

WJG

World Journal of Gastroenterology®

Indexed and Abstracted in:

Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Digital Object Identifier. ISI, Thomson Reuters, 2009 Impact Factor: 2.092 (33/65 Gastroenterology and Hepatology).

Volume 16 Number 47
December 21, 2010

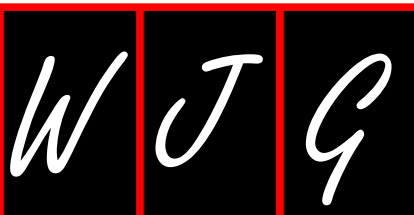
World J Gastroenterol
2010 December 21; 16(47): 5907-6034

Online Submissions

www.wjgnet.com/1007-9327/office
www.wjgnet.com

Printed on Acid-free Paper

世界胃肠病学杂志



Editorial Board

2010-2013

The *World Journal of Gastroenterology* Editorial Board consists of 1144 members, representing a team of worldwide experts in gastroenterology and hepatology. They are from 60 countries, including Albania (1), Argentina (8), Australia (29), Austria (14), Belgium (12), Brazil (10), Brunei Darussalam (1), Bulgaria (2), Canada (20), Chile (3), China (69), Colombia (1), Croatia (2), Cuba (1), Czech (4), Denmark (8), Ecuador (1), Egypt (2), Estonia (2), Finland (8), France (24), Germany (75), Greece (14), Hungary (10), India (26), Iran (6), Ireland (7), Israel (12), Italy (101), Japan (112), Jordan (1), Kuwait (1), Lebanon (3), Lithuania (2), Malaysia (1), Mexico (10), Moldova (1), Netherlands (29), New Zealand (2), Norway (11), Pakistan (2), Poland (11), Portugal (4), Romania (3), Russia (1), Saudi Arabia (3), Serbia (3), Singapore (10), South Africa (2), South Korea (32), Spain (38), Sweden (18), Switzerland (11), Thailand (1), Trinidad and Tobago (1), Turkey (24), United Arab Emirates (2), United Kingdom (82), United States (249), and Uruguay (1).

HONORARY EDITORS-IN-CHIEF

James L Boyer, *New Haven*
Ke-Ji Chen, *Beijing*
Martin H Floch, *New Haven*
Emmet B Keeffe, *Palo Alto*
Geng-Tao Liu, *Beijing*
Lein-Ray Mo, *Tainan*
Eamonn M Quigley, *Cork*
Rafiq A Sheikh, *Sacramento*
Nicholas J Talley, *Rochester*
Ming-Lung Yu, *Kaohsiung*

PRESIDENT AND EDITOR-IN-CHIEF

Lian-Sheng Ma, *Beijing*

ACADEMIC EDITOR-IN-CHIEF

Tauseef Ali, *Oklahoma City*
Mauro Bortolotti, *Bologna*
Tarkan Karakan, *Ankara*
Weekitt Kittisupamongkol, *Bangkok*
Anastasios Koulaouzidis, *Edinburgh*
Bo-Rong Pan, *Xi'an*
Sylvia LF Pender, *Southampton*
Max S Petrov, *Auckland*
George Y Wu, *Farmington*

STRATEGY ASSOCIATE EDITORS-IN-CHIEF

Peter Draganov, *Florida*
Hugh J Freeman, *Vancouver*
Maria C Gutiérrez-Ruiz, *Mexico*
Kazuhiro Hanazaki, *Kochi*
Akio Inui, *Kagoshima*
Kalpesh Jani, *Baroda*
Javier S Martin, *Punta del Este*

Natalia A Osna, *Omaha*
Wei Tang, *Tokyo*
Alan BR Thomson, *Edmonton*
Harry HX Xia, *Hanover*
Jesus K Yamamoto-Furusho, *Mexico*
Yoshio Yamaoka, *Houston*

ASSOCIATE EDITORS-IN-CHIEF

You-Yong Lu, *Beijing*
John M Luk, *Singapore*
Hiroshi Shimada, *Yokohama*

GUEST EDITORIAL BOARD MEMBERS

Chien-Jen Chen, *Taipei*
Yang-Yuan Chen, *Changhua*
Jen-Hwey Chiu, *Taipei*
Seng-Kee Chuah, *Kaohsiung*
Wan-Long Chuang, *Kaohsiung*
Ming-Chih Hou, *Taipei*
Kevin Cheng-Wen Hsiao, *Taipei*
Po-Shiuan Hsieh, *Taipei*
Tsung-Hui Hu, *Kaohsiung*
Wen-Hsin Huang, *Taichung*
Chao-Hung Hung, *Kaohsiung*
I-Rue Lai, *Taipei*
Teng-Yu Lee, *Taichung*
Ching Chung Lin, *Taipei*
Hui-Kang Liu, *Taipei*
Hon-Yi Shi, *Kaohsiung*
Chih-Chi Wang, *Kaohsiung*
Jin-Town Wang, *Taipei*
Cheng-Shyong Wu, *Chia-Yi*
Jaw-Ching Wu, *Taipei*
Jiunn-Jong Wu, *Tainan*
Ming-Shiang Wu, *Taipei*

Ta-Sen Yeh, *Taoyuan*
Hsu-Heng Yen, *Changhua*
Ming-Whei Yu, *Taipei*

MEMBERS OF THE EDITORIAL BOARD



Albania

Bashkim Resuli, *Tirana*



Argentina

Julio H Carri, *Córdoba*
Eduardo de Santibañes, *Buenos Aires*
Bernardo Frider, *Buenos Aires*
Carlos J Pirola, *Buenos Aires*
Bernabe Matias Quesada, *Buenos Aires*
Silvia Sookoian, *Buenos Aires*
Adriana M Torres, *Rosario*
Maria Ines Vaccaro, *Buenos Aires*



Australia

Leon Anton Adams, *Nedlands*
Richard Anderson, *Victoria*
Minoti V Apte, *New South Wales*
Andrew V Biankin, *Sydney*
Filip Braet, *Sydney*
Christopher Christophi, *Melbourne*
Philip G Dinning, *Koagarah*
Guy D Eslick, *Sydney*
Michael A Fink, *Melbourne*

Robert JL Fraser, *Daw Park*
 Jacob George, *Westmead*
 Mark D Gorrell, *Sydney*
 Alexander G Heriot, *Melbourne*
 Michael Horowitz, *Adelaide*
 John E Kellow, *Sydney*
 William Kemp, *Melbourne*
 Finlay A Macrae, *Victoria*
 Daniel Markovich, *Brisbane*
 Vance Matthews, *Melbourne*
 Phillip S Oates, *Perth*
 Shan Rajendra, *Tasmania*
 Rajvinder Singh, *Elizabeth Vale*
 Ross C Smith, *Sydney*
 Kevin J Spring, *Brisbane*
 Nathan Subramaniam, *Brisbane*
 Phil Sutton, *Melbourne*
 Cuong D Tran, *North Adelaide*
 Debbie Trinder, *Fremantle*
 David Ian Watson, *Bedford Park*



Austria

Herwig R Cerwenka, *Graz*
 Ashraf Dahaba, *Graz*
 Peter Ferenci, *Vienna*
 Valentin Fuhrmann, *Vienna*
 Alfred Gangl, *Vienna*
 Alexander M Hirschl, *Wien*
 Kurt Lenz, *Linz*
 Dietmar Öfner, *Salzburg*
 Markus Peck-Radosavljevic, *Vienna*
 Markus Raderer, *Vienna*
 Stefan Riss, *Vienna*
 Georg Roth, *Vienna*
 Michael Trauner, *Graz*
 Thomas Wild, *Kapellerfeld*



Belgium

Rudi Beyaert, *Gent*
 Benedicte Y De Winter, *Antwerp*
 Inge I Depoortere, *Leuven*
 Olivier Detry, *Liège*
 Philip Meuleman, *Ghent*
 Marc Peeters, *De Pintelaan*
 Freddy Penninckx, *Leuven*
 Jean-Yves L Reginster, *Liège*
 Mark De Ridder, *Brussels*
 Etienne M Sokal, *Brussels*
 Kristin Verbeke, *Leuven*
 Eddie Wisse, *Keerbergen*



Brazil

José LF Caboclo, *São José do Rio Preto*
 Roberto J Carvalho-Filho, *São Paulo*
 Jaime Natan Eisig, *São Paulo*
 Andre Castro Lyra, *Salvador*
 Marcelo Lima Ribeiro, *Braganca Paulista*
 Joao Batista Teixeira Rocha, *Santa Maria*
 Heitor Rosa, *Goiania*
 Damiao C Moraes Santos, *Rio de Janeiro*
 Ana Cristina Simões e Silva, *Belo Horizonte*
 Eduardo Garcia Vilela, *Belo Horizonte*



Brunei Darussalam

Vui Heng Chong, *Bandar Seri Begawan*



Bulgaria

Zahariy Krastev, *Sofia*
 Mihaela Petrova, *Sofia*



Canada

Alain Bitton, *Montreal*
 Michael F Byrne, *Vancouver*
 Kris Chadee, *Calgary*
 Wangxue Chen, *Ottawa*
 Ram Prakash Galwa, *Ottawa*
 Philip H Gordon, *Montreal*
 Waliul Khan, *Ontario*
 Qiang Liu, *Saskatoon*
 John K Marshall, *Ontario*
 Andrew L Mason, *Alberta*
 Kostas Pantopoulos, *Quebec*
 Nathalie Perreault, *Sherbrooke*
 Baljinder Singh Salh, *Vancouver*
 Eldon Shaffer, *Calgary*
 Martin Storr, *Calgary*
 Pingchang Yang, *Hamilton*
 Eric M Yoshida, *Vancouver*
 Claudia Zwingmann, *Montreal*



Chile

Marcelo A Beltran, *La Serena*
 Xabier De Aretxabala, *Santiago*
 Silvana Zanlungo, *Santiago*



China

Hui-Jie Bian, *Xi'an*
 San-Jun Cai, *Shanghai*
 Guang-Wen Cao, *Shanghai*
 Xiao-Ping Chen, *Wuhan*
 Chi-Hin Cho, *Hong Kong*
 Zong-Jie Cui, *Beijing*
 Jing-Yuan Fang, *Shanghai*
 De-Liang Fu, *Shanghai*
 Ze-Guang Han, *Shanghai*
 Chun-Yi Hao, *Beijing*
 Ming-Liang He, *Hong Kong*
 Ching-Lung Lai, *Hong Kong*
 Simon Law, *Hong Kong*
 Yuk-Tong Lee, *Hong Kong*
 En-Min Li, *Shantou*
 Fei Li, *Beijing*
 Yu-Yuan Li, *Guangzhou*
 Zhao-Shen Li, *Shanghai*
 Xing-Hua Lu, *Beijing*
 Yi-Min Mao, *Shanghai*
 Qin Su, *Beijing*
 Paul Kwong-Hang Tam, *Hong Kong*
 Yuk Him Tam, *Hong Kong*
 Ren-Xiang Tan, *Nanjing*
 Wei-Dong Tong, *Chongqing*
 Eric WC Tse, *Hong Kong*

Fu-Sheng Wang, *Beijing*
 Xiang-Dong Wang, *Shanghai*
 Nathalie Wong, *Hong Kong*
 Justin CY Wu, *Hong Kong*
 Wen-Rong Xu, *Zhenjiang*
 An-Gang Yang, *Xi'an*
 Wei-Cheng You, *Beijing*
 Chun-Qing Zhang, *Jinan*
 Jian-Zhong Zhang, *Beijing*
 Xiao-Peng Zhang, *Beijing*
 Xuan Zhang, *Beijing*



Colombia

Germán Campuzano-Maya, *Medellín*



Croatia

Tamara Cacev, *Zagreb*
 Marko Duvnjak, *Zagreb*



Cuba

Damian C Rodriguez, *Havana*



Czech

Jan Bures, *Hradec Kralove*
 Milan Jirsa, *Praha*
 Marcela Kopacova, *Hradec Kralove*
 Pavel Trunečka, *Prague*



Denmark

Leif Percival Andersen, *Copenhagen*
 Asbjørn M Drewes, *Aalborg*
 Morten Frisch, *Copenhagen*
 Jan Mollenhauer, *Odense*
 Morten Hylander Møller, *Holte*
 Søren Rafaelsen, *Vejle*
 Jorgen Rask-Madsen, *Skodsborg*
 Peer Wille-Jørgensen, *Copenhagen*



Ecuador

Fernando E Sempértogui, *Quito*



Egypt

Zeinab Nabil Ahmed, *Cairo*
 Hussein M Atta, *El-Minia*



Estonia

Riina Salupere, *Tartu*
 Tamara Vorobjova, *Tartu*



Finland

Saila Kauhanen, *Turku*

Thomas Kietzmann, *Oulu*
 Kaija-Leena Kolho, *Helsinki*
 Jukka-Pekka Mecklin, *Jyväskylä*
 Minna Nyström, *Helsinki*
 Pauli Antero Puolakkainen, *Turku*
 Juhani Sand, *Tampere*
 Lea Veijola, *Helsinki*



France

Claire Bonithon-Kopp, *Dijon*
 Lionel Bueno, *Toulouse*
 Sabine Colnot, *Paris*
 Catherine Daniel, *Lille Cedex*
 Alexis Desmoulière, *Limoges*
 Thabut Dominique, *Paris*
 Francoise L Fabiani, *Angers*
 Jean-Luc Faucheron, *Grenoble*
 Jean Paul Galmiche, *Nantes cedex*
 Boris Guiu, *Dijon*
 Paul Hofman, *Nice*
 Laurent Huwart, *Paris*
 Juan Iovanna, *Marseille*
 Abdel-Majid Khatib, *Paris*
 Philippe Lehours, *Bordeaux*
 Flavio Maina, *Marseille*
 Patrick Marcellin, *Paris*
 Rene Gerolami Santandera, *Marseille*
 Annie Schmid-Alliana, *Nice cedex*
 Alain L Servin, *Châtenay-Malabry*
 Stephane Supiot, *Nantes*
 Baumert F Thomas, *Strasbourg*
 Jean-Jacques Tuech, *Rouen*
 Frank Zerbib, *Bordeaux Cedex*



