominal aorta disease[19] and characterization of the common carotid artery[20].

In the present study, one year of administration of EPA significantly improved regional arterial stiffness of the ascending aorta but not baPWV. There are several published reports showing that baPWV was improved by the administration of EPA[2,14,15], in which patients were treated with EPA for at least 2 years. The discrepancy between the present study and previous reports in the effect of EPA on baPWV may be due to the difference in the length of EPA administration. The observation that the effect of EPA on arterial stiffness was not detected by baPWV also suggests that the strain rate of the ascending aorta may be a more sensitive marker of arteriosclerosis than baPWV. Finally, the relatively small number of pa-

tients examined and the lack of a control group need to be recognized as limitations of this study.

In conclusion, the strain rate of the ascending aorta was a sensitive and blood pressure-independent marker of arteriosclerosis. Administration of EPA for one year led to an improvement in regional arterial stiffness as indicated by strain rate, even though there was no change in blood pressure or serum cholesterol levels.

## COMMENTS

### Background

Eicosapentaenoic acid (EPA) is derived from fish oil. It was previously reported that administration of EPA reduces the incidence of cardiovascular diseases. However, whether EPA has any effect on regional arterial stiffness has been unclear till now.

### Research frontiers

This study evaluates the efficacy of EPA on arterial stiffness assessed by the strain rate of the ascending aorta.

### Innovations and breakthroughs

This is the first study to report that administration of EPA for one year resulted in an improvement of regional arterial stiffness independently of blood pressure or serum cholesterol levels.

### Applications

It has been reported that arterial stiffness is associated with an increased incidence of cardiovascular events, and appropriate management of arteriosclerosis is clinically important especially in the early stage of cardiovascular diseases. EPA administration reduces arterial stiffness measured by the strain rate of the ascending aorta and may result in the reduction of the incidence of cardiovascular diseases.

### Peer review

The study is well designed.

## REFERENCES


1 **Tomiyama H**, Takazawa K, Osa S, Hirose K, Hirai A, Iketani T, Monden M, Sanoyama K, Yamashina A. Do eicosapentaenoic acid supplements attenuate age-related increases in arterial stiffness in patients with dyslipidemia?: A preliminary study. *Hypertens Res* 2005; **28**: 651-655

2 **Kris-Etherton PM**, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002; **106**: 2747-2757

3 **Haiden M**, Kimura Y, Miyasaka Y, Aota Y, Dote K, Takada A, Iwasaka T. New index of regional arterial stiffness assessed by tissue Doppler imaging. *Acta Cardiol* 2008; **63**: 603-608

4 **Makin AJ**, Chung NA, Silverman SH, Lip GY. Vascular endothelial growth factor and tissue factor in patients with established peripheral artery disease: a link between angiogenesis and thrombogenesis? *Clin Sci* (*Lond*) 2003; **104**: 397-404

5 **Lazarous DF**, Unger EF, Epstein SE, Stine A, Arevalo JL, Chew EY, Quyyumi AA. Basic fibroblast growth factor in patients with intermittent claudication: results of a phase I trial. *J Am Coll Cardiol* 2000; **36**: 1239-1244

6 **Wilkinson IB**, Cockcroft JR, Webb DJ. Pulse wave analysis and arterial stiffness. *J Cardiovasc Pharmacol* 1998; **32** Suppl 3: S33-S37

7 **Voigt JU**, Arnold MF, Karlsson M, Hübbert L, Kukulski T, Hatle L, Sutherland GR. Assessment of regional longitudinal myocardial strain rate derived from doppler myocardial imaging indexes in normal and infarcted myocardium. *J Am Soc Echocardiogr* 2000; **13**: 588-598

8 **Heimdal A**, Støylen A, Torp H, Skjaerpe T. Real-time strain rate imaging of the left ventricle by ultrasound. *J Am Soc Echocardiogr* 1998; **11**: 1013-1019

9 **Miyasaka Y**, Haiden M, Kamihata H, Nishiue T, Iwasaka T. Usefulness of strain rate imaging in detecting ischemic myocardium during dobutamine stress. *Int J Cardiol* 2005; **102**: 225-231

10 **Laurent S**, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**: 1236-1241

11 **Fukuhara M**, Matsumura K, Ansai T, Takata Y, Sonoki K, Akifusa S, Wakisaka M, Hamasaki T, Fujisawa K, Yoshida A, Fujii K, Iida M, Takehara T. Prediction of cognitive function by arterial stiffness in the very elderly. *Circ J* 2006; **70**: 756-761

12 **Hatsuda S**, Shoji T, Shinohara K, Kimoto E, Mori K, Fukumoto S, Koyama H, Emoto M, Nishizawa Y. Regional arterial stiffness associated with ischemic heart disease in type 2 diabetes mellitus. *J Atheroscler Thromb* 2006; **13**: 114-121

13 **Lehmann ED**, Hopkins KD, Rawesh A, Joseph RC, Kongola K, Coppack SW, Gosling RG. Relation between number of cardiovascular risk factors/events and noninvasive Doppler ultrasound assessments of aortic compliance. *Hypertension* 1998; **32**: 565-569

14 **Mita T**, Watada H, Ogihara T, Nomiyama T, Ogawa O, Kinoshita J, Shimizu T, Hirose T, Tanaka Y, Kawamori R. Eicosapentaenoic acid reduces the progression of carotid intima-media thickness in patients with type 2 diabetes. *Atherosclerosis* 2007; **191**: 162-167

15 **Hino A**, Adachi H, Toyomasu K, Yoshida N, Enomoto M, Hiratsuka A, Hirai Y, Satoh A, Imaizumi T. Very long chain N-3 fatty acids intake and carotid atherosclerosis: an epidemiological study evaluated by ultrasonography. *Atherosclerosis* 2004; **176**: 145-149

16 **Asmar R**, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995; **26**: 485-490

17 **Koji Y**, Tomiyama H, Ichihashi H, Nagae T, Tanaka N, Takazawa K, Ishimaru S, Yamashina A. Comparison of ankle-brachial pressure index and pulse wave velocity as markers of the presence of coronary artery disease in subjects with a high risk of atherosclerotic cardiovascular disease. *Am J Cardiol* 2004; **94**: 868-872