Germany

Erwin Biecker, *Siegburg*
 Hubert Blum, *Freiburg*
 Thomas Bock, *Tuebingen*
 Dean Bogoevski, *Hamburg*
 Elfriede Bollschweiler, *Köln*
 Jürgen Borlak, *Hannover*
 Christa Buechler, *Regensburg*
 Jürgen Büning, *Lübeck*
 Elke Cario, *Essen*
 Bruno Christ, *Halle/Saale*
 Christoph F Dietrich, *Bad Mergentheim*
 Ulrich R Fölsch, *Kiel*
 Nikolaus Gassler, *Aachen*
 Markus Gerhard, *Munich*
 Dieter Glebe, *Giessen*
 Ralph Graeser, *Freiburg*
 Axel M Gressner, *Aachen*
 Nils Habbe, *Marburg*
 Thilo Hackert, *Heidelberg*
 Wolfgang Hagmann, *Heidelberg*
 Dirk Haller, *Freising*
 Philip D Hard, *Giessen*
 Claus Hellerbrand, *Regensburg*
 Klaus R Herrlinger, *Stuttgart*
 Eberhard Hildt, *Berlin*
 Andrea Hille, *Goettingen*
 Joerg C Hoffmann, *Berlin*
 Philippe N Khalil, *Munich*
 Andrej Khandoga, *Munich*
 Jorg Kleeff, *Munich*
 Ingmar Königsrainer, *Tübingen*
 Peter Konturek, *Erlangen*

Stefan Kubicka, *Hannover*
 Joachim Labenz, *Siegen*
 Michael Linnebacher, *Rostock*
 Jutta Elisabeth Lüttges, *Riegelsberg*
 Peter Malfertheiner, *Magdeburg*
 Oliver Mann, *Hamburg*
 Peter N Meier, *Hannover*
 Sabine Mihm, *Göttingen*
 Klaus Mönkemüller, *Bottrop*
 Jonas Mudter, *Erlangen*
 Sebastian Mueller, *Heidelberg*
 Robert Obermaier, *Freiburg*
 Matthias Ocker, *Erlangen*
 Stephan Johannes Ott, *Kiel*
 Gustav Paumgartner, *Munich*
 Christoph Reichel, *Bad Brückenau*
 Markus Reiser, *Bochum*
 Steffen Rickes, *Magdeburg*
 Elke Roeb, *Giessen*
 Christian Rust, *Munich*
 Hans Scherubl, *Berlin*
 Martin K Schilling, *Homburg*
 Joerg F Schlaak, *Essen*
 Rene Schmidt, *Freiburg*
 Andreas G Schreyer, *Regensburg*
 Karsten Schulmann, *Bochum*
 Henning Schulze-Bergkamen, *Mainz*
 Manfred V Singer, *Mannheim*
 Jens Standop, *Bonn*
 Jurgen M Stein, *Frankfurt*
 Ulrike S Stein, *Berlin*
 Wolfgang R Stremmel, *Heidelberg*
 Harald F Teutsch, *Ulm*
 Hans L Tillmann, *Leipzig*
 Christian Trautwein, *Aachen*
 Joerg Trojan, *Frankfurt*
 Arndt Vogel, *Hannover*
 Siegfried Wagner, *Deggendorf*
 Frank Ulrich Weiss, *Greifswald*
 Fritz von Weizsäcker, *Berlin*
 Thomas Wex, *Magdeburg*
 Stefan Wirth, *Wuppertal*
 Marty Zdichavsky, *Tübingen*



Greece

Helen Christopoulou-Aletra, *Thessaloniki*
 T Choli-Papadopoulos, *Thessaloniki*
 Tsianos Epameinondas, *Ioannina*
 Ioannis Kanellos, *Thessaloniki*
 Elias A Kouroumalis, *Heraklion*
 Ioannis E Koutroubakis, *Heraklion*
 Michael Koutsilieris, *Athens*
 Andreas Larentzakis, *Athens*
 Emanuel K Manesis, *Athens*
 Spilios Manolakopoulos, *Athens*
 Konstantinos Mimidis, *Alexandroupolis*
 George Papatheodoridis, *Athens*
 Spiros Sgouros, *Athens*
 Evangelos Tsiambas, *Ag Paraskevi Attiki*



Hungary

György M Buzás, *Budapest*
 László Czakó, *Szeged*
 Gyula Farkas, *Szeged*
 Peter Hegyi, *Szeged*
 Peter L Lakatos, *Budapest*

Yvette Mándi, *Szeged*
 Zoltan Rakonczay, *Szeged*
 Ferenc Sipos, *Budapest*
 Zsuzsa Szondy, *Debrecen*
 Gabor Veres, *Budapest*



India

Philip Abraham, *Mumbai*
 Vineet Ahuja, *New Delhi*
 Giriraj Ratan Chandak, *Hyderabad*
 Devinder Kumar Dhawan, *Chandigarh*
 Radha K Dhiman, *Chandigarh*
 Pankaj Garg, *Panchkula*
 Pramod Kumar Garg, *New Delhi*
 Debidas Ghosh, *Midnapore*
 Uday C Ghoshal, *Lucknow*
 Bhupendra Kumar Jain, *Delhi*
 Ashok Kumar, *Lucknow*
 Bikash Medhi, *Chandigarh*
 Sri P Misra, *Allahabad*
 Gopal Nath, *Varanasi*
 Samiran Nundy, *New Delhi*
 Jagannath Palepu, *Mumbai*
 Vandana Panda, *Mumbai*
 Benjamin Perakath, *Tamil Nadu*
 Ramesh Roop Rai, *Jaipur*
 Nageshwar D Reddy, *Hyderabad*
 Barjesh Chander Sharma, *New Delhi*
 Virendra Singh, *Chandigarh*
 Rupjyoti Talukdar, *Guwahati*
 Rakesh Kumar Tandon, *New Delhi*
 Jai Dev Wig, *Chandigarh*



Iran

Mohammad Abdollahi, *Tehran*
 Peyman Adibi, *Isfahan*
 Seyed-Moayed Alavian, *Tehran*
 Seyed Mohsen Dehghani, *Shiraz*
 Reza Malekzadeh, *Tehran*
 Alireza Mani, *Tehran*



Ireland

Billy Bourke, *Dublin*
 Ted Dinan, *Cork*
 Catherine Greene, *Dublin*
 Ross McManus, *Dublin*
 Anthony P Moran, *Galway*
 Marion Rowland, *Dublin*



Israel

Simon Bar-Meir, *Hashomer*
 Alexander Becker, *Afula*
 Abraham R Eliakim, *Haifa*
 Sigal Fishman, *Tel Aviv*
 Boris Kirshtein, *Beer Sheva*
 Eli Magen, *Ashdod*
 Menachem Moshkowitz, *Tel-Aviv*
 Assy Nimer, *Safed*
 Shmuel Odes, *Beer Sheva*
 Mark Pines, *Bet Dagan*
 Ron Shaoul, *Haifa*
 Ami D Sperber, *Beer-Sheva*



Italy

Donato F Altomare, *Bari*
 Piero Amodio, *Padova*
 Angelo Andriulli, *San Giovanni Rotondo*
 Paolo Angeli, *Padova*
 Bruno Annibale, *Rome*
 Paolo Aurello, *Rome*
 Salvatore Auricchio, *Naples*
 Antonio Basoli, *Rome*
 Claudio Bassi, *Verona*
 Gabrio Bassotti, *Perugia*
 Mauro Bernardi, *Bologna*
 Alberto Biondi, *Rome*
 Luigi Bonavina, *Milano*
 Guglielmo Borgia, *Naples*
 Roberto Berni Canani, *Naples*
 Maria Gabriella Caruso, *Bari*
 Fausto Catena, *Bologna*
 Giuseppe Chiarioni, *Vareggio*
 Michele Cicala, *Rome*
 Dario Conte, *Milano*
 Francesco Costa, *Pisa*
 Antonio Craxi, *Palermo*
 Salvatore Cucchiara, *Rome*
 Giuseppe Currò, *Messina*
 Mario M D'Elios, *Florence*
 Mirko D'Onofrio, *Verona*
 Silvio Danese, *Milano*
 Roberto de Franchis, *Milano*
 Paola De Nardi, *Milan*
 Giovanni D De Palma, *Naples*
 Giuliana Decorti, *Trieste*
 Gianlorenzo Dionigi, *Varese*
 Massimo Falconi, *Verona*
 Silvia Fargion, *Milan*
 Giammarco Fava, *Ancona*
 Francesco Feo, *Sassari*
 Alessandra Ferlini, *Ferrara*
 Alessandro Ferrero, *Torino*
 Mirella Fraquelli, *Milan*
 Luca Frulloni, *Verona*
 Giovanni B Gaeta, *Napoli*
 Antonio Gasbarrini, *Rome*
 Edoardo G Giannini, *Genoa*
 Alessandro Granito, *Bologna*
 Fabio Grizzi, *Milan*
 Salvatore Gruttadauria, *Palermo*
 Pietro Invernizzi, *Milan*
 Achille Iolascon, *Naples*
 Angelo A Izzo, *Naples*
 Ezio Laconi, *Cagliari*
 Giovanni Latella, *L'Aquila*
 Massimo Leverro, *Rome*
 Francesco Luzzza, *Catanzaro*
 Lucia Malaguarnera, *Catania*
 Francesco Manguso, *Napoli*
 Pier Mannuccio Mannucci, *Milan*
 Giancarlo Mansueto, *Verona*
 Giulio Marchesini, *Bologna*
 Mara Massimi, *Coppito*
 Giovanni Milito, *Rome*
 Giuseppe Montalto, *Palermo*
 Giovanni Monteleone, *Rome*
 Luca Morelli, *Trento*
 Giovanni Musso, *Torino*
 Mario Nano, *Torino*
 Gerardo Nardone, *Napoli*
 Riccardo Nascimbeni, *Brescia*
 Valerio Nobili, *Rome*
 Fabio Pace, *Milan*
 Nadia Peparini, *Rome*

Marcello Persico, *Naples*
 Mario Pescatori, *Rome*
 Raffaele Pezzilli, *Bologna*
 Alberto Piperno, *Monza*
 Anna C Piscaglia, *Rome*
 Piero Portincasa, *Bari*
 Michele Reni, *Milan*
 Vittorio Ricci, *Pavia*
 Oliviero Riggio, *Rome*
 Mario Rizzetto, *Torino*
 Ballarin Roberto, *Modena*
 Gerardo Rosati, *Potenza*
 Franco Roviello, *Siena*
 Cesare Ruffolo, *Treviso*
 Massimo Rugge, *Padova*
 Marco Scarpa, *Padova*
 Carmelo Scarpignato, *Parma*
 Giuseppe Sica, *Rome*
 Marco Silano, *Rome*
 Pierpaolo Sileri, *Rome*
 Vincenzo Stanghellini, *Bologna*
 Fiorucci Stefano, *Perugia*
 Giovanni Tarantino, *Naples*
 Alberto Tommasini, *Trieste*
 Guido Torzilli, *Rozzano Milan*
 Cesare Tosetti, *Porretta Terme*
 Antonello Trecca, *Rome*
 Vincenzo Villanacci, *Brescia*
 Lucia Ricci Vitiani, *Rome*
 Marco Vivarelli, *Bologna*



Japan

Kyoichi Adachi, *Izumo*
 Yasushi Adachi, *Sapporo*
 Takafumi Ando, *Nagoya*
 Akira Andoh, *Otsu*
 Masahiro Arai, *Tokyo*
 Hitoshi Asakura, *Tokyo*
 Kazuo Chijiwa, *Miyazaki*
 Yuichiro Eguchi, *Saga*
 Itaru Endo, *Yokohama*
 Munechika Enjoji, *Fukuoka*
 Yasuhiro Fujino, *Akashi*
 Mitsuhiro Fujishiro, *Tokyo*
 Kouhei Fukushima, *Sendai*
 Masanori Hatakeyama, *Tokyo*
 Keiji Hirata, *Kitakyushu*
 Toru Hiyama, *Higashihiroshima*
 Masahiro Iizuka, *Akita*
 Susumu Ikehara, *Osaka*
 Kenichi Ikejima, *Bunkyo-ku*
 Yutaka Inagaki, *Kanagawa*
 Hiromi Ishibashi, *Nagasaki*
 Shunji Ishihara, *Izumo*
 Toru Ishikawa, *Niigata*
 Toshiyuki Ishiwata, *Tokyo*
 Hajime Isomoto, *Nagasaki*
 Yoshiaki Iwasaki, *Okayama*
 Satoru Kakizaki, *Gunma*
 Terumi Kamisawa, *Tokyo*
 Mototsugu Kato, *Sapporo*
 Naoya Kato, *Tokyo*
 Takumi Kawaguchi, *Kurume*
 Yohei Kida, *Kainan*
 Shogo Kikuchi, *Aichi*
 Tsuneo Kitamura, *Chiba*
 Takashi Kobayashi, *Tokyo*
 Yasuhiro Koga, *Isehara*
 Takashi Kojima, *Sapporo*
 Norihiro Kokudo, *Tokyo*
 Masatoshi Kudo, *Osaka*
 Shin Maeda, *Tokyo*
 Satoshi Mamori, *Hyogo*
 Atsushi Masamune, *Sendai*
 Yasushi Matsuzaki, *Tsukuba*
 Kenji Miki, *Tokyo*
 Toshihiro Mitaka, *Sapporo*
 Hiroto Miwa, *Hyogo*
 Kotaro Miyake, *Tokushima*
 Manabu Morimoto, *Yokohama*
 Yoshiharu Motoo, *Kanazawa*
 Yoshiaki Murakami, *Hiroshima*
 Yoshiki Murakami, *Kyoto*
 Kunihiko Murase, *Tsushima*
 Akihito Nagahara, *Tokyo*
 Yuji Naito, *Kyoto*
 Atsushi Nakajima, *Yokohama*
 Hisato Nakajima, *Tokyo*
 Hiroki Nakamura, *Yamaguchi*
 Shotaro Nakamura, *Fukuoka*
 Akimasa Nakao, *Nagoya*
 Shuhei Nishiguchi, *Hyogo*
 Mikio Nishioka, *Niihama*
 Keiji Ogura, *Tokyo*
 Susumu Ohmada, *Maebashi*
 Hirohide Ohnishi, *Akita*
 Kenji Okajima, *Nagoya*
 Kazuichi Okazaki, *Osaka*
 Morikazu Onji, *Ehime*
 Satoshi Osawa, *Hamamatsu*
 Hidetsugu Saito, *Tokyo*
 Yutaka Saito, *Tokyo*
 Naoaki Sakata, *Sendai*
 Yasushi Sano, *Chiba*
 Tokihiko Sawada, *Tochigi*
 Tomohiko Shimatan, *Hiroshima*
 Yukihiko Shimizu, *Kyoto*
 Shinji Shimoda, *Fukuoka*
 Yoshio Shirai, *Niigata*
 Masayuki Sho, *Nara*
 Shoichiro Sumi, *Kyoto*
 Hidekazu Suzuki, *Tokyo*
 Masahiro Tajika, *Nagoya*
 Yoshihisa Takahashi, *Tokyo*
 Toshinari Takamura, *Kanazawa*
 Hiroaki Takeuchi, *Kochi*
 Yoshitaka Takuma, *Okayama*
 Akihiro Tamori, *Osaka*
 Atsushi Tanaka, *Tokyo*
 Shinji Tanaka, *Hiroshima*
 Satoshi Tanno, *Hokkaido*
 Shinji Togo, *Yokohama*
 Hitoshi Tsuda, *Tokyo*
 Hiroyuki Uehara, *Osaka*
 Masahito Uemura, *Kashihara*
 Yoshiyuki Ueno, *Sendai*
 Mitsuyoshi Urashima, *Tokyo*
 Takuya Watanabe, *Niigata*
 Satoshi Yamagiwa, *Niigata*
 Taketo Yamaguchi, *Chiba*
 Mitsunori Yamakawa, *Yamagata*
 Takayuki Yamamoto, *Yokkaichi*
 Yutaka Yata, *Maebashi*
 Hiroshi Yoshida, *Tokyo*
 Norimasa Yoshida, *Kyoto*
 Yuichi Yoshida, *Osaka*
 Kentaro Yoshika, *Toyoake*
 Hitoshi Yoshiji, *Nara*
 Katsutoshi Yoshizato, *Higashihiroshima*
 Tomoharu Yoshizumi, *Fukuoka*



Jordan

Ismail Matalka, *Irbid*

**Kuwait**

Islam Khan, *Safat*

**Lebanon**

Bassam N Abboud, *Beirut*
Ala I Sharara, *Beirut*
Rita Slim, *Beirut*

**Lithuania**

Giedrius Barauskas, *Kaunas*
Limas Kupcinskas, *Kaunas*

**Malaysia**

Andrew Seng Boon Chua, *Ipoh*

**Mexico**

Richard A Awad, *Mexico*
Aldo Torre Delgadillo, *Mexico*
Diego Garcia-Compean, *Monterrey*
Paulino M Hernández Magro, *Celaya*
Miguel Angel Mercado, *Distrito Federal*
Arturo Panduro, *Jalisco*
Omar Vergara-Fernandez, *Tlalpan*
Saúl Villa-Trevio, *Mexico*

**Moldova**

Igor Mishin, *Kishinev*

**Netherlands**

Ulrich Beuers, *Amsterdam*
Lee Bouwman, *Leiden*
Albert J Bredenoord, *Nieuwegein*
Lodewijk AA Brosens, *Utrecht*
J Bart A Crusius, *Amsterdam*
Wouter de Herder, *Rotterdam*
Pieter JF de Jonge, *Rotterdam*
Robert J de Knecht, *Rotterdam*
Wendy W Johanna de Leng, *Utrecht*
Annemarie de Vries, *Rotterdam*
James CH Hardwick, *Leiden*
Frank Hoentjen, *Haarlem*
Misha Luyer, *Sittard*
Jeroen Maljaars, *Maastricht*
Gerrit A Meijer, *Amsterdam*
Servaas Morré, *Amsterdam*
Chris JJ Mulder, *Amsterdam*
John Plukker, *Groningen*
Albert Frederik Pull ter Gunne, *Tilburg*
Paul E Sijens, *Groningen*
BW Marcel Spanier, *Arnhem*
Shiri Sverdlov, *Maastricht*
Maarten Tushuizen, *Amsterdam*
Jantine van Baal, *Heidelberglaan*
Astrid van der Velde, *The Hague*
Karel van Erpecum, *Utrecht*
Loes van Keimpema, *Nijmegen*

Robert Christiaan Verdonk, *Groningen*
Erwin G Zoetendal, *Wageningen*

**New Zealand**

Andrew S Day, *Christchurch*

**Norway**

Olav Dalgard, *Oslo*
Trond Peder Flaten, *Trondheim*
Reidar Fossmark, *Trondheim*
Rasmus Goll, *Tromsø*
Ole Høie, *Arendal*
Asle W Medhus, *Oslo*
Espen Melum, *Oslo*
Trine Olsen, *Tromsø*
Eyvind J Paulssen, *Tromsø*
Jon Arne Søreide, *Stavanger*
Kjetil Søreide, *Stavanger*

**Pakistan**

Shahab Abid, *Karachi*
Syed MW Jafri, *Karachi*

**Poland**

Marek Bebenek, *Wroclaw*
Tomasz Brzozowski, *Cracow*
Halina Cichoż-Lach, *Lublin*
Andrzej Dabrowski, *Bialystok*
Hanna Gregorek, *Warsaw*
Marek Hartleb, *Katowice*
Beata Jolanta Jabłońska, *Katowice*
Stanislaw J Konturek, *Krakow*
Jan Kulig, *Krakow*
Dariusz M Lebensztejn, *Bialystok*
Julian Swierczynski, *Gdansk*

**Portugal**

Raquel Almeida, *Porto*
Ana Isabel Lopes, *Lisboa Codex*
Ricardo Marcos, *Porto*
Guida Portela-Gomes, *Estoril*

**Romania**

Dan L Dumitrascu, *Cluj*
Adrian Saftoiu, *Craiova*
Andrada Seicean, *Cluj-Napoca*

**Russia**

Vasiliy I Reshetnyak, *Moscow*

**Saudi Arabia**

Ibrahim A Al Mofleh, *Riyadh*
Abdul-Wahed Meshikhes, *Qatif*
Faisal Sanai, *Riyadh*

**Serbia**

Tamara M Alempijevic, *Belgrade*
Dusan M Jovanovic, *Sremska Kamenica*
Zoran Krivokapic, *Belgrade*

**Singapore**

Madhav Bhatia, *Singapore*
Kong Weng Eu, *Singapore*
Brian Kim Poh Goh, *Singapore*
Khek-Yu Ho, *Singapore*
Kok Sun Ho, *Singapore*
Fock Kwong Ming, *Singapore*
London Lucien Ooi, *Singapore*
Nagarajan Perumal, *Singapore*
Francis Seow-Choen, *Singapore*

**South Africa**

Rosemary Joyce Burnett, *Pretoria*
Michael Kew, *Cape Town*

**South Korea**

Sang Hoon Ahn, *Seoul*
Sung-Gil Chi, *Seoul*
Myung-Gyu Choi, *Seoul*
Hoon Jai Chun, *Seoul*
Yeun-Jun Chung, *Seoul*
Young-Hwa Chung, *Seoul*
Kim Donghee, *Seoul*
Ki-Baik Hahm, *Incheon*
Sun Pyo Hong, *Geonggi-do*
Seong Gyu Hwang, *Seongnam*
Hong Joo Kim, *Seoul*
Jae J Kim, *Seoul*
Jin-Hong Kim, *Suwon*
Nayoung Kim, *Seongnam-si*
Sang Geon Kim, *Seoul*
Seon Hahn Kim, *Seoul*
Sung Kim, *Seoul*
Won Ho Kim, *Seoul*
Jeong Min Lee, *Seoul*
Kyu Taek Lee, *Seoul*
Sang Kil Lee, *Seoul*
Sang Yeoup Lee, *Gyeongsangnam-do*
Yong Chan Lee, *Seoul*
Eun-Yi Moon, *Seoul*
Hyoung-Chul Oh, *Seoul*
Seung Woon Paik, *Seoul*
Joong-Won Park, *Goyang*
Ji Kon Ryu, *Seoul*
Si Young Song, *Seoul*
Marie Yeo, *Suwon*
Byung Chul Yoo, *Seoul*
Dae-Yeul Yu, *Daejeon*

**Spain**

Maria-Angeles Aller, *Madrid*
Raul J Andrade, *Málaga*
Luis Aparisi, *Valencia*
Gloria González Aseguinolaza, *Navarra*
Matias A Avila, *Pamplona*

Fernando Azpiroz, *Barcelona*
 Ramon Bataller, *Barcelona*
 Belén Beltrán, *Valencia*
 Adolfo Benages, *Valencia*
 Josep M Bordas, *Barcelona*
 Lisardo Boscá, *Madrid*
 Luis Bujanda, *San Sebastián*
 Juli Busquets, *Barcelona*
 Matilde Bustos, *Pamplona*
 José Julián calvo Andrés, *Salamanca*
 Andres Cardenas, *Barcelona*
 Antoni Castells, *Barcelona*
 Fernando J Corrales, *Pamplona*
 J EDomínguez-Muñoz, *Santiago de Compostela*
 Juan Carlos Laguna Egea, *Barcelona*
 Isabel Fabregat, *Barcelona*
 Antoni Farré, *Barcelona*
 Vicente Felipo, *Valencia*
 Laureano Fernández-Cruz, *Barcelona*
 Luis Grande, *Barcelona*
 Angel Lanas, *Zaragoza*
 Juan-Ramón Larrubia, *Guadalajara*
 María IT López, *Jaén*
 Juan Macías, *Seville*
 Javier Martin, *Granada*
 José Manuel Martin-Villa, *Madrid*
 Julio Mayol, *Madrid*
 Mireia Miquel, *Sabadell*
 Albert Parés, *Barcelona*
 Jesús M Prieto, *Pamplona*
 Pedro L Majano Rodriguez, *Madrid*
 Joan Roselló-Catafau, *Barcelona*
 Eva Vaquero, *Barcelona*



Sweden

Lars Erik Agréus, *Stockholm*
 Mats Andersson, *Stockholm*
 Roland Andersson, *Lund*
 Mauro D'Amato, *Huddinge*
 Evangelos Kalaitzakis, *Gothenburg*
 Greger Lindberg, *Stockholm*
 Annika Lindblom, *Stockholm*
 Sara Lindén, *Göteborg*
 Hanns-Ulrich Marschall, *Stockholm*
 Pär Erik Myreliid, *Linköping*
 Åke Nilsson, *Lund*
 Helena Nordenstedt, *Stockholm*
 Kjell Öberg, *Uppsala*
 Lars A Pahlman, *Uppsala*
 Stefan G Pierzynowski, *Lund*
 Sara Regnér, *Malmö*
 Bobby Tingstedt, *Lund*
 Zongli Zheng, *Stockholm*



Switzerland

Pascal Bucher, *Geneva*
 Michelangelo Foti, *Geneva*
 Jean L Frossard, *Geneva*
 Andreas Geier, *Zürich*
 Pascal Gervaz, *Geneva*
 Gerd A Kullak-Ublick, *Zürich*
 Fabrizio Montecucco, *Geneva*
 Paul M Schneider, *Zürich*
 Felix Stickel, *Berne*
 Bruno Stieger, *Zürich*
 Inti Zlobec, *Basel*



Trinidad and Tobago

Shivananda Nayak, *Mount Hope*



Turkey

Sinan Akay, *Tekirdag*
 Metin Basaranoglu, *Istanbul*
 Yusuf Bayraktar, *Ankara*
 A Mithat Bozdayi, *Ankara*
 Hayrullah Derici, *Balıkesir*
 Eren Ersoy, *Ankara*
 Mukaddes Esrefoglu, *Malatya*
 Can Goen, *Kutahya*
 Selin Kapan, *Istanbul*
 Aydin Karabacakoglu, *Konya*
 Cuneyt Kayaalp, *Malatya*
 Kemal Kismet, *Ankara*
 Seyfettin Köklü, *Ankara*
 Mehmet Refik Mas, *Etilik-Ankara*
 Osman C Ozdogan, *Istanbul*
 Bülent Salman, *Ankara*
 Orhan Sezgin, *Mersin*
 Ilker Tasci, *Ankara*
 Müge Tecder-Ünal, *Ankara*
 Ahmet Tekin, *Mersin*
 Mesut Tez, *Ankara*
 Ekmel Tezel, *Ankara*
 Özlem Yilmaz, *Izmir*



United Arab Emirates

Fikri M Abu-Zidan, *Al-Ain*
 Sherif M Karam, *Al-Ain*



United Kingdom

Simon Afford, *Birmingham*
 Navneet K Ahluwalia, *Stockport*
 Mohamed H Ahmed, *Southampton*
 Basil Ammori, *Salford*
 Lesley A Anderson, *Belfast*
 Chin Wee Ang, *Liverpool*
 Yeng S Ang, *Wigan*
 Anthony TR Axon, *Leeds*
 Kathleen B Bamford, *London*
 Jim D Bell, *London*
 John Beynon, *Swansea*
 Chris Briggs, *Sheffield*
 Geoffrey Burnstock, *London*
 Alastair D Burt, *Newcastle*
 Jeff Butterworth, *Shrewsbury*
 Jeremy FL Cobbold, *London*
 Jean E Crabtree, *Leeds*
 Tatjana Crnogorac-Jurcevic, *London*
 William Dickey, *Londonderry*
 Sunil Dolwani, *Cardiff*
 Emad M El-Omar, *Aberdeen*
 A M El-Tawil, *Birmingham*
 Charles B Ferguson, *Belfast*
 Andrew Fowell, *Southampton*
 Piers Gatenby, *London*
 Daniel R Gaya, *Edinburgh*
 Anil George, *London*
 Rob Glynne-Jones, *Northwood*
 Jason CB Goh, *Birmingham*
 Gianpiero Gravante, *Leicester*