18 **Yamashina A**, Tomiyama H, Arai T, Koji Y, Yambe M, Motobe H, Glunizia Z, Yamamoto Y, Hori S. Nomogram of the relation of brachial-ankle pulse wave velocity with blood pressure. *Hypertens Res* 2003; **26**: 801-806

19 **Harada K**, Yasuoka K, Shimada Y. Usefulness of tissue doppler imaging for assessing aortic wall stiffness in children with the Marfan syndrome. *Am J Cardiol* 2004; **93**: 1072-1075

20 **Schmidt-Trucksäss A**, Grathwohl D, Schmid A, Boragk R, Upmeier C, Keul J, Huonker M. Assessment of carotid wall motion and stiffness with tissue Doppler imaging. *Ultrasound Med Biol* 1998; **24**: 639-646


**S- Editor** Cheng JX **L- Editor** Logan S **E- Editor** Zhang DN

World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
wjc@wjgnet.com
doi:10.4330/wjc.v4.i8.260

*World J Cardiol* 2012 August 26; 4(8): 260-263
ISSN 1949-8462 (online)


CASE REPORT

# MRI-guided ablation of wide complex tachycardia in a univentricular heart

Theresa Reiter, Oliver Ritter, Peter Nordbeck, Meinrad Beer, Wolfgang Rudolf Bauer

Theresa Reiter, Oliver Ritter, Peter Nordbeck, Wolfgang Rudolf Bauer, Department of Internal Medicine I, University Hospital Wuerzburg, 97080 Wuerzburg, Germany
Meinrad Beer, Department of Radiology, University Hospital Wuerzburg, 97080 Wuerzburg, Germany
Author contributions: Reiter T wrote the paper, researched the literature and performed the procedure; Ritter O, Nordbeck P and Bauer WR performed the procedure and critically reviewed the paper; Beer M contributed to imaging and critical review.
Correspondence to: Theresa Reiter, MD, Department of Internal Medicine I, University Hospital Wuerzburg, 97080 Wuerzburg, Germany. theresa.reiter@gmx.de
Telephone: +49-931-2010 Fax: +49-931-408114
Received: June 29, 2011 Revised: September 2, 2011
Accepted: September 9, 2011
Published online: August 26, 2012

## Abstract

Magnetic resonance imaging can be used for preprocedural assessment of complex anatomy for radiofrequency (RF) ablations, e.g., in a univentricular heart. This case report features the treatment of a young patient with a functionally univentricular heart who suffered from persistent sudden onset tachycardia with wide complexes that required RF ablation as treatment.



**Key words:** Magnetic resonance imaging; Ablation; Univentricular heart; Fontan's Operation; Ventricular tachycardia

**Peer reviewers:** Brian Olshansky, MD, Professor of Medicine, Cardiac Electrophysiology, University of Iowa Hospitals, 200 Hawkins Drive, Room 4426a JCP, Iowa City, IA 52242, United States; Richard G Trohman, Professor of Medicine, Rush University Medical Center, 1653 West Congress Parkway, Room 983 Jelke, Chicago, IL 60612, United States

Reiter T, Ritter O, Nordbeck P, Beer M, Bauer WR. MRI-guided ablation of wide complex tachycardia in a univentricular heart. *World J Cardiol* 2012; 4(8): 260-263 Available from: URL: http://www.wjgnet.com/1949-8462/full/v4/i8/260.htm DOI: http://dx.doi.org/10.4330/wjc.v4.i8.260

## INTRODUCTION

Patients with a univentricular heart are born with a unique cardiac anatomy, including a wide range of heterogenic morphologies. The heart usually consists of a functionally single main ventricle that is associated with a hypoplastic or rudimentary second ventricular chamber. The anatomy of the outflow and inflow tract can also be altered, for example a double inlet or common atrioventricular canal can exist. Tricuspid or mitral atresia is often found. The clinical presentation depends on the exact anatomic features, but congestive heart failure commonly develops. A possible treatment is a complex surgical procedure, called Fontan's operation, that ensures patient survival beyond childhood and teenage years. Fontan's operation forms a total cavopulmonal anastomosis that connects the venae cavae directly to the pulmonary system without participation of the right atrium and ventricle. With increasing age, the patients often develop long-term side effects, the most common being cardiac arrhythmia, hepatic dysfunction and thrombosis[1]. Cardiac arrhythmias can be very resistant to medical treatment, thus requiring ablation therapy. Ablation therapy has been proven to be a very reliable treatment, with high long-term success rates[2]. The unique anatomy can be challenging for this procedure[3-9]. Magnetic resonance imaging (MRI) is a sensitive tool for soft tissue imaging and can be of great help in planning such an intervention.

## CASE REPORT

A 17-year-old boy with wide complex tachycardia (heart rate approximately 230 bpm), presented to our emergency room with dizziness and angina (Figure 1A). The

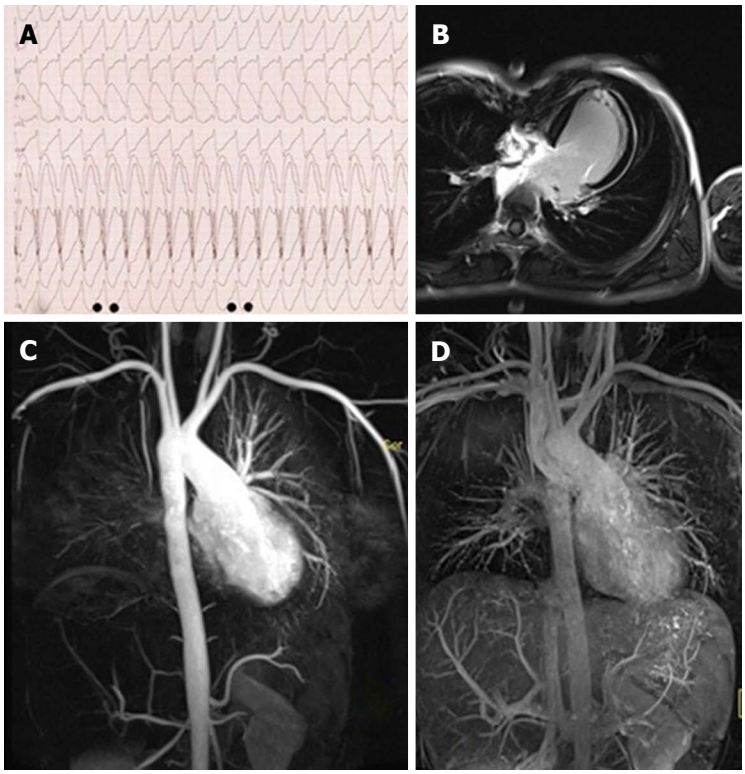



**Figure 1 Wide complex tachycardia.** A: Electrocardiographic findings in the emergency room; B: Long-axis late gadolinium enhancement view, main chamber and one outflow tract; C: Magnetic resonance (MR) angiography, arterial phase [maximum intensity projection (MIP)]; D: MR-angiography, venous phase (MIP).