Brian Green, *Belfast*
 William Greenhalf, *Liverpool*
 Indra N Guha, *Nottingham*
 Stefan G Hübscher, *Birmingham*
 Robin Hughes, *London*
 Pali Hungin, *Stockton*
 Nawfal Hussein, *Nottingham*
 Clement W Imrie, *Glasgow*
 Janusz AZ Jankowski, *Oxford*
 Sharad Karandikar, *Birmingham*
 Peter Karayiannis, *London*
 Shahid A Khan, *London*
 Patricia F Lalor, *Birmingham*
 John S Leeds, *Sheffield*
 Ian Lindsey, *Oxford*
 Hong-Xiang Liu, *Cambridge*
 Dileep N Lobo, *Nottingham*
 Graham MacKay, *Glasgow*
 Mark Edward McAlindon, *Sheffield*
 Anne McCune, *Bristol*
 Donald Campbell McMillan, *Glasgow*
 Giorgina Mieli-Vergani, *London*
 Jamie Murphy, *London*
 Guy Fairbairn Nash, *Poole*
 James Neuberger, *Birmingham*
 Patrick O'Dwyer, *Glasgow*
 Christos Paraskeva, *Bristol*
 Richard Parker, *North Staffordshire*
 Thamara Perera, *Birmingham*
 Kondragunta Rajendra Prasad, *Leeds*
 D Mark Pritchard, *Liverpool*
 Alberto Quaglia, *London*
 Akhilesh B Reddy, *Cambridge*
 Kevin Robertson, *Glasgow*
 Sanchoy Sarkar, *Liverpool*
 John B Schofield, *Kent*
 Marco Senzolo, *Padova*
 Venkatesh Shanmugam, *Derby*
 Paul Sharp, *London*
 Chew Thean Soon, *Manchester*
 Aravind Suppiah, *East Yorkshire*
 Noriko Suzuki, *Middlesex*
 Simon D Taylor-Robinson, *London*
 Frank I Tovey, *London*
 A McCulloch Veitch, *Wolverhampton*
 Vamsi R Velchuru, *Lowestoft*
 Sumita Verma, *Brighton*
 Catherine Walter, *Cheltenham*
 Julian RF Walters, *London*
 Roger Williams, *London*



United States

Kareem M Abu-Elmagd, *Pittsburgh*
 Sami R Achem, *Florida*
 Golo Ahlenstiel, *Bethesda*
 Bhupinder S Anand, *Houston*
 M Ananthanarayanan, *New York*
 Balamurugan N Appakalal, *Minneapolis*
 Dimitrios V Avgerinos, *New York*
 Shashi Bala, *Worcester*
 Anthony J Bauer, *Pittsburgh*
 Kevin E Behrns, *Gainesville*
 Roberto Bergamaschi, *New York*
 Henry J Binder, *New Haven*
 Edmund J Bini, *New York*
 Wojciech Blonski, *Philadelphia*
 Mark Bloomston, *Columbus*
 Edward L Bradley III, *Sarasota*
 Carla W Brady, *Durham*

David A Brenner, *San Diego*
 Adeel A Butt, *Pittsburgh*
 Shi-Ying Cai, *New Haven*
 Justin MM Cates, *Nashville*
 Eugene P Ceppa, *Durham*
 Jianyuan Chai, *Long Beach*
 Ronald S Chamberlain, *Livingston*
 Fei Chen, *Morgantown*
 Xian-Ming Chen, *Omaha*
 Ramsey Chi-man Cheung, *Palo Alto*
 Denesh Chitkara, *East Brunswick*
 Clifford S Cho, *Madison*
 Parimal Chowdhury, *Arkansas*
 John David Christein, *Birmingham*
 Thomas Clancy, *Boston*
 Ana J Coito, *Los Angeles*
 Ricardo Alberto Cruciani, *New York*
 Joseph J Cullen, *Iowa City*
 Mark J Czaja, *New York*
 Mariana D Dabeva, *Bronx*
 Jessica A Davila, *Houston*
 Conor P Delaney, *Cleveland*
 Laurie DeLeve, *Los Angeles*
 Anthony J Demetris, *Pittsburgh*
 Sharon DeMorrow, *Temple*
 Bijan Eghtesad, *Cleveland*
 Yoram Elitsur, *Huntington*
 Mohamad A Eloubeidi, *Alabama*
 Wael El-Rifai, *Nashville*
 Sukru H Emre, *New Haven*
 Giamila Fantuzzi, *Chicago*
 Ashkan Farhadi, *Irvine*
 Ronnie Fass, *Tucson*
 Martín E Fernández-Zapico, *Rochester*
 Alessandro Fichera, *Chicago*
 Josef E Fischer, *Boston*
 Piero Marco Fisichella, *Maywood*
 Fritz Francois, *New York*
 Glenn T Furuta, *Aurora*
 T Clark Gamblin, *Pittsburgh*
 Henning Gerke, *Iowa City*
 Jean-Francois Geschwind, *Baltimore*
 R Mark Ghobrial, *Texas*
 John F Gibbs, *Buffalo*
 Shannon S Glaser, *Temple*
 Ajay Goel, *Dallas*
 Jon C Gould, *Madison*
 Eileen F Grady, *San Francisco*
 James H Grendell, *New York*
 John R Grider, *Richmond*
 Anna S Gukovskaya, *Los Angeles*
 Chakshu Gupta, *St. Joseph*
 Grigoriy E Gurvits, *New York*
 Hai-Yong Han, *Phoenix*
 Yuan-Ping Han, *Los Angeles*
 Imran Hassan, *Springfield*
 Charles P Heise, *Madison*
 Lisa J Herrinton, *Oakland*
 Oscar Joe Hines, *Los Angeles*
 Samuel B Ho, *San Diego*
 Steven Hochwald, *Gainesville*
 Richard Hu, *Los Angeles*
 Eric S Hungness, *Chicago*
 Jamal A Ibdah, *Columbia*
 Atif Iqbal, *Omaha*
 Hartmut Jaeschke, *Tucson*
 Donald M Jensen, *Chicago*
 Robert Jensen, *Bethesda*
 Leonard R Johnson, *Memphis*
 Andreas M Kaiser, *Los Angeles*
 JingXuan Kang, *Charlestown*
 John Y Kao, *Michigan*
 Randeep Singh Kashyap, *New York*
 Rashmi Kaul, *Tulsa*

Jonathan D Kaunitz, *Los Angeles*
 Stephen M Kavic, *Baltimore*
 Ali Keshavarzian, *Chicago*
 Amir Maqbul Khan, *Marshall*
 Kusum K Kharbanda, *Omaha*
 Chang Kim, *West Lafayette*
 Dean Y Kim, *Detroit*
 Miran Kim, *Providence*
 Burton I Korelitz, *New York*
 Josh Korzenik, *Boston*
 Richard A Kozarek, *Seattle*
 Alyssa M Krasinskas, *Pittsburgh*
 Shiu-Ming Kuo, *Buffalo*
 Michelle Lai, *Boston*
 Michael Leitman, *New York*
 Dong-Hui Li, *Houston*
 Ming Li, *New Orleans*
 Zhiping Li, *Baltimore*
 Gary R Lichtenstein, *Philadelphia*
 Chen Liu, *Gainesville*
 Zhang-Xu Liu, *Los Angeles*
 Craig D Logsdon, *Houston*
 Kaye M Reid Lombardo, *Rochester*
 Michael R Lucey, *Madison*
 Kirk Ludwig, *Wisconsin*
 James D Luketich, *Pittsburgh*
 Patrick M Lynch, *Houston*
 John S Macdonald, *New York*
 Willis C Maddrey, *Dallas*
 Mercedes Susan Mandell, *Aurora*
 Christopher Mantyh, *Durham*
 Wendy M Mars, *Pittsburgh*
 John Marshall, *Columbia*
 Robert CG Martin, *Louisville*
 Laura E Matarese, *Pittsburgh*
 Craig J McClain, *Louisville*
 Lynne V McFarland, *Washington*
 David J McGee, *Shreveport*
 Valentina Medici, *Sacramento*
 Stephan Menne, *New York*
 Didier Merlin, *Atlanta*
 George Michalopoulos, *Pittsburgh*
 James M Millis, *Chicago*
 Pramod K Mistry, *New Haven*
 Emiko Mizoguchi, *Boston*
 Huanbiao Mo, *Denton*
 Robert C Moesinger, *Ogden*
 Smruti R Mohanty, *Chicago*
 John Morton, *Stanford*
 Peter L Moses, *Burlington*
 Sandeep Mukherjee, *Omaha*
 Million Mulugeta, *Los Angeles*
 Michel M Murr, *Tampa*
 Pete Muscarella, *Columbus*
 Ece A Mutlu, *Chicago*
 Masaki Nagaya, *Boston*
 Laura E Nagy, *Cleveland*
 Aejaz Nasir, *Tampa*
 Udayakumar Navaneethan, *Cincinnati*
 Stephen JD O'Keefe, *Pittsburgh*
 Robert D Odze, *Boston*
 Giuseppe Orlando, *Winston Salem*
 Pal Pacher, *Rockville*
 Georgios Papachristou, *Pittsburgh*
 Jong Park, *Tampa*
 William R Parker, *Durham*
 Mansour A Parsi, *Cleveland*
 Marco Giuseppe Patti, *Chicago*
 Zhiheng Pei, *New York*
 CS Pitchumoni, *New Brunswick*
 Parviz M Pour, *Omaha*
 Xiaofa Qin, *Newark*
 Florencia Georgina Que, *Rochester*
 Massimo Raimondo, *Jacksonville*

Raymund R Razonable, *Minnesota*
 Kevin Michael Reavis, *Orange*
 Robert V Rege, *Dallas*
 Douglas K Rex, *Indianapolis*
 Victor E Reyes, *Galveston*
 Basil Rigas, *New York*
 Richard A Rippe, *Chapel Hill*
 Alexander S Rosemurgy, *Tampa*
 Philip Rosenthal, *San Francisco*
 Raul J Rosenthal, *Weston*
 Joel H Rubenstein, *Ann Arbor*
 Shawn D Safford, *Norfolk*
 Rabih M Salloum, *Rochester*
 Bruce E Sands, *Boston*
 Tor C Savidge, *Galveston*
 Michael L Schilsky, *New Haven*
 Beat Schnüriger, *California*
 Robert E Schoen, *Pittsburgh*
 Matthew James Schuchert, *Pittsburgh*
 Ekihiro Seki, *La Jolla*
 Le Shen, *Chicago*
 Perry Shen, *Winston-Salem*
 Stuart Sherman, *Indianapolis*
 Mitchell L Shiffman, *Richmond*
 Shivendra Shukla, *Columbia*
 Bronislaw L Slomiany, *Newark*
 Scott Steele, *Fort Lewis*
 Branko Stefanovic, *Tallahassee*
 Lygia Stewart, *San Francisco*
 Luca Stocchi, *Cleveland*
 Daniel S Straus, *Riverside*
 Robert Todd Striker, *Madison*
 Jonathan Strosberg, *Tampa*
 Christina Surawicz, *Seattle*
 Patricia Sylla, *Boston*
 Wing-Kin Syn, *Durham*
 Yvette Taché, *Los Angeles*
 Kazuaki Takabe, *Richmond*
 Kam-Meng Tchou-Wong, *New York*
 Klaus Thaler, *Columbia*
 Charles Thomas, *Oregon*
 Natalie J Torok, *Sacramento*
 George Triadafilopoulos, *Stanford*
 Chung-Jyi Tsai, *Lexington*
 Thérèse Tuohy, *Salt Lake City*
 Andrew Ukleja, *Florida*
 Santhi Swaroop Vege, *Rochester*
 Aaron Vinik, *Norfolk*
 Dinesh Vyas, *Washington*
 Arnold Wald, *Wisconsin*
 Scott A Waldman, *Philadelphia*
 Jack R Wands, *Providence*
 Jiping Wang, *Boston*
 Irving Waxman, *Chicago*
 Wilfred M Weinstein, *Los Angeles*
 Steven D Wexner, *Weston*
 John W Wiley, *Ann Arbor*
 Jackie Wood, *Ohio*
 Jian Wu, *Sacramento*
 Wen Xie, *Pittsburgh*
 Guang-Yin Xu, *Galveston*
 Fang Yan, *Nashville*
 Radha Krishna Yellapu, *New York*
 Anthony T Yeung, *Philadelphia*
 Zobair M Younossi, *Virginia*
 Liqing Yu, *Winston-Salem*
 Run Yu, *Los Angeles*
 Ruben Zamora, *Pittsburgh*
 Michael E Zenilman, *New York*
 Mark A Zern, *Sacramento*
 Lin Zhang, *Pittsburgh*
 Martin D Zielinski, *Rochester*
 Michael A Zimmerman, *Colorado*

**EDITORIAL****5907** Reverse cholesterol transport revisited*van der Velde AE***TOPIC HIGHLIGHT****5908** Reverse cholesterol transport: From classical view to new insights*van der Velde AE***5916** Scavenger receptor BI: A multi-purpose player in cholesterol and steroid metabolism*Hoekstra M, Van Berkel TJC, Van Eck M***5925** Ecto-F₁-ATPase: A moonlighting protein complex and an unexpected apoA-I receptor*Vantourout P, Radojkovic C, Lichtenstein L, Pons V, Champagne E, Martinez LO***5936** Biliary cholesterol secretion: More than a simple ABC*Dijkers A, Tietge UJF***5946** A new framework for reverse cholesterol transport: Non-biliary contributions to reverse cholesterol transport*Temel RE, Brown JM***5953** From blood to gut: Direct secretion of cholesterol *via* transintestinal cholesterol efflux*Vrins CLJ***5958** Thyroid hormones and thyroid hormone receptors: Effects of thyromimetics on reverse cholesterol transport*Pedrelli M, Pramfalk C, Parini P***ORIGINAL ARTICLE****5965** Multiplex RT-PCR-based detections of CEA, CK20 and EGFR in colorectal cancer patients*Tsouma A, Aggeli C, Lembessis P, Zografos GN, Korkolis DP, Pectasides D, Skondra M, Pissimissis N, Tzonou A, Koutsilieris M*

- 5975 Relationship between COX-2 and cell cycle-regulatory proteins in patients with esophageal squamous cell carcinoma

Huang JX, Xiao W, Chen WC, Lin MS, Song ZX, Chen P, Zhang YL, Li FY, Qian RY, Salminen E

BRIEF ARTICLE

- 5982 Benefit of combination β -blocker and endoscopic treatment to prevent variceal rebleeding: A meta-analysis

Funakoshi N, Ségalas-Largey F, Duny Y, Oberti F, Valats JC, Bismuth M, Daurès JP, Blanc P

- 5993 Hepatocellular carcinoma treated with transarterial chemoembolization: Dynamic perfusion-CT in the assessment of residual tumor

Ippolito D, Bonaffini PA, Ratti L, Antolini L, Corso R, Fazio F, Sironi S

- 6001 Immune phenotype in children with therapy-naïve remitted and relapsed Crohn's disease

Cseh A, Vasarhelyi B, Molnar K, Szalay B, Svec P, Treszl A, Dezsofi A, Lakatos PL, Arato A, Tulassay T, Veres G

- 6010 Gastroesophageal flap valve status distinguishes clinical phenotypes of large hiatal hernia

Kaneyama H, Kaise M, Arakawa H, Arai Y, Kanazawa K, Tajiri H

- 6016 Diagnosis and surgical treatment of primary hepatic lymphoma

Yang XW, Tan WF, Yu WL, Shi S, Wang Y, Zhang YL, Zhang YJ, Wu MC

- 6020 Meta-analysis of ADH1B and ALDH2 polymorphisms and esophageal cancer risk in China

Zhang GH, Mai RQ, Huang B

- 6026 Prognostic values of chromosome 18q microsatellite alterations in stage II colonic carcinoma

Wang W, Wang GQ, Sun XW, Chen G, Li YF, Zhang LY, Qiu HB, Huang CY, Zhan YQ, Zhou ZW

ACKNOWLEDGMENTS I Acknowledgments to reviewers of *World Journal of Gastroenterology*

APPENDIX I Meetings
I-VI Instructions to authors

AIM AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, DOI: 10.3748) is a weekly, open-access, peer-reviewed journal supported by an editorial board of 1144 experts in gastroenterology and hepatology from 60 countries.

The major task of *WJG* is to report rapidly the most recent results in basic and clinical research on esophageal, gastrointestinal, liver, pancreas and biliary tract diseases, *Helicobacter pylori*, endoscopy and gastrointestinal surgery, including: gastroesophageal reflux disease, gastrointestinal bleeding, infection and tumors; gastric and duodenal disorders; intestinal inflammation, microflora and immunity; celiac disease, dyspepsia and nutrition; viral hepatitis, portal hypertension, liver fibrosis, liver cirrhosis, liver transplantation, and metabolic liver disease; molecular and cell biology; geriatric and pediatric gastroenterology; diagnosis and screening, imaging and advanced technology.

FLYLEAF

I-VII Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiao-Fang Liu*
Responsible Electronic Editor: *Xiao-Mei Zheng*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Lin Tian*
Proofing Editorial Office Director: *Jian-Xia Cheng*

NAME OF JOURNAL
World Journal of Gastroenterology

LAUNCH DATE
October 1, 1995

RESPONSIBLE INSTITUTION
Department of Science and Technology of Shanxi Province

SPONSOR
Taiyuan Research and Treatment Center for Digestive Diseases, 77 Shuangta Xijie, Taiyuan 030001, Shanxi Province, China

EDITING
Editorial Board of *World Journal of Gastroenterology*, Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-5908-0039
Fax: +86-10-8538-1893
E-mail: wjg@wjgnet.com
<http://www.wjgnet.com>

PUBLISHING
Baishideng Publishing Group Co., Limited, Room 1701, 17/F, Henan Building, No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-3115-8812
Telephone: +852-5804-2046
E-mail: baishideng@wjgnet.com
<http://www.wjgnet.com>

SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd., Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
<http://www.wjgnet.com>

PRINT SUBSCRIPTION
RMB 245 Yuan for each issue, RMB 11760 Yuan for one year.

ONLINE SUBSCRIPTION
One-Year Price 864.00 USD

PUBLICATION DATE
December 21, 2010

CSSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

HONORARY EDITORS-IN-CHIEF
James L. Boyer, *New Haven*
Ke-Ji Chen, *Beijing*
Martin H Floch, *New Haven*
Geng-Tao Liu, *Beijing*
Emmet B Keefe, *Palo Alto*
Lein-Ray Mo, *Tainan*
Eamonn M Quigley, *Cork*
Rafiq A Sheikh, *Sacramento*
Nicholas J Talley, *Rochester*
Ming-Lung Yu, *Kaohsiung*

PRESIDENT AND EDITOR-IN-CHIEF
Lian-Sheng Ma, *Beijing*

ACADEMIC EDITOR-IN-CHIEF
Tauseef Ali, *Oklahoma*
Mauro Bortolotti, *Bologna*
Tarkan Karakan, *Ankara*
Weekitt Kittisupamongkol, *Bangkok*
Anastasios Koulaouzidis, *Edinburgh*
Gerd A Kullak-Ublick, *Zürich*
Bo-Rong Pan, *Xi'an*
Sylvia LF Pender, *Southampton*
Max S Petrov, *Auckland*
George Y Wu, *Farmington*

STRATEGY ASSOCIATE EDITORS-IN-CHIEF
Peter Draganov, *Florida*
Hugh J Freeman, *Vancouver*
Maria Concepción Gutiérrez-Ruiz, *México*
Kazuhiro Hanazaki, *Kochi*

Akio Inui, *Kagoshima*
Kalpesh Jani, *Baroda*
Javier S Martin, *Punta del Este*
Natalia A Osna, *Omaha*
Wei Tang, *Tokyo*
Alan BR Thomson, *Edmonton*
Harry HX Xia, *Hanover*

ASSOCIATE EDITORS-IN-CHIEF
You-Yong Lu, *Beijing*
John M Luk, *Pokfulam*
Hiroshi Shimada, *Yokohama*

EDITORIAL OFFICE
Jian-Xia Cheng, Director
World Journal of Gastroenterology
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-5908-0039
Fax: +86-10-8538-1893
E-mail: wjg@wjgnet.com
<http://www.wjgnet.com>

COPYRIGHT
© 2010 Baishideng. All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior permission of Baishideng. Authors are required to grant *World Journal of Gastroenterology* an exclusive license to publish.

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

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1007-9327/g_info_20100315215714.htm. If you do not have web access please contact the editorial office.

ONLINE SUBMISSION
<http://www.wjgnet.com/1007-9327/office>

Benefit of combination β -blocker and endoscopic treatment to prevent variceal rebleeding: A meta-analysis

Natalie Funakoshi, Frédérique Ségalas-Largey, Yohan Duny, Frédéric Oberti, Jean-Christophe Valats, Michael Bismuth, Jean-Pierre Daurès, Pierre Blanc

Natalie Funakoshi, Frédérique Ségalas-Largey, Jean-Christophe Valats, Michael Bismuth, Pierre Blanc, Department of Hepato-gastroenterology B, Saint Eloi Hospital, University Hospital of Montpellier, 34295 Montpellier Cedex 5, France
 Yohan Duny, Jean-Pierre Daurès, Department of Statistics, University Hospital of Nîmes, place du Pr R. Debré, 30029 Nîmes Cedex 9, France

Frédéric Oberti, Department of Hepato-gastroenterology, University Hospital of Angers, 4 rue Larrey, 49933 Angers Cedex 9, France

Author contributions: Funakoshi N and Ségalas-Largey F were involved in acquisition of data, analysis and interpretation of data, and drafting of the manuscript; Oberti F was involved in acquisition, analysis and interpretation of data; Duny Y was involved in analysis and interpretation of data and statistical analysis; Valats JC and Bismuth M provided technical support and were involved in study supervision; Daurès JP was involved in study concept and design, statistical analysis and study supervision; Blanc P was involved in study concept and design, analysis and interpretation of data, critical revision of the manuscript and study supervision.

Correspondence to: Pierre Blanc, MD, PhD, Department of Hepato-gastroenterology B, Saint Eloi Hospital, University Hospital of Montpellier, 80 rue Augustin Fliche, 34295 Montpellier Cedex 5, France. pblanc34@yahoo.fr

Telephone: +33-4-67337077 Fax: +33-4-67337077

Received: June 29, 2010 Revised: September 7, 2010

Accepted: September 14, 2010

Published online: December 21, 2010

Main outcomes were overall and 6, 12 and 24 mo re-bleeding rates, as well as overall and 6, 12 and 24 mo mortality. Two statistical methods were used: Yusuf-Peto, and Der Simonian and Laird. Inter-trial heterogeneity was systematically taken into account.

RESULTS: Seventeen randomised controlled trials were included, 14 with SCL and 3 with BL. Combination β -blocker and endoscopic treatment significantly reduced rebleeding rates at 6, 12 and 24 mo and overall [odds ratio (OR): 2.20, 95% confidence interval (CI): 1.69-2.85, $P < 0.0001$] compared to endoscopic treatment alone. Mortality at 24 mo was significantly lower for the combined treatment group (OR: 1.83, 95% CI: 1.16-2.90, $P = 0.009$), as well as overall mortality (OR: 1.43, 95% CI: 1.03-1.98, $P = 0.03$).

CONCLUSION: Combination therapy should thus be recommended as the first line treatment for secondary prophylaxis of oesophageal variceal bleeding.

© 2010 Baishideng. All rights reserved.

Key words: Oesophageal varices; Portal hypertension; Cirrhosis; Secondary prevention; β -blockers; Banding ligation

Peer reviewers: Mercedes Susan Mandell, MD, PhD, Department of Anesthesiology, University of Colorado Health Sciences Ctr., 12401 E. 17th Ave, B113 Aurora, CO 80045, United States; Sri P Misra, Professor, Gastroenterology, Moti Lal Nehru Medical College, Allahabad 211001, India

Abstract

AIM: To determine whether the association of β -blockers with endoscopic treatment is superior to endoscopic treatment alone for the secondary prophylaxis of oesophageal variceal bleeding.

METHODS: Randomised controlled trials comparing sclerotherapy (SCL) with SCL plus β -blockers (BB) or banding ligation (BL) with BL plus BB were identified.

Funakoshi N, Ségalas-Largey F, Duny Y, Oberti F, Valats JC, Bismuth M, Daurès JP, Blanc P. Benefit of combination β -blocker and endoscopic treatment to prevent variceal rebleeding: A meta-analysis. *World J Gastroenterol* 2010; 16(47): 5982-5992 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v16/i47/5982.htm> DOI: <http://dx.doi.org/10.3748/wjg.v16.i47.5982>

INTRODUCTION

Upper gastrointestinal bleeding from ruptured oesophageal varices is the main complication of portal hypertension and is one of the leading causes of death in patients with cirrhosis. It is estimated that 70% of patients who have survived a first episode of variceal bleeding subsequently rebleed^[1]. Secondary prophylaxis of variceal bleeding is thus of utmost importance for these patients.

The use of β -blockers alone has been shown to decrease the risk of recurrent bleeding in cirrhotic patients^[2-4]. Endoscopic treatments [sclerotherapy (SCL) and banding ligation (BL)] are also effective in preventing rebleeding in patients with portal hypertension. It has been demonstrated that sclerotherapy decreases the risk of recurrent bleeding and improves survival in cirrhotic patients compared to placebo^[5,6]. Banding ligation is currently the endoscopic therapy of choice as it has been shown to be safer and more effective in preventing rebleeding than sclerotherapy^[7-10]. However, sclerotherapy continues to be routinely used in a certain number of countries. Combining pharmacological and endoscopic treatment may be more effective than either treatment alone as they act through different mechanisms, thus enhancing each other's therapeutic effect. Many randomised controlled trials have been undertaken to determine whether β -blockers have an additional beneficial role when combined with sclerotherapy or banding ligation to prevent rebleeding. The results of these studies are controversial. Sørensen^[11] suggested that β -blockers and sclerotherapy had no additive effect in the prevention of variceal rebleeding, whereas a number of trials have reported favourable results when banding ligation is combined with β -blockers^[12,13]. The recommendations of the American College of Gastroenterology^[14] state that combined endoscopic and pharmacological therapy is the most effective for secondary prophylaxis, whereas the Baveno IV Consensus conference^[15] recommends either β -blockers, banding ligation or both; the authors add that combined therapy is probably the best treatment, but that more trials are needed to prove this. The aim of this meta-analysis is therefore to determine whether the association of β -blockers with endoscopic treatment (sclerotherapy or banding ligation) leads to decreased rebleeding rates and improved survival in patients with portal hypertension compared to endoscopic treatment alone.

MATERIALS AND METHODS

Source of trials

All randomised controlled trials comparing endoscopic treatment alone (sclerotherapy or banding ligation) with a combination of endoscopic treatment associated with β -blockers for the prevention of variceal rebleeding were identified. Trials were retrieved using MEDLINE (1950 to October 2009) and Web of Science (1900 to October 2009), by using the terms "secondary prophylaxis variceal bleeding, endoscopic therapy, β -blockers, sclerotherapy and variceal rebleeding". Conference abstracts from the American Association for the Study of the Liver, Euro-

pean Association for the Study of the Liver, the Digestive Disease Week, the United European Gastroenterology Week and the French National Society of Gastroenterology between 1980 and 2009 were manually searched. The list of published articles or abstracts was verified and completed through an in depth study of the references quoted in each article. All trials included were peer-reviewed (full articles published in peer reviewed journals or abstracts selected by a peer committee). The final search was performed on April 30, 2010.

Study selection

The trials selected for this meta-analysis met the following criteria: (1) randomised controlled trials published as abstracts, letters to the editor or peer-reviewed articles; (2) patient population: patients presenting portal hypertension (with or without cirrhosis) and oesophageal varices which had previously bled and had not received prior β -blocker or endoscopic treatment; and (3) interventions: treatment with sclerotherapy or banding ligation alone or concomitant treatment with β -blockers (administered from the start of endoscopic treatment) and sclerotherapy or banding ligation; in parallel treatment groups. We chose to exclude studies which associated β -blockers with nitrates or studies in which β -blockers were commenced only after completion of endoscopic therapy. No language restrictions were applied.

Data extraction and quality assessment

Data extraction and quality assessment were performed by three independent reviewers (Ségalas-Largey F, Oberti F and Blanc P). Discrepancies were resolved through discussion before analyses. Trial quality was evaluated using criteria established by Poynard^[16] and Nicolucci *et al.*^[17], simplified and adapted for portal hypertension by Pagliaro *et al.*^[18]. For each trial, two separate scores were calculated using Poynard's and Pagliaro's criteria; each score was expressed as a percentage of the highest score possible. In addition, we noted for each trial randomisation, investigator blinding, estimation of sample size and intention-to-treat analysis.

Data synthesis and analysis

Primary end-points were all-cause rebleeding rates and mortality at 6, 12 and 24 mo, as well as overall rebleeding and mortality rates as reported at end of follow-up. All-cause rebleeding was defined as upper gastrointestinal bleeding of any source. We chose this as the primary outcome as endoscopic treatment of oesophageal varices may induce bleeding related to oesophageal ulcers. Results were determined at different time points in order to take into account variations in follow-up duration between trials. For each time point, raw data was extracted from studies when available using Kaplan-Meier survival curves.

A meta-analysis including all trials (sclerotherapy and banding ligation) was performed, as well as subgroup analyses of trials using sclerotherapy and trials using banding ligation.