tachycardia had been present for more than 3 h at the time of presentation. The patient maintained hemodynamic stability. Acute treatment included administration of adenosine, which had no effect on the tachycardia. Administration of ajmaline successfully terminated the tachycardia. The lack of an effect of adenosine led to the conclusion that supraventricular tachycardia (atrioventricular node reentry or accessory pathway) was very unlikely. The acute treatment was followed up by an invasive electrophysiological (EP) study during the patient's stay at our hospital.

The patient had been born with a hypoplastic right ventricle and atrium, and atresia of the tricuspid valve. The functionally univentricular heart with a ventricular septal defect and L-malposition of the main arteries had been treated with Fontan's operation at the age of 4 years. Besides these cardiac conditions, the patient suffered from hypofunction of the thyroid gland and attention deficit hyperactivity disorder. At the time of admission, the patient was treated with medikinet (methylphenidate) and aggrenox (acetylsalicylic acid and dipyridamol).

In this complex case with a univentricular heart and prior cardiac surgery (Fontan's operation to form a total cavopulmonal anastomosis without participation of the right atrium and ventricle), we chose to examine the patient using MRI before the EP study. There are several advantages of MRI: first, it provides actual information on cardiac anatomy beyond operative notes; second, it offers better anatomical information and, in particular, better soft tissue contrast than echocardiography, which is important for exploring access routes (MR angiography) to the cardiac chambers; and third, contrast-enhanced late enhancement (LE) imaging can indicate intramural scars in contrast to CARTO3 alone, which is dependent on endocardial voltages. Furthermore CARTO3 cannot provide preprocedural information on anatomy.

A 3T Trio (Siemens, Erlangen, Germany) system was used for the MRI studies. 3D-MR angiography demonstrated the dextroposition of the aorta and an anastomosis between the venae cavae and the pulmonary arteries (Figure 1C and D). Steady-state free precession (SSFP true-FISP) imaging (images not shown) revealed a ventricular left-right shunt in the basal area as well as a ventricular septal patch. Septal hypokinetic activity with a remaining ejection fraction of 49% and a cardiac index of 3.3 L/min/m$^2$ was documented. After administration of gadolinium-based contrast agent, the LE scan showed a hypoplastic right atrium and right ventricle (Figure 1B). Except for subtle signal enhancement at the site of the septal patch, no left ventricular scar/fibrosis was detected (Figure 2B).

The actual EP study was performed using CARTO3 with a single 7F Navistar Thermocool D-Type/3.5 mm/115 cm catheter (Biosense Webster, Diamond Bar, CA, United States). The arterial access was chosen in accordance with the specific anatomy and the MRI scans showed no direct venous connection to the cardiac main chamber.

During the EP evaluation, all attempts using programmed stimulation to induce the tachycardia failed, even under isoprenaline. However, occasional premature ventricular complexes (PVCs) were detected. Supraventricular stimulation was not possible since the right atrium could not be reached due to anatomical obstacles in the univentricular heart, and the left atrium could not be stimulated in a reliable fashion by retrograde access *via*

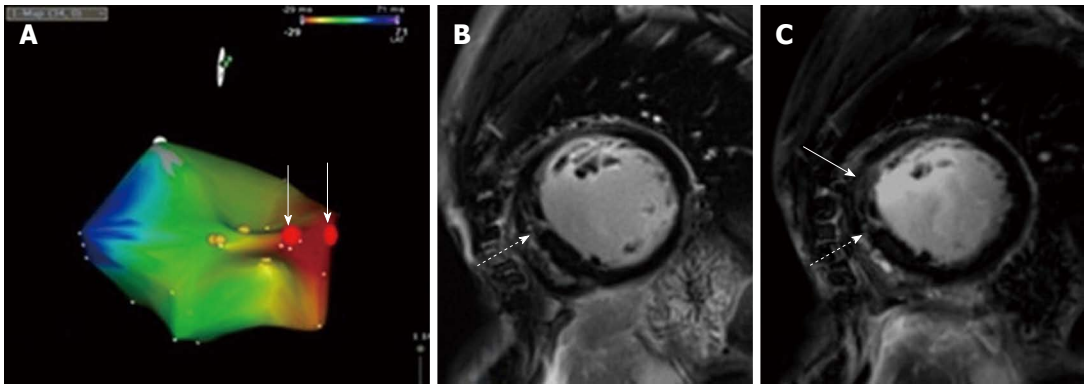



**Figure 2 Tachycardia origin and post-ablation scan.** A: Carto3. Yellow: His Bundle; red: area of earliest activation; red dots marked by white arrows: ablation sites; B: Short axis ate gadolinium enhancement (LGE) prior to ablation with no areas indicating scars. Note area of the septal patch (white arrow); C: Short axis LGE post-ablation: the ablation lesion is close to the area of the septal patch (white arrow).

the left ventricle.

Validation of tachycardia origin was achieved with two approaches. Stimulation of the septal wall showed a QRS morphology similar to the complexes during the tachycardia. Secondly PVCs with electrocardiographic morphology similar to that found during tachycardia were used to create a CARTO3-based 3D-activation map, localizing the origin of earliest activation at the same septal area as the pace map. The PVCs were identical to the documented wide complex tachycardia, suggesting a triggered focus as origin. No areas with low voltage signals were detected which corresponds with the lack of scars/fibrosis in the MRI. His potentials were detected near this focus, indicating close proximity of the bundle (Figure 2A). However, bundle branch reentry tachycardia seemed extremely unlikely, since we had no reproducible induction of the ventricular tachycardia (VT). Since induction of VT failed, we could not see a stable His or bundle branch potential that would have preceded each ventricular activation and which then could indicate a bundle branch reentry[10].