Table 1 Study characteristics

Author	Country	Publication type	n	Length of follow-up (mo)
Combination therapy <i>vs</i> sclerotherapy				
Westaby <i>et al</i> ^[36]	United Kingdom	Article	53	6
Jensen <i>et al</i> ^[37]	Denmark	Article	31	12
Bertoni <i>et al</i> ^[38]	Italy	Letter	28	2
Gerunda <i>et al</i> ^[39]	Italy	Abstract	60	6
Lundell <i>et al</i> ^[40]	Sweden	Article	41	8
Kanazawa <i>et al</i> ^[32]	Japan	Abstract	43	27
Vinel <i>et al</i> ^[41]	France	Article	74	3
Acharya <i>et al</i> ^[42]	India	Article	114	24
Avgerinos <i>et al</i> ^[43]	Greece	Article	85	23.9
Villanueva <i>et al</i> ^[33]	Spain	Article	40	26
Vickers <i>et al</i> ^[44]	United Kingdom	Article	73	24
Elsayed <i>et al</i> ^[34]	Egypt	Article	178	21
Benedeto-Stojanov <i>et al</i> ^[45]	Yugoslavia	Abstract	65	39
Dowidar <i>et al</i> ^[35]	Egypt	Article	40	16.2
Combination therapy <i>vs</i> banding ligation				
Abdel-Rahim <i>et al</i> ^[46]	Egypt	Abstract	50	< 3
Lo <i>et al</i> ^[12]	China	Article	122	12
de la Peña <i>et al</i> ^[13]	Spain	Article	84	16

Statistical methods

All results were expressed as odds ratio (OR), with a 95% confidence interval (CI). Results were first calculated using a fixed-effect model (Collins *et al*^[19]). Heterogeneity was calculated using Breslow-Day's test. When significant heterogeneity was found, both the OR and *P*-heterogeneity were subsequently calculated using a random-effect model (DerSimonian *et al*^[20]). This model takes into account heterogeneity by providing a more conservative estimate of treatment effect with wider confidence intervals in order to adjust for inter-trial variability. *P*-heterogeneity was initially considered significant if < 0.05 ; however, when *P*-heterogeneity tended towards significance (i.e. between 0.05 and 0.10), we preferred to take the precaution of calculating results using the random-effect model. The percentage of variability beyond chance was estimated using the I^2 statistic^[21]. Publication bias was assessed using the Egger Test^[22] and represented graphically using funnel plots^[23] plotting the natural log of the OR *vs* its standard error. The Trim and Fill analysis for publication bias was performed using Duval and Tweedie's methods^[24]. Additionally, the failsafe number according to Orwin's formula^[25] was calculated, which represents the number of non-significant studies which would be necessary to reduce the effect size to a non-significant value. All analyses were performed using Comprehensive Meta-analysis software (version 2.2.048 New Jersey, USA, 2008).

RESULTS

Study identification and selection

Our search identified 229 potentially relevant references. Two hundred and six reports were excluded when it was obvious they did not meet inclusion criteria. A total of 23 reports were considered for detailed analysis. Four studies were excluded as they associated β -blockers with nitrates^[26-29]. Two studies were excluded as they started β -blocker therapy after completion of endoscopic ther-

apy^[30,31]. Seventeen studies were included in the meta-analysis.

Study characteristics

Study characteristics are reported in Table 1. Fourteen trials^[32-45] comparing sclerotherapy with combination sclerotherapy plus β -blockers were included with a total of 925 patients. Among these 925 patients, 887 were analysed: 435 were treated by sclerotherapy alone and 452 by sclerotherapy plus β -blocker. Thirty-eight patients from the trial of Elsayed *et al*^[34] were not included as they were excluded from the study after randomisation for various reasons (non compliance, loss to follow up, shunt surgery). Ten studies were published as full articles^[33-37,40-44], three in abstract form^[32,39,45] and one as a letter to the editor^[38]. One study was published in Spanish^[33].

Three articles comparing banding ligation with combined banding ligation and β -blocker therapy were included, with a total of 256 patients^[12,13,46]. Among these 256 patients, 252 were analysed. Four patients from the trial of de la Peña *et al*^[13] were excluded after randomisation due to withdrawal (3 patients) or diagnosis of lymphoma (one patient). One hundred and twenty-five were treated with banding ligation alone and 128 with banding ligation plus β -blockers. Two trials were published as full articles^[12,13] and one in abstract form^[46].

Patient characteristics are shown in Table 2. Chronic liver disease was the most common cause of portal hypertension in all studies and was mainly due to alcohol abuse in 9 trials^[12,33,36-41,44], to viral infection in 3 trials^[12,42,43] and to schistosomiasis in 2 trials^[34,35]. The aetiology of liver disease was not reported in three studies^[32,45,46]. In 8 studies, only patients with cirrhosis were included^[32,33,37,39-41,43,45]. Most patients had mild or severe liver disease in 9 studies^[12,13,34-38,40,44]. However, in the study by Avgerinos *et al*^[43], the majority of patients were Child's class A, whereas in 3 trials Child's class C patients were not included^[33,39,42]. Severity of liver disease was either incompletely reported

Table 2 Combination therapy *vs* banding ligation

Author	Mean age (yr)	Men (%)	Non cirrhotic portal hypertension (%)	Alcoholic liver disease (%)	Child class A-B-C (%)	Size of varices small-medium-large (%)
Combination therapy <i>vs</i> sclerotherapy						
Westaby <i>et al</i> ^[36]	48.6	62	17	43	16-43-41	0-34-66
Jensen <i>et al</i> ^[37]	46.5	87	0	84	26-45-29	3-32-65
Bertoni <i>et al</i> ^[38]	59.1	64	0	57	32-32-36	7-46.5-46.5
Gerunda <i>et al</i> ^[39]	NA	NA	0	50	NA	NA
Lundell <i>et al</i> ^[40]	56.4	54	0	63	22-27-51	NA
Kanazawa <i>et al</i> ^[32]	NA	NA	0	NA	NA	NA
Vinel <i>et al</i> ^[41]	55.7	78	0	89	NA	0-32-68
Acharya <i>et al</i> ^[42]	34.7	85	11	7	60-40-0	0-0-100
Avgerinos <i>et al</i> ^[43]	58.2	72	0	26	74-19-7	8-45-47
Villanueva <i>et al</i> ^[33]	56.8	57.5	0	50	30-70-0	7.5-62.5-30
Vickers <i>et al</i> ^[44]	55.1	59	15	40	26-51-23	7-26-64
Elsayed <i>et al</i> ^[34]	43.0	84	0	NA	55-29-16	NA
Benedeto-Stojanov <i>et al</i> ^[45]	NA	NA	0	NA	NA	NA
Dowidar <i>et al</i> ^[35]	46.0	90	0	0	45-50-5	20-72.5-7.5
Combination therapy <i>vs</i> banding ligation						
Abdel-Rahim <i>et al</i> ^[46]	NA	NA	NA	NA	NA	NA
Lo <i>et al</i> ^[12]	52.0	77	0	30	19-47-34	0-42-58
de la Peña <i>et al</i> ^[13]	60.0	75	0	66	15-56-29	21-54-25

NA: Not available.

Table 3 Combination therapy *vs* sclerotherapy

Study	Randomisation	Investigator blinding	Estimate of sample size	Intention to treat analysis	Poynard's quality score (%)	Pagliaro's quality score (%)
Combination therapy <i>vs</i> sclerotherapy						
Westaby <i>et al</i> ^[36]	Yes	No	No	No	31	35
Jensen <i>et al</i> ^[37]	Yes	Double blinded	No	No	65	67
Bertoni <i>et al</i> ^[38]	Yes	Single blinded	No	No	54	44
Gerunda <i>et al</i> ^[39]	Yes	No	No	No	19	12
Lundell <i>et al</i> ^[40]	Yes	Single blinded	No	Yes	50	61
Kanazawa <i>et al</i> ^[32]	Yes	No	No	No	19	18
Vinel <i>et al</i> ^[41]	Yes	No	Yes	Yes	73	43
Acharya <i>et al</i> ^[42]	Yes	Double blinded	Yes	Yes	92	96
Avgerinos <i>et al</i> ^[43]	Yes	Single blinded	Yes	Yes	77	83
Villanueva <i>et al</i> ^[33]	Yes	No	No	No	55	67
Vickers <i>et al</i> ^[44]	Yes	Single blinded	Yes	Yes	83	74
Elsayed <i>et al</i> ^[34]	Yes	No	No	No	50	31
Benedeto-Stojanov <i>et al</i> ^[45]	Yes	NA	NA	NA	29	8
Dowidar <i>et al</i> ^[35]	Yes	Single blinded	No	No	54	50
Combination therapy <i>vs</i> banding ligation						
Abdel-Rahim <i>et al</i> ^[46]	Yes	NA	NA	NA	8	17
Lo <i>et al</i> ^[12]	Yes	Single blinded	Yes	Yes	81	85
de la Peña <i>et al</i> ^[13]	Yes	No	Yes	No	69	82

NA: Not available.

or not mentioned at all in 5 studies^[32,39,41,45,46]. Variceal size was medium or large for the majority of patients in 11 trials^[12,13,33,35-38,41-44] and was not reported in 5 others^[32,34,39,40,45]. Sclerotherapy was performed with polidocanol in 5 studies^[37,38,40-42], ethanolamine in 6 studies^[33-36,43,44] and aetoxisclerol in one study^[45]. The sclerosing agent was not reported in 2 trials^[32,39]. Banding ligation was performed with multi-band ligators at intervals varying from 10 to 21 d, until complete variceal eradication was achieved. Propranolol was the β -blocker used in 12 trials^[32,34-37,40-46] and nadolol in 5 trials^[12,13,33,38,39]. The time to eradication of oesophageal varices was reported in 13 trials^[12,13,33-38,40-44]. In

the sclerotherapy plus β -blocker group the mean time to eradication of varices was slightly shorter (166 d-5.7 sessions) than in the sclerotherapy group (171 d-6 sessions). For patients treated with banding ligation, eradication was achieved in 44 d (3.3 sessions) *vs* 42 d (3.15 sessions) in the banding ligation plus β -blocker group. β -blockers were administered from the start of sclerotherapy until eradication in 7 studies^[35-41], whereas in 5 studies^[32-34,42,44], β -blockers were given both during and following variceal eradication. Follow-up duration for sclerotherapy studies ranged from 2 to 39 mo (mean 16.6 mo). Follow-up duration for banding ligation studies ranged from < 3 to

Table 4 Meta-analysis comparing endoscopic therapy (sclerotherapy or banding ligation) with combined endoscopic and β -blocker therapy

	SCL/BL, n/N (%)	SCL/BL + BB, n/N (%)	No. of trials analysed	I^2	OR (95% CI)	P for heterogeneity	P -value
All-cause rebleeding							
6 mo	121/410 (29.5)	83/428 (19.4)	11	36	1.70 (1.24-2.34) ¹	0.11	0.01
12 mo	142/376 (37.8)	85/392 (21.7)	10	62.3	2.22 (1.25-3.99) ²	0.004	0.007
24 mo	106/272 (40.0)	80/285 (28.1)	7	50	1.67 (0.99-2.81) ²	0.08	0.05
Overall	211/537 (39.3)	132/561 (23.5)	16	12.8	2.20 (1.69-2.85) ¹	0.31	< 0.0001
Mortality							
6 mo	39/309 (12.6)	33/319 (10.3)	9	0	1.23 (0.75-2.04) ¹	0.53	0.41
12 mo	33/246 (13.4)	30/259 (11.6)	7	0	1.18 (0.69-1.99) ¹	0.79	0.55
24 mo	58/230 (25.2)	37/244 (15.2)	6	0	1.83 (1.16-2.90) ¹	0.92	0.009
Overall	98/536 (18.3)	76/560 (13.6)	16	0	1.43 (1.03-1.98) ¹	0.97	0.03

¹Fixed effect model; ²Random effect model. SCL: Sclerotherapy; BL: Banding ligation; BB: β -blockers; OR: Odds ratio; CI: Confidence interval.

16 mo (mean 10.3 mo). Overall follow-up duration ranged from 2 to 39 mo (mean 15.4 mo).

Quality assessment

Variables defining study quality are presented in Table 3. All trials were correctly randomised. Three trials were double-blinded^[12,37,42] and six trials were single-blinded^[13,35,38,40,43,44]. Sample size was calculated in six trials. Six studies^[12,40-44] were performed on intention-to-treat basis. The quality scores determined by Poynard's criteria and by Pagliaro's criteria were strongly correlated.

Outcome measures

All-cause rebleeding: The all-cause rebleeding rate was reported in all studies except for the trial of Lundell *et al.*^[40]. For sclerotherapy trials, 162 patients rebleed in the sclerotherapy group (39.2%) whereas 110 patients (25.4%) rebleed in the sclerotherapy plus β -blocker group. Four sclerotherapy trials^[32,34,37,41] found rebleeding rates to be significantly lower in the sclerotherapy plus β -blocker group; the difference was not significant for the remaining 10 studies. For banding ligation studies, 49 patients bled in the banding ligation only group (39.5%), whereas 22 patients bled in the banding ligation plus β -blocker group (17.2%). Two banding ligation studies found rebleeding rates to be significantly lower in the banding ligation plus β -blocker group^[12,13]. The third study^[46] also found bleeding rates to be lower in this group, without specifying whether the difference was significant or not. When sclerotherapy and banding ligation studies were pooled, a total of 211 patients (39.3%) bled in the endoscopic therapy only group, and 132 (23.5%) bled in the endoscopic therapy plus β -blocker group.

When sclerotherapy and banding ligation trials were pooled for meta-analysis (Table 4), rebleeding rates were significantly lower in the endoscopic therapy plus β -blocker group at 6 and 12 mo, and for overall end-of-follow-up bleeding rates (at 6 mo, OR: 1.70, 95% CI: 1.24-2.34, $P = 0.01$; at 12 mo, OR: 2.22, 95% CI: 1.25-3.99, $P = 0.007$; overall OR: 2.20, 95% CI: 1.69-2.85, $P < 0.0001$). At 24 mo, the decrease in rebleeding in favour of the endoscopic plus β -blocker group was at the limit of significance (OR: 1.67, 95% CI: 0.99-2.81,

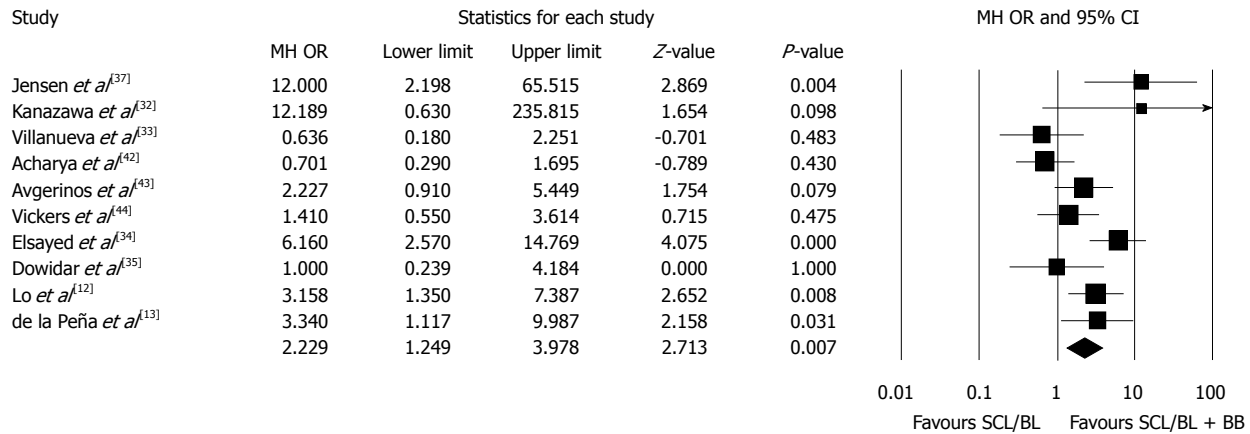
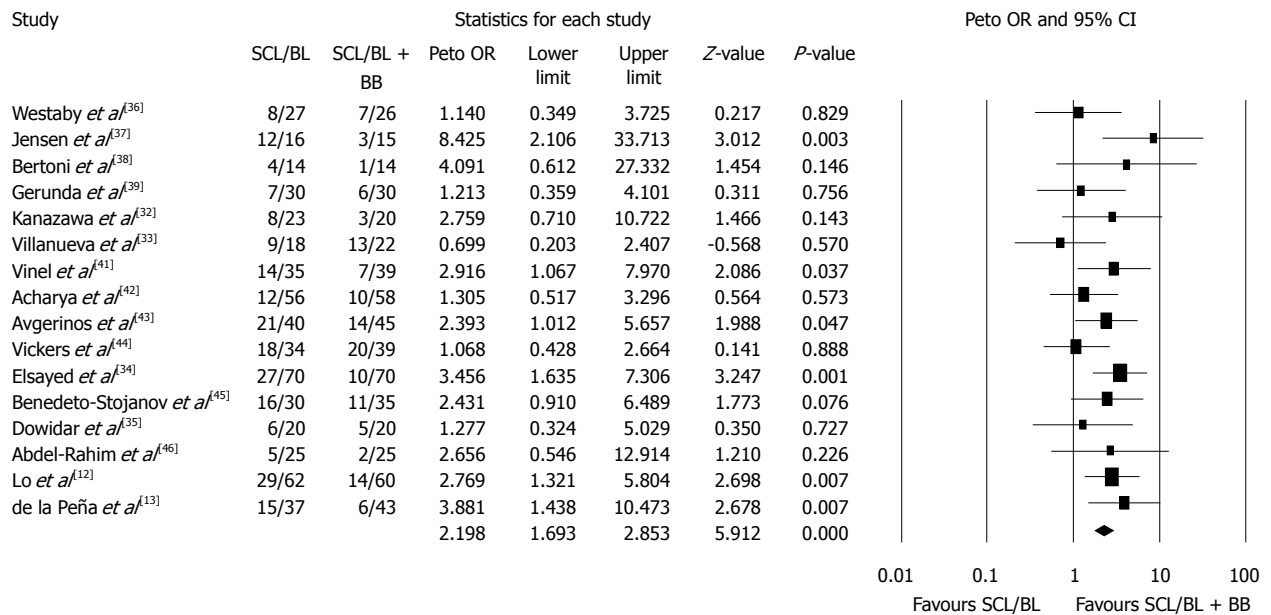
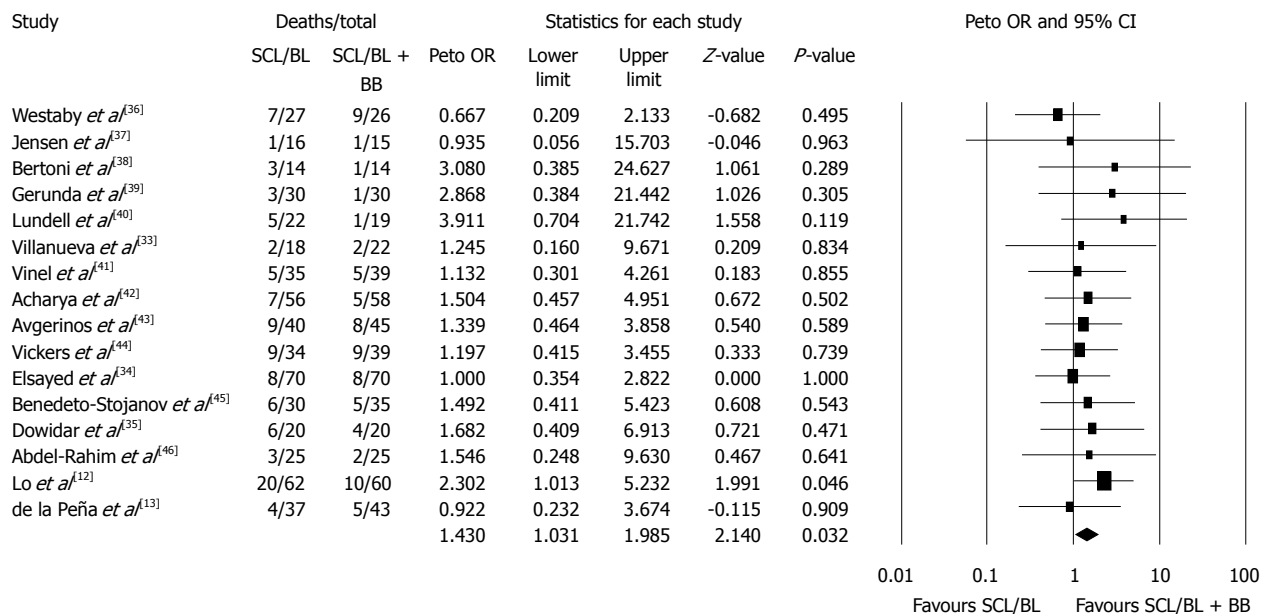
$P = 0.05$). All funnel plots were symmetrical; the failsafe numbers were 8, 16 and 33, respectively, for bleeding rates at 6 and 12 mo and overall. The Egger tests were negative for publication bias ($P = 0.47$, $P = 0.31$, $P = 0.39$, respectively). Forest plots for 12 mo and overall rebleeding rates are shown in Figure 1A and B.

Mortality: Mortality was reported in all studies except for the trial of Kanazawa *et al.*^[32]. In sclerotherapy trials, 71 patients died in the sclerotherapy group (17.2%), whereas 59 deaths occurred in the sclerotherapy plus β -blocker group (13.7%). In banding ligation trials, 27 patients died in the banding ligation group (21.8%), whereas 17 patients died in the banding ligation plus β -blocker group (13.3%). None of the sclerotherapy or banding ligation trials reported a significant difference in mortality between the two treatment arms. When sclerotherapy and banding ligation studies were taken together, a total of 98 patients died in the endoscopic therapy group (18.3%) and 76 died in the endoscopic therapy plus β -blocker group (13.6%).

No significant difference in mortality rates was present at 6 and 12 mo. However, at 24 mo a significant difference in mortality in favour of the combination therapy (endoscopy plus β -blocker) group appeared (OR: 1.83, 95% CI: 1.16-2.90, $P = 0.009$). Overall mortality rates were also significantly decreased in the combination therapy group (OR: 1.43, 95% CI: 1.03-1.98, $P = 0.03$), as shown in Table 4. Funnel plots seemed symmetrical, and the failsafe number for both mortality at 24 mo and overall mortality was 2. The Egger test did not find evidence of publication bias ($P = 0.17$ and $P = 0.34$, respectively). Forest plots for overall and 24 mo mortality are shown in Figure 1C and D.

Subgroup analyses

Sclerotherapy trials: A subgroup analysis was performed including sclerotherapy trials only. The rebleeding rates at 6, 12 and 24 mo were lower in the sclerotherapy plus β -blocker group, but the difference was not significant (Table 5). When overall end-of-follow-up rebleeding rates were taken into account, the difference was significantly lower in favour of the sclerotherapy plus β -blocker group (OR: 2.00, 95% CI: 1.49-2.69, $P < 0.0001$). The failsafe number was 54, the funnel plot seemed symmetrical and

A Study**B** Study**C** Study

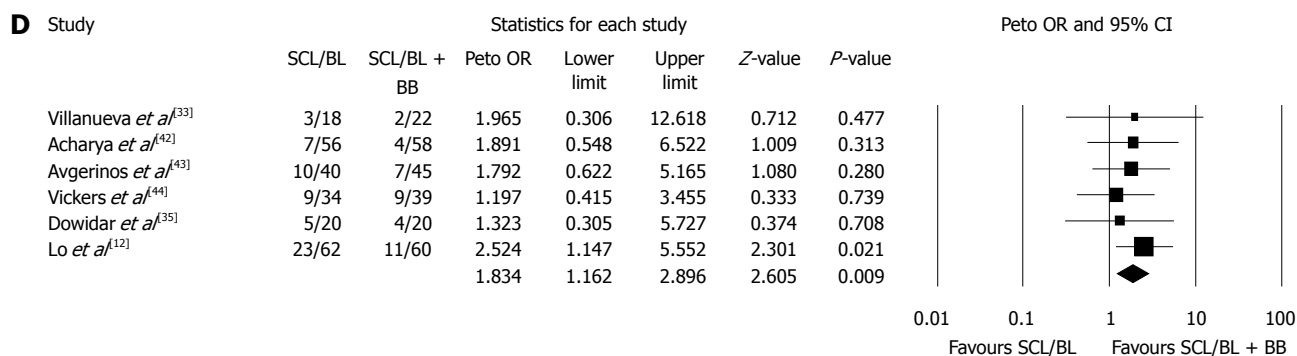


Figure 1 Meta-analysis for rebleeding at 12 mo (A), overall rebleeding (B), overall mortality (C) and mortality at 24 mo (D) for trials comparing combined endoscopic treatment (sclerotherapy or banding ligation) and β -blockers with endoscopic treatment alone. SCL: Sclerotherapy; BL: Banding ligation; BB: β -blockers; OR: Odds ratio; CI: Confidence interval.

Table 5 Subgroup meta-analysis including trials comparing sclerotherapy with sclerotherapy and β -blockers

	SCL, n/N (%)	SCL + BB, n/N (%)	No. of trials analysed	I^2	OR (95% CI)	P for heterogeneity	P-value
All-cause rebleeding							
6 mo	91/311 (29.2)	74/325 (22.8)	9	5.8	1.36 (0.95-1.95) ¹	0.39	0.09
12 mo	105/277 (38.0)	69/289 (23.9)	8	69.0	2.03 (0.97-4.25) ²	0.002	0.06
24 mo	61/173 (35.3)	56/182 (30.8)	5	45.7	1.26 (0.80-2.00) ¹	0.12	0.33
Overall	162/413 (39.2)	110/433 (25.4)	13	20.7	2.00 (1.49-2.69) ¹	0.23	< 0.0001
Mortality							
6 mo	30/247 (12.1)	29/259 (11.2)	8	0	1.07 (0.61-1.87) ¹	0.57	0.82
12 mo	21/184 (11.4)	23/199 (11.6)	6	0	0.98 (0.52-1.85) ¹	0.83	0.96
24 mo	34/168 (20.2)	26/184 (14.1)	5	0	1.56 (0.89-2.73) ¹	0.97	0.12
Overall	71/412 (17.2)	59/432 (13.7)	13	0	1.33 (0.91-1.94) ¹	0.97	0.14

¹Fixed effect model; ²Random effect model. SCL: Sclerotherapy; BL: Banding ligation; BB: β -blockers; OR: Odds ratio; CI: Confidence interval.

Table 6 Subgroup meta-analysis including trials comparing banding ligation with banding ligation and β -blockers

	BL, n/N (%)	BL + BB, n/N (%)	No. of trials analysed	I^2	OR (95% CI)	P for heterogeneity	P-value
Overall all-cause rebleeding	49/124 (39.5)	22/128 (17.2)	3	0	3.16 (1.76-5.34) ¹	0.85	< 0.0001
Mortality	27/124 (21.8)	17/128 (13.3)	3	0	1.78 (0.92-3.43) ¹	0.53	0.09

¹Fixed effect model. SCL: Sclerotherapy; BL: Banding ligation; BB: β -blockers; OR: Odds ratio; CI: Confidence interval.

the Egger test did not indicate publication bias ($P = 0.46$). No significant difference in mortality rates was present at 6, 12, 24 mo or with overall end-of-follow-up mortality (Table 5).

Banding ligation trials: A subgroup analysis was performed including the three banding ligation trials (Table 6). Outcomes were significantly in favour of banding ligation plus β -blockers concerning overall bleeding rates (OR: 3.16, 95% CI: 1.76-5.34, $P < 0.0001$). The failsafe number was at 4, and the Egger test did not indicate publication bias ($P = 0.47$). No significant difference was present for mortality. Analyses at different time-points were not performed due to insufficient data.

DISCUSSION

The results of this meta-analysis show that the association of endoscopic treatment with β -blockers is more effective

in secondary prophylaxis of oesophageal variceal bleeding than endoscopic treatment alone, with a significant decrease in rebleeding rates overall and at all time points (6, 12 and 24 mo). We have shown for the first time a significant decrease in mortality rates with combined β -blocker and endoscopic treatment over endoscopic treatment alone, with significantly decreased overall and 24 mo mortality rates. Banding ligation is currently the preferred endoscopic treatment for oesophageal varices as it has been shown to be superior due to less recurrent bleeding, fewer complications, and lower mortality rates^[7,9,10,47-49]. However, we chose to include studies using sclerotherapy in our meta-analysis, as it continues to be widely used in the developing world, where schistosomiasis, one of the leading causes of portal hypertension worldwide^[50], and viral B cirrhosis are prevalent.