Despite the close proximity of the focus to the bundle of His, radiofrequency (RF) ablation at a sufficient distance from the delicate bundle of His region was feasible. After the ablation, no PVCs were detected. A post-ablational LE MRI scan showed the ablation scar located at the septal wall close to the patch that had been used for closing the ventricular defect (Figure 2C).

In addition to the EP evaluation and ablation, optimization of the patient's medical treatment was undertaken. Medikinet (methylphenidate) can be pro-arrhythmic[11] and might have contributed to the development of arrhythmias in the univentricular heart after Fontan's operation. At present, 8 mo after the ablation, the patient is in good health and, to date, there has been no recurrence of the tachycardia.

Patients with a univentricular heart often exhibit very complex heart pathologies even if treated early with Fontan's operation[12]. After this surgical procedure, heart anatomy and function remain idiosyncratic[13]. A strong association with cardiac arrhythmias has been described, and which might be challenging to treat[1,14]. MRI might offer essential therapeutic help, as it provides a very good insight into the anatomy of these hearts, thus allowing better planning of sometimes necessary EP procedures[15]. MRI can also be used to delineate ablation lesions in patients[2]. As shown in the current case, the synopsis of morphological and structural information and a thorough evaluation of the electrical activities can result in superior guidance and successful ablation in such difficult cases. Written consent for publication was obtained from the patient's guardian.

## REFERENCES

1 **Yamanaka O**, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. *Cathet Cardiovasc Diagn* 1990; **21**: 28-40
2 **Desmet W**, Vanhaecke J, Vrolix M, Van de Werf F, Piessens J, Willems J, de Geest H. Isolated single coronary artery: a review of 50,000 consecutive coronary angiographies. *Eur Heart J* 1992; **13**: 1637-1640
3 **Cilliers A**, Gewillig M. Fontan procedure for univentricular hearts: have changes in design improved outcome? *Cardiovasc J S Afr* 2002; **13**: 111-116
4 **de Groot NM**, Lukac P, Blom NA, van Kuijk JP, Pedersen AK, Hansen PS, Delacretaz E, Schalij MJ. Long-term outcome of ablative therapy of postoperative supraventricular tachycardias in patients with univentricular heart: a European multicenter study. *Circ Arrhythm Electrophysiol* 2009; **2**: 242-248
5 **Giannakoulas G**, Dimopoulos K, Yuksel S, Inuzuka R, Pijuan-Domenech A, Hussain W, Tay EL, Gatzoulis MA, Wong T. Atrial tachyarrhythmias late after Fontan operation are related to increase in mortality and hospitalization. *Int J Cardiol* 2012; **157**: 221-226
6 **Kaemmerer H**, Bauer U, Pensl U, Oechslin E, Gravenhorst V, Franke A, Hager A, Balling G, Hauser M, Eicken A, Hess J. Management of emergencies in adults with congenital cardiac disease. *Am J Cardiol* 2008; **101**: 521-525
7 **Khairy P**, Fernandes SM, Mayer JE, Triedman JK, Walsh EP, Lock JE, Landzberg MJ. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation* 2008; **117**: 85-92
8 **Nürnberg JH**, Ovroutski S, Alexi-Meskishvili V, Ewert P, Hetzer R, Lange PE. New onset arrhythmias after the extracardiac conduit Fontan operation compared with the intraatrial lateral tunnel procedure: early and midterm results.

*Ann Thorac Surg* 2004; **78**: 1979-1988; discussion 1988
9 **Wolf CM**, Seslar SP, den Boer K, Juraszek AL, McGowan FX, Cowan DB, Del Nido P, Triedman JK, Berul CI, Walsh EP. Atrial remodeling after the Fontan operation. *Am J Cardiol* 2009; **104**: 1737-1742
10 **Caceres J**, Jazayeri M, McKinnie J, Avitall B, Denker ST, Tchou P, Akhtar M. Sustained bundle branch reentry as a mechanism of clinical tachycardia. *Circulation* 1989; **79**: 256-270
11 http: //ch.oddb.org/de; as cited on 2011/06/23
12 **Gaca AM**, Jaggers JJ, Dudley LT, Bisset GS. Repair of congenital heart disease: a primer--Part 2. *Radiology* 2008; **248**: 44-60
13 **Kurotobi S**, Sano T, Naito H, Matsushita T, Takeuchi M, Kogaki S, Arisawa J, Matsuda H, Okada S. Regional ventricular systolic abnormalities caused by a rudimentary chamber in patients with univentricular hearts. *Am J Cardiol* 1998; **82**: 86-92
14 **Delacretaz E**, Ganz LI, Soejima K, Friedman PL, Walsh EP, Triedman JK, Sloss LJ, Landzberg MJ, Stevenson WG. Multi atrial maco-re-entry circuits in adults with repaired congenital heart disease: entrainment mapping combined with three-dimensional electroanatomic mapping. *J Am Coll Cardiol* 2001; **37**: 1665-1676
15 **Weiss F**, Habermann CR, Lilje C, Sasse K, Kühne T, Weil J, Adam G. [MRI in postoperative assessment of univentricular heart disease: correlation with echocardiography and angiography]. *Rofo* 2002; **174**: 1537-1543

**S- Editor** Cheng JX **L- Editor** Cant MR **E- Editor** Zhang DN

World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
wjc@wjgnet.com
doi:10.4330/wjc.v4.i8.264

*World J Cardiol* 2012 August 26; 4(8): 264-266
ISSN 1949-8462 (online)


CASE REPORT

# Acute coronary syndrome in a patient with a single coronary artery arising from the right sinus of Valsalva

Crista Liesting, Jasper Jan Brugts, Marcellinus Johannes Maria Kofflard, Attila Dirkali

Crista Liesting, Jasper Jan Brugts, Marcellinus Johannes Maria Kofflard, Attila Dirkali, Department of Cardiology, Albert Schweitzer Hospital, 3318 AT Dordrecht, The Netherlands
Author contributions: All authors contributed equally to this paper.
Correspondence to: Crista Liesting, MD, Department of Cardiology, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT Dordrecht, The Netherlands. c.liesting@asz.nl
Telephone: +31-78-6542258 Fax: +31-78-6543258
Received: June 4, 2012 Revised: June 20, 2012
Accepted: June 27, 2012
Published online: August 26, 2012

## Abstract

Coronary artery anomalies are usually encountered as coincidental findings during coronary angiography or at autopsy. Life threatening symptoms, such as arrhythmias, syncope, myocardial infarction, or sudden death, can occur in up to 20% of patients. However, the majority of anomalies (80%) are benign and asymptomatic. A single coronary artery (SCA) is one of the most rarely seen coronary anomalies with an incidence of 0.05%. We report the case of a 55-year old male patient who presented with symptoms of chest pain associated with an acute myocardial infarction. Coronary angiography revealed an anomalous left main coronary artery (LMCA) originating from the right coronary ostium, and an occluded distal right coronary artery. The occluded distal right coronary artery was successfully treated by thrombosuction and stenting. In order to confirm the origin and course of the SCA, multi-slice computed tomography (MSCT) of the heart was performed after coronary angiography. MSCT showed that the anomalous LMCA originated from the right coronary artery ostium and then passed the interventricular septum, instead of being intra arterial, and under the right ventricular infundibulum. The anomalous LMCA was classified as R-Ⅱ S subtype according to Lipton's classification.



**Key words:** Single coronary artery; Single coronary artery anomaly; Coronary angiography; Multi-slice computed angiography

**Peer reviewers:** Hiroyasu Ueda, MD, PhD, Department of Cardiology, Sumitomo Hospital, 5-3-20, Nakanoshima, Kita-ku, Osaka 530-0005, Japan; Zhonghua Sun, Professor, Department of Medical Imaging, Curtin University of Technology, Kent Street, Perth 6102, Australia

Liesting C, Brugts JJ, Kofflard MJM, Dirkali A. Acute coronary syndrome in a patient with a single coronary artery arising from the right sinus of Valsalva. *World J Cardiol* 2012; 4(8): 264-266 Available from: URL: http://www.wjgnet.com/1949-8462/full/v4/i8/264.htm DOI: http://dx.doi.org/10.4330/wjc.v4.i8.264

## INTRODUCTION

A single coronary artery (SCA), defined as an artery that arises from the aortic trunk from a single coronary ostium and supplies the entire heart, is rare. Coronary anomalies are inborn errors, and life-threatening symptoms, such as arrhythmias, syncope, myocardial infarction, or sudden death, can occur in up to 20% of patients. However, the majority of anomalies (80%) are benign and asymptomatic[1]. They are usually encountered as coincidental findings during coronary angiography or at autopsy.

The incidence of a left main coronary artery (LMCA) originating from the ostium of the right coronary artery (RCA) is very low (0.05%)[2]. There are several classifications for coronary artery anomalies. Lipton proposed a classification of solitary coronary arteries in 1979 which combined two previous classifications defined by Smith in 1950 and Ogden and Goodyer in 1970.

## CASE REPORT

A 55-year old man presented at the emergency depart-

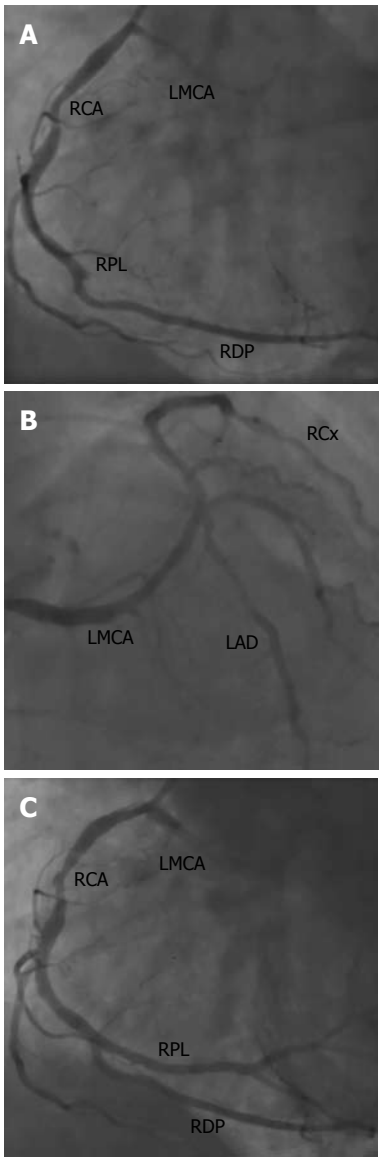



**Figure 1 Angiographic view.** A:Origin of the left main coronary artery in the ostium of the right coronary artery. The ramus posterolateralis (RPL)-branch is occluded; B: The course of the left main coronary artery to the left anterior descending and ramus circumflex; C: Angiographic result of the ramus posterolateralis branch after percutaneous coronary intervention with thrombosuction, balloon dilatation and stent implantation. RCA: Right coronary artery; LMCA: Left main coronary artery; RDP: Ramus descendens posterior; LAD: Left anterior descending; RCx: Ramus circumflex.

ment with progressive typical anginal symptoms for a few days. The patient's medical history showed no cardiovascular diseases and his sole risk factor was current smoking. Physical examination revealed a blood pressure of 115/80 mmHg with a regular pulse of 64 beats per minute, heart murmurs were absent and there were no signs of heart failure.

Laboratory assessment disclosed evidence of myocardial injury, but was otherwise unremarkable: troponin T (0.49 μg/L, normal < 0.10 μg/L) and creatine kinase (805 E/L, normal < 200 E/L). Electrocardiography demonstrated a sinus rhythm of 68 beats per minute and ST depression of 2 mm in leads V2-V4. The patient was admitted to our hospital with a non-ST elevated myocardial infarction and, after treatment with appropriate medication, his chest pain disappeared.

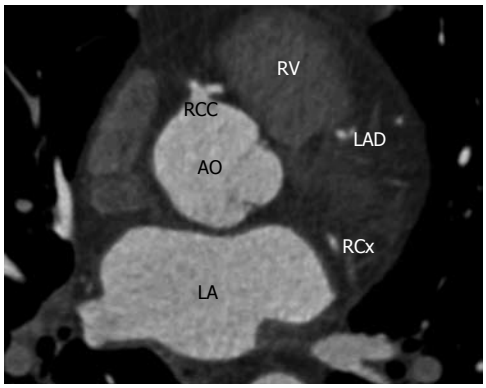



**Figure 2 Multi-slice computed tomography showed the anomalous left main coronary artery originating from the ostium of the right coronary artery.** AO: Aorta; LA: Left atrium; RV: Right ventricle; RCC: Right coronary cusp; LAD: Left anterior descending; RCx: Ramus circumflex.

The day after admission, chest pain reappeared and the electrocardiogram now showed sinus rhythm with ST elevation in leads Ⅱ, Ⅲ, aVF and 1 mm ST depression in V2-V5 without the presence of pathological Q waves. Thereupon, coronary angiography was performed immediately. The angiogram demonstrated a SCA: the LMCA originated from the ostium of the RCA (Figure 1A and B). There was a borderline lesion in the proximal RCA and an occlusion of the posterolateral branch of the RCA (Figure 1A). Thrombosuction and stenting of the occluded branch was performed successfully (Figure 1C). In order to confirm the origin and course of the anomalous LMCA, multi-slice computerized tomography (MSCT) of the heart was performed (Figure 2). The results showed the anomalous LMCA originating from the ostium of the RCA and passing the interventricular septum, rather than being intra arterial, then under the right ventricular infundibulum (Figure 3). The anomalous LMCA was classified as R-Ⅱ S subtype (Table 1).

## DISCUSSION

Most coronary artery anomalies are asymptomatic and are usually encountered as coincidental findings during coronary angiography or autopsy[1]. The most commonly seen coronary artery anomaly include the left anterior descending and ramus circumflex (RCx) arteries arising from separate ostia in the left sinus of Valsalva. The RCx artery arising from the right sinus of Valsalva, the RCA arising from the left sinus of Valsalva, and coronary artery fistulae are also commonly seen. An isolated SCA anomaly is one of the most rarely seen coronary anomalies[3]. These coronary anomalies are classified by Lipton according to the site of origin from the left and right coronary arteries, the anatomical distribution on the ventricular surface, and according to the relationship with the ascending aorta and the pulmonary artery (Table 1)[3]. Our case provides an example of a SCA arising from the right sinus of Val-

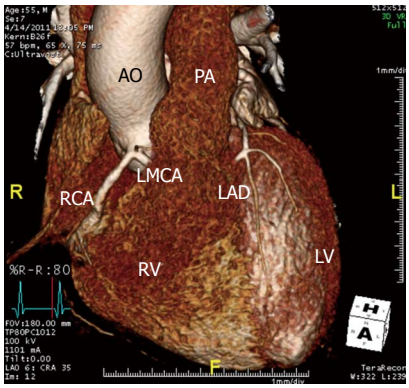



**Figure 3 Reconstructed 3-dimensional image demonstrates that the anomalous left main coronary artery originates from the ostium of the right coronary artery.** The LMCA proceeds intraseptal (R-Ⅱ S subtype). AO: Aorta; LV: Left ventricle; LMCA: Left main coronary artery; RV: Right ventricle; LAD: Left anterior descending; RCA: Right coronary artery; PA: Pulmonary artery.

**Table 1 Angiographic classification of a single coronary artery proposed by Lipton in 1979[3]**

| | | |
|---|---|---|
| **Ostial location** | **R** | Right sinus of Valsalva |
| | **L** | Left sinus of Valsalva |
| **Anatomical distribution** | **I** | Single coronary artery with normal right or left coursing (RC or LC) |
| | **II** | After leaving the right or left sinus the single coronary artery crosses at the base of the heart as a large transverse trunk in order to supply the contralateral coronary artery |
| | **III** | Single coronary artery arising from the right sinus, with the left anterior descending and circumflex arteries from separate coronary artery trunks instead of a single trunk immediately at the exit |
| **Course of the transfer branch** | **A** | Anterior to the large vessels (anterior to the right ventricle) |
| | **B** | Between the aorta and pulmonary artery |
| | **P** | Posterior to the large vessels |
| | **S** | Septal type (above the interventricular septum) |
| | **C** | Combined type |

salva and which had an initial common trunk that gave rise to both the RCA and a long LMCA which followed a prepulmonic intraseptal course (R-Ⅱ S subtype), which is rare and non-malignant[4]. In patients with a SCA and an intra arterial course, sudden death may take place since the coronary artery is compressed between the aorta and the pulmonary artery during vigorous exercise[4].

Coronary angiography is the gold standard for the evaluation of coronary artery disease. However, in the case of coronary anomalies, further evaluation by MSCT or cardiac magnetic resonance imaging is recommended to determine the course of the anomaly and prognosis. The excellent spatial resolution of MSCT makes this technique very suitable to detect the relationship of the anomalous vessels with the aorta, pulmonary artery and cardiac structures[5]. It is a safe technique and provides detailed 3-dimensional reconstructions that may be difficult to obtain with invasive angiography.

In our patient, we diagnosed the SCA by coronary angiography and further delineated the course of the anomalous coronary artery in relation to the aorta and pulmonary artery by MSCT. The management of patients with a SCA includes a conservative approach in most patients, but in the case of an intra arterial course, coronary artery bypass grafting is the treatment of choice to prevent sudden death[5].

The incidence of a LMCA originating from the ostium of the RCA is very low (0.05%). Our case of a 55-year old male patient with this coronary anomaly underwent MSCT to confirm the origin. The anomalous LMCA passed the interventricular septum and therefore was classified as R-Ⅱ S subtype according to Lipton's classification.

## REFERENCES

1 **Yamanaka O**, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. *Cathet Cardiovasc Diagn* 1990; **21**: 28-40
2 **Desmet W**, Vanhaecke J, Vrolix M, Van de Werf F, Piessens J, Willems J, de Geest H. Isolated single coronary artery: a review of 50,000 consecutive coronary angiographies. *Eur Heart J* 1992; **13**: 1637-1640
3 **Lipton MJ**, Barry WH, Obrez I, Silverman JF, Wexler L. Isolated single coronary artery: diagnosis, angiographic classification, and clinical significance. *Radiology* 1979; **130**: 39-47
4 **Basso C**, Corrado D, Thiene G. Congenital coronary artery anomalies as an important cause of sudden death in the young. *Cardiol Rev* 2001; **9**: 312-317
5 **Thomas D**, Salloum J, Montalescot G, Drobinski G, Artigou JY, Grosgogeat Y. Anomalous coronary arteries coursing between the aorta and pulmonary trunk: clinical indications for coronary artery bypass. *Eur Heart J* 1991; **12**: 832-834

**S- Editor** Cheng JX **L- Editor** Cant MR **E- Editor** Zhang DN

World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
wjc@wjgnet.com
www.wjgnet.com

*World J Cardiol* 2012 August 26; 4(8): I
ISSN 1949-8462 (online)




# Acknowledgments to reviewers of *World Journal of Cardiology*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Cardiology*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

**Gani Bajraktari, Professor,** Service of Cardiology, University Clinical Centre of Kosova, Prishtina 10000, Yugoslavia

**Paul Erne, MD, Professor, Head,** Department of Cardiology, Luzerner Kantonsspital, CH-6000 Luzern 16, Switzerland

**Dr. Shinro Matsuo,** Kanazawa University, 13-1 Takaramachi, Kanazawa 920-8641, Japan

**Brian Olshansky, MD, Professor** of Medicine, Cardiac Electrophysiology, University of Iowa Hospitals, 200 Hawkins Drive, Room 4426a JCP, Iowa City, IA 52242, United States

**Zhonghua Sun, Professor,** Department of Medical Imaging, Curtin University of Technology, Kent Street, Perth 6102, Australia

**Masamichi Takano, MD, PhD,** Cardiovascular Center, Chiba-Hokusoh Hospital, Nippon Medical School, 1715 Kamakari, Imba, Chiba 270-1694, Japan

**Hiroki Teragawa, MD, PhD,** Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

**Richard G Trohman, Professor** of Medicine, Rush University Medical Center, 1653 West Congress Parkway, Room 983 Jelke, Chicago, IL 60612, United States

**Hiroyasu Ueda, MD, PhD,** Department of Cardiology, Sumitomo Hospital, 5-3-20, Nakanoshima, Kita-ku, Osaka 530-0005, Japan

World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
wjc@wjgnet.com
www.wjgnet.com

*World J Cardiol* 2012 August 26; 4(8): I
ISSN 1949-8462 (online)




## Events Calendar 2012

January 18-21, 2012
Ninth Gulf Heart Association Conference
Muscat, Oman

January 27, 2012
ESC Global Scientific Activities at the 23rd Annual Conference of the Saudi Heart Association
Riyadh, Saudi Arabia

January 29–31, 2012
Integrated management of acute and chronic coronary artery disease
Innsbruck, Austria

January 30, 2012
Webinar on "Best of Euroecho 2011"
Sophia Antipolis, France

February 1-3, 2012
American Heart Association and American Stroke Association International Stroke Conference 2012
New Orleans, Louisiana, United States

February 3-5, 2012
6th Asian-Pacific Congress Of Heart Failure 2012
Chiang Mai, Thailand

February 9, 2012
4th British Society for Heart Failure Medical Training Meeting
London, United Kingdom

February 23–25, 2012
Advanced Invasive Cardiac Electrophysiology
Sophia Antipolis, France

February 24–26, 2012
International Congress of Cardiology
Hong Kong, China

February 28, 2012
Echocardiography evaluation of patient with multivalvular disease
Sophia Antipolis, France

February 29-March 3, 2012
Winter ISHNE 2012
Zakopane, Poland

March 8–10, 2012
Cardiac Pacing, ICD and Cardiac Resynchronisation
Vienna, Austria

March 8–10, 2012
24th Colombian Congress of Cardiology and Cardiovascular Surgery
Cali, Colombia

March 10-11, 2012
23rd International Meeting "Cardiology Today"
Limassol, Cyprus

March 14-18, 2012
Ninth Mediterranean Meeting on Hypertension and Atherosclerosis
Antalya, Turkey

March 15-17, 2012
e-Cardiology 2012
Osijek, Croatia

March 15-18, 2012
China Interventional Therapeutics 2012-CIT
Beijing, China

March 16-17, 2012
12th Annual Spring Meeting on Cardiovascular Nursing
Copenhagen, Denmark

March 16-17, 2012
3rd European Meeting: Adult Congenital Heart Disease
Munich, Germany

March 16-18, 2012
JCS2012 - The 76th Annual Scientific Meeting
Fukuoka, Japan

March 20–23, 2012
32nd International Symposium on Intensive Care and Emergency Medicine
Brussels, Belgium

March 25-29, 2012
16th International Symposium On Atherosclerosis 2012
Sydney, Australia

March 28–31, 2012
Rome Cardiology Forum 2012
Rome, Italy

March 28–31, 2012
Annual Spring Meeting of the Finnish Cardiac Society 2012
Helsinki, Finland

March 30-April 1, 2012
Frontiers In CardioVascular Biology 2012
London, United Kingdom

April 5-7, 2012
EAE Teaching Course on New echocardiographic techniques for myocardial function imaging
Sofia, Bulgaria

April 12-14, 2012
Cardiovascular Risk Reduction: Leading The Way In Prevention 2012
National Harbor, MD, USA

April 12-15, 2012
NHAM Annual Scientific Meeting 2012
Kuala Lumpur, Malaysia

April 18-21, 2012
World Congress of Cardiology Scientific Sessions 2012
Dubai, United Arab Emirates

April 19-21, 2012
Delivering Patient Care in Heart Failure
Sophia Antipolis, France

April 20-22, 2012
7th Clinical Update on Cardiac MRI and CT
Cannes, France

April 25-27, 2012
Angioplasty Summit 2012
Seoul, South Korea

April 25-28, 2012
The 61st International Congress of the European Society of Cardiovascular and Endovascular Surgery
Dubrovnik, Croatia

April 28-29, 2012
24th Annual Scientific Meeting of the SCS
Singapore, Singapore

May 3–5, 2012
EuroPRevent 2012
Dublin, Ireland

May 15–18, 2012
EuroPCR Congress 2012
Paris, France

May 17-20, 2012
2nd International Meeting On Cardiac Problems In Pregnancy 2012
Berlin, Germany

May 19-22, 2012
Heart Failure 2012
Belgrade, Serbia

May 23-26, 2012
46th Annual meeting of the Association for European Pediatric and Congenital Cardiology
Istanbul, Turkey

May 26-27, 2012
Cardiovascular Spring Meeting 2012
Vienna, Austria

June 7–9, 2012
6th Congress of Asian Society of Cardiovascular Imaging
Bangkok, Thailand

June 7-9, 2012
6th Congress of Asian Society of Cardiovascular Imaging 2012
Bangkok, Thailand

June 15–17, 2012
13th Annual Cardiology Update
Bhurban, Pakistan

June 21-24, 2012
10th International Pulmonary Hypertension Conference and Scientific Sessions 2012
Orlando, Florida, United States

July 19-22, 2012
13th Annual South African Heart Congress
Sun City, South Africa

August 16-19, 2012
60th annual scientific meeting of CSANZ
Brisbane, Australia

August 25-29, 2012
ESC Congress 2012
Munich, Germany

September 29-October 4, 2012
International Society of Hypertension 24th Annual Scientific Meeting 2012
Sydney, Australia

October 4-6, 2012
Magnetic Resonance in Cardiology
Riva Del Garda, Italy

October 20-23, 2012
Acute Cardiac Care 2012
Istanbul, Turkey

World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
wjc@wjgnet.com
www.wjgnet.com

*World J Cardiol* 2012 August 26; 4(8): I-V
ISSN 1949-8462 (online)




## GENERAL INFORMATION

*World Journal of Cardiology* (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a monthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 362 experts in cardiology from 43 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

### *Maximization of personal benefits*

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJC* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article *via* online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJC* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJC* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

### *Aims and scope*

The major task of *WJC* is to rapidly report the most recent developments in the research by the cardiologists. *WJC* accepts papers on the following aspects related to cardiology: arrhythmias, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, paediatrics, nursing, and health promotion. We also encourage papers that cover all other areas of cardiology as well as basic research.

### *Columns*

The columns in the issues of *WJC* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in cardiology; (9) Brief Articles: To briefly report the novel and innovative findings in cardiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJC*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of cardiology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in cardiology.

### *Name of journal*

*World Journal of Cardiology*

### *ISSN*

ISSN 1949-8462 (online)

### *Editor-in-chief*



### *Editorial office*

Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: wjc@wjgnet.com
http://www.wjgnet.com

***Indexed and Abstracted in***
PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.

***Published by***
Baishideng Publishing Group Co., Limited

## SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

***Biostatistical editing***
Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

***Conflict-of-interest statement***
In the interests of transparency and to help reviewers assess any potential bias, *WJC* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

***Statement of informed consent***
Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

***Statement of human and animal rights***
When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

## SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

***Online submissions***
Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/esps/. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1949-8462/g_info_20100316161927.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjc@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

## MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

### *Title page*

**Title:** Title should be less than 12 words.

**Running title:** A short running title of less than 6 words should be provided.

**Authorship:** Authorship credit should be in accordance with the standard proposed by ICMJE, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

**Institution:** Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

**Author contributions:** The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

**Supportive foundations:** The complete name and number of supportive foundations should be provided, e.g. Supported by National Natural Science Foundation of China, No. 30224801

**Correspondence to:** Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

**Telephone and fax:** Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-85381892 Fax: +86-10-85381893

**Peer reviewers:** All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJC*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

### *Abstract*

There are unstructured abstracts (no less than 256 words) and structured abstracts (no less than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no less than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no less than 140 words); RESULTS (no less than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

### *Key words*

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

### *Text*

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312194155.htm.

### *Illustrations*

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

### *Tables*

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

### *Notes in tables and illustrations*

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as $^{1}$F, $^{2}$F, $^{3}$F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

### *Acknowledgments*

Brief acknowledgments of persons who have made genuine con-

tributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

## REFERENCES

### *Coding system*

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

### *PMID and DOI*

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

### *Style for journal references*

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

### *Style for book references*

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

### *Format*

**Journals**

*English journal article (list all authors and include the PMID where applicable)*

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

*Chinese journal article (list all authors and include the PMID where applicable)*

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

*In press*

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

*Organization as author*

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

*No author given*

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

*Volume with supplement*

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

*Issue with no volume*

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

*No volume or issue*

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

**Books**

*Personal author(s)*

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

*Author(s) and editor(s)*

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

*Conference proceedings*

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

*Conference paper*

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal** (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

**Patent** (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

### *Statistical data*

Write as mean ± SD or mean ± SE.

### *Statistical expression*

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as $\chi^2$ (in Greek), related coefficient as *r* (in italics), degree of freedom as $\upsilon$ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

### *Units*

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h,

blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; $CO_2$ volume fraction, 50 mL/L $CO_2$, not 5% $CO_2$; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312200347.htm.

***Abbreviations***

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

***Italics***

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

***Examples for paper writing***

**Editorial:** http://www.wjgnet.com/1949-8462/g_info_20100312192220.htm

**Frontier:** http://www.wjgnet.com/1949-8462/g_info_20100312192753.htm

**Topic highlight:** http://www.wjgnet.com/1949-8462/g_info_20100312192932.htm

**Observation:** http://www.wjgnet.com/1949-8462/g_info_20100312193224.htm

**Guidelines for basic research:** http://www.wjgnet.com/1949-8462/g_info_20100312193436.htm

**Guidelines for clinical practice:** http://www.wjgnet.com/1949-8462/g_info_20100312193624.htm

**Review:** http://www.wjgnet.com/1949-8462/g_info_20100312193839.htm

**Original articles:** http://www.wjgnet.com/1949-8462/g_info_20100312194155.htm

**Brief articles:** http://www.wjgnet.com/1949-8462/g_info_20100312194443.htm

**Case report:** http://www.wjgnet.com/1949-8462/g_info_20100312194652.htm

**Letters to the editor:** http://www.wjgnet.com/1949-8462/g_info_20100312195004.htm

**Book reviews:** http://www.wjgnet.com/1949-8462/g_info_20100312195306.htm

**Guidelines:** http://www.wjgnet.com/1949-8462/g_info_20100312195423.htm

## SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of *WJC*. The revised version including manuscript and high-resolution image figures (if any) should be re-submited online (http://www.wjgnet.com/esps/). The author should send the copyright transfer letter, responses to the reviewers, English language Grade B certificate (for non-native speakers of English) and final manuscript checklist to wjc@wjgnet.com.

***Language evaluation***

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

***Copyright assignment form***

Please download a Copyright assignment form from http://www.wjgnet.com/1949-8462/g_info_20100312200118.htm.

***Responses to reviewers***

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312195923.htm.

***Proof of financial support***

For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

***Links to documents related to the manuscript***

*WJC* will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

***Science news releases***

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

***Publication fee***

*WJC* is an international, peer-reviewed, Open-Access, online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 600 USD per article. Editorial, topic highlights, book reviews and letters to the editor are published free of charge.