The superiority of combination β -blocker and endoscopic treatment in reducing rebleeding rates may be explained by their synergistic action, with β -blockers reduc-

ing portal hypertension, while sclerotherapy and banding ligation act focally on the oesophagus. Although overall rebleeding rates are significantly in favour of combination therapy for sclerotherapy trials alone, when studies using banding ligation are added to those using sclerotherapy, the decrease in rebleeding rates in the combination therapy group becomes significant at 6, 12 and 24 mo, and remains significant overall. These results are robust as the failsafe numbers (i.e. number of medium sized non significant studies needed to reduce the effect size to a non significant value) are relatively high (8, 16 and 33 for 6 mo, 12 mo and overall bleeding rates, respectively). This may be due to the fact that all the banding ligation studies were in favour of combination therapy concerning rebleeding rates^[12,13]. Indeed, the subgroup analysis including banding ligation studies only was strongly in favour of combined treatment concerning bleeding rates ($P < 0.0001$). However, we are aware that the number of studies using banding ligation included in this meta-analysis is relatively low ($n = 3$) compared to the number of studies using sclerotherapy ($n = 14$). This difference is due to the fact that sclerotherapy is an older and more widespread technique compared to banding ligation, and that the highly significant results in favour of combined therapy in the three banding ligation studies would not have been conducive to the completion of further similar studies. Kumar *et al.*^[28] suggested that the pooling of sclerotherapy and banding ligation studies as in the meta-analysis of Gonzalez *et al.*^[51] would lead to inferior results for endoscopic therapy as sclerotherapy is known to be inferior to banding ligation for the treatment of variceal bleeding. We therefore decided to perform a subgroup analysis including only banding ligation trials as suggested by a recent editorial^[52], which showed a significant decrease in rebleeding rates for banding ligation associated with β -blockers. Although only three studies were concerned, this result is relatively robust as four additional medium-sized non significant studies would be needed to render the result insignificant.

As with bleeding rates, a significant difference in mortality in favour of the combination β -blocker and endoscopic therapy group appeared when sclerotherapy and banding ligation studies were pooled. A significant difference was present overall and at 24 mo, perhaps due to the fact that the numbers of deaths at 6 and 12 mo were too low to reveal any significant statistical difference [at 6 mo: 39/309 (12.6%) for the endoscopic therapy group and 33/319 (10.3%) for the combined therapy group; at 12 mo 33/246 (13.4%) and 30/259 (11.6%), respectively]. It could be hypothesised that this decrease in mortality may be due to reduced bleeding rates, but one must keep in mind that although mortality rates are a standard end-point of all clinical trials and meta-analyses concerning variceal bleeding, it is difficult to attribute decreased mortality to decreased bleeding rates in a cirrhotic population prone to various life-threatening complications. β -blockers could have a beneficial effect on survival independent of their preventative effect on variceal bleeding as they act globally by reducing portal hypertension, and it has been suggested that they may reduce the frequency of complications

of cirrhosis such as ascites, hepato-renal syndrome, portal hypertensive gastropathy^[53,54] and spontaneous bacterial peritonitis^[55,56]. However, the results concerning decreased mortality in the combination endoscopic and β -blocker therapy group must be interpreted with caution as the failsafe number is relatively low: only two additional medium-sized non significant studies would be necessary in order to render the results insignificant. Additional studies with long term follow-up, preferably using banding ligation, are necessary in order to confirm these results.

Three meta-analyses have been previously published concerning combination therapy. The meta-analyses of Gonzalez *et al.*^[51] and Ravipati *et al.*^[57] compared combination treatment with endoscopic treatment (sclerotherapy or banding ligation) alone, and found a significant difference in rebleeding rates in favour of combination therapy, whereas results were non-significant for mortality. The meta-analysis of Ravipati *et al.*^[57] included 11 sclerotherapy trials, compared to 14 trials (148 additional patients) in our meta-analysis. Cheung *et al.*^[58] performed a small meta-analysis including four trials comparing banding ligation with banding ligation plus β -blockers, and did not find any significant difference for either mortality or bleeding rates. The meta-analysis of Gonzalez *et al.*^[51] included 23 trials. However, in contrast to our meta-analysis, these three meta-analyses^[51,57,58] included studies associating β -blockers with nitrates, as well as studies in which β -blockers were introduced only at the end of variceal eradication. We decided not to include these studies for both medical and methodological reasons. Firstly, there is no proof in current literature that the association of nitrates with β -blockers is superior to β -blockers alone concerning bleeding rates and mortality. One non-blinded trial found a significantly lower bleeding rate for patients treated with nadolol plus isosorbide mononitrate^[59]; however, two larger, more recent double-blinded placebo controlled trials^[60,61] were unable to confirm these results, with a greater number of side effects noted in the nitrate group^[60]. This association, which is poorly tolerated in certain patients, has therefore not yet been recommended by either the Baveno IV Consensus^[15], or the American College of Gastroenterology^[14]. Secondly, optimal combination therapy would entail introducing β -blockers at the beginning of endoscopic treatment as they would protect against bleeding recurrence before complete eradication, by reducing portal hypertension. We therefore chose not to include studies which started β -blocker treatment after eradication. However, we included all studies which started β -blockers at the beginning of eradication regardless of whether β -blocker treatment was continued after eradication or discontinued at the end of the eradication programme, as so far no studies have shown a difference in superiority between these two treatment protocols. Thirdly, including studies in which β -blockers are associated with nitrates or started only after eradication may considerably increase intertrial heterogeneity due to differences in treatment protocols. This methodological aspect has been an object of criticism in a recent editorial concerning a previous meta-analysis^[52]. We therefore did not include studies associating β -blockers

with nitrates. Our stricter study inclusion criteria may lead to more precise conclusions concerning optimal treatment modalities.

The results of clinical trials and meta-analyses especially should always be interpreted with caution. A recent trial comparing banding ligation alone with banding ligation associated with drug therapy^[28] did not find any significant difference in bleeding rates or mortality. However, in this trial drug therapy consisted of β -blockers associated with nitrates, as opposed to β -blockers alone, as in the trials included in the present meta-analysis. Our meta-analysis was limited by variations in quality of the studies included, and by lack of data concerning studies published as abstracts or letters, for which trial and patient characteristics were incomplete. The time over which data was included in this study was relatively large (1986-2005), which may contribute to inter-trial heterogeneity as improvements in patient care over time would affect bleeding and mortality outcomes. Data was insufficient to determine the effect of the date of trials on outcome. Likewise, subgroup analyses according to criteria such as Child's class, origin of cirrhosis or variceal size were not performed due to incomplete data. We nonetheless decided to include abstracts and letters in our meta-analysis in order to ensure optimal data analysis (246 additional patients). Adverse events were difficult to evaluate as the quality of reporting varied and most trials did not distinguish serious from non serious events. Nine studies did not perform intention-to-treat analysis whereas 2 did not state whether this was the case or not, which may lead to overestimation of treatment effect. Calculation of outcome measures at different time points reduced heterogeneity due to varying follow-up durations, but these results were limited by the fact that not all studies expressed outcome measures according to follow-up time. Ideally, a meta-analysis would include individual patient data with updated follow-up, but in our case these data were not available and we therefore had to rely on group data provided by each study. Nevertheless, we aimed to ensure the robustness of our meta-analysis results by calculating the failsafe number for each significant result, which was not estimated in previous meta-analyses^[51,57,58].

In conclusion, we show that combination endoscopic and β -blocker therapy is more effective than endoscopic therapy alone in secondary prophylaxis of variceal bleeding, with a significant decrease in bleeding rates and mortality. With banding ligation becoming more and more widespread, we believe that combination β -blocker and banding ligation therapy should be recommended as first line prophylactic treatment in cirrhotic patients who have already bled from oesophageal varices.

COMMENTS

Background

Upper gastro-intestinal bleeding from ruptured oesophageal varices is a frequent and serious complication of cirrhosis. It has been estimated that 70% of patients who survive a first variceal bleeding episode subsequently rebleed. Secondary prophylaxis of variceal bleeding is therefore crucial in the management of these patients.

Research frontiers

Both β -blockers and endoscopic treatment (alone or in combination) have been used to prevent variceal rebleeding. However, there is currently no consensus as to which treatments are the most effective in secondary prophylaxis of variceal bleeding.

Innovations and breakthroughs

This meta-analysis shows for the first time that mortality is significantly decreased when β -blockers are associated with either sclerotherapy or banding ligation compared to endoscopic therapy alone. Bleeding rates are also decreased with combination β -blocker and endoscopic therapy.

Applications

The results suggest that combination β -blocker and endoscopic therapy should be recommended as the first line treatment for the secondary prophylaxis of oesophageal variceal bleeding. Additional studies with long-term follow-up are needed to confirm the results concerning mortality.

Peer review

This topic is important and there is still a considerable difference of opinion in the literature. The authors have done an exacting job of describing the conditions of their meta-analysis so that the readers can easily put the findings into the context of their own practice.

REFERENCES

- 1 **Graham DY**, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology* 1981; **80**: 800-809
- 2 **Lebrech D**, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. *N Engl J Med* 1981; **305**: 1371-1374
- 3 **Garden OJ**, Mills PR, Birnie GG, Murray GD, Carter DC. Propranolol in the prevention of recurrent variceal hemorrhage in cirrhotic patients. A controlled trial. *Gastroenterology* 1990; **98**: 185-190
- 4 **Terés J**, Bosch J, Bordas JM, Garcia Pagán JC, Feu F, Cirera I, Rodés J. Propranolol versus sclerotherapy in preventing variceal rebleeding: a randomized controlled trial. *Gastroenterology* 1993; **105**: 1508-1514
- 5 **de Franchis R**, Primignani M. Endoscopic treatments for portal hypertension. *Semin Liver Dis* 1999; **19**: 439-455
- 6 **D'Amico G**, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis* 1999; **19**: 475-505
- 7 **Stiegmann GV**, Goff JS, Michaletz-Onody PA, Korula J, Lieberman D, Saeed ZA, Reveille RM, Sun JH, Lowenstein SR. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. *N Engl J Med* 1992; **326**: 1527-1532
- 8 **Laine L**, el-Newihi HM, Migikovsky B, Sloane R, Garcia F. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. *Ann Intern Med* 1993; **119**: 1-7
- 9 **Gimson AE**, Ramage JK, Panos MZ, Hayllar K, Harrison PM, Williams R, Westaby D. Randomised trial of variceal banding ligation versus injection sclerotherapy for bleeding oesophageal varices. *Lancet* 1993; **342**: 391-394
- 10 **Lo GH**, Lai KH, Cheng JS, Hwu JH, Chang CF, Chen SM, Chiang HT. A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. *Hepatology* 1995; **22**: 466-471
- 11 **Sørensen TI**. Failure of combined efforts: propranolol and sclerotherapy do not add up to the prevention of variceal bleeding. *J Hepatol* 1993; **19**: 197-199
- 12 **Lo GH**, Lai KH, Cheng JS, Chen MH, Huang HC, Hsu PI, Lin CK. Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal rebleeding: a prospective, randomized trial. *Hepatology* 2000; **32**: 461-465
- 13 **de la Peña J**, Brullet E, Sanchez-Hernández E, Rivero M, Ver-

- gara M, Martin-Lorente JL, Garcia Suárez C. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. *Hepatology* 2005; **41**: 572-578
- 14 **Garcia-Tsao G**, Sanyal AJ, Grace ND, Carey WD. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Am J Gastroenterol* 2007; **102**: 2086-2102
 - 15 **de Franchis R**. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005; **43**: 167-176
 - 16 **Poynard T**. [Evaluation of the methodological quality of randomized therapeutic trials] *Presse Med* 1988; **17**: 315-318
 - 17 **Nicolucci A**, Grilli R, Alexanian AA, Apolone G, Torri V, Liberati A. Quality, evolution, and clinical implications of randomized, controlled trials on the treatment of lung cancer. A lost opportunity for meta-analysis. *JAMA* 1989; **262**: 2101-2107
 - 18 **Pagliaro L**, D'Amico G, Sörensen TI, Lebrech D, Burroughs AK, Morabito A, Tiné F, Politi F, Traina M. Prevention of first bleeding in cirrhosis. A meta-analysis of randomized trials of nonsurgical treatment. *Ann Intern Med* 1992; **117**: 59-70
 - 19 **Collins R**, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med* 1988; **318**: 1162-1173
 - 20 **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-188
 - 21 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558
 - 22 **Egger M**, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634
 - 23 **Sterne JA**, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001; **54**: 1046-1055
 - 24 **Duval S**, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56**: 455-463
 - 25 **Orwin R**. A fail-safe N for effect size in meta-analysis. *J Educ Stat* 1983: 157-159
 - 26 **Jain A**, Kumar A, Tyagi P, Sharma B, Sarin SK. Endoscopic Variceal Ligation (EVL) Plus Propranolol (P) and Isosorbide Mononitrate (ISMN) Versus Endoscopic Variceal Ligation Alone in Secondary Prophylaxis of Variceal Bleeding: A Prospective Randomised Controlled Trial [Abstract]. *Am J Gastroenterol* 2006; **101**: S179
 - 27 **Jha S**, Kumar A, Sharma B, Sarin SK. Endoscopic variceal ligation (EVL) plus propranolol and isosorbide mononitrate versus EVL alone in secondary prophylaxis of variceal bleeding: a prospective RCT [Abstract]. *Hepatology* 2007; **46**: A250
 - 28 **Kumar A**, Jha SK, Sharma P, Dubey S, Tyagi P, Sharma BC, Sarin SK. Addition of propranolol and isosorbide mononitrate to endoscopic variceal ligation does not reduce variceal rebleeding incidence. *Gastroenterology* 2009; **137**: 892-901, 901.e1
 - 29 **Ahmad I**, Khan AA, Alam A, Butt AK, Shafqat F, Sarwar S. Propranolol, isosorbide mononitrate and endoscopic band ligation-alone or in varying combinations for the prevention of esophageal variceal rebleeding. *J Coll Physicians Surg Pak* 2009; **19**: 283-286
 - 30 **Lo GH**, Lai KH, Lee SD, Tsai YT, Lo KJ. Does propranolol maintain post-sclerotherapy variceal obliteration? A prospective randomized study. *J Gastroenterol Hepatol* 1993; **8**: 358-362
 - 31 **Sollano J**, Chan M, Ismael A, Babaran R, Lim E. Propranolol prevents rebleeding after variceal ligation [Abstract]. *Gastrointest Endosc* 2001; **53**: AB143
 - 32 **Kanazawa H**, Watari A, Matsusaka S, Tada N, Miyata K, Saitoh H, Yoshizawa M, Kuroda H, Kobayashi M. [Prospective controlled study of elective sclerotherapy plus oral propranolol for prevention of recurrent bleeding in cirrhotics with recent variceal hemorrhage] *Nippon Shokakibyo Gakkai Zasshi* 1991; **88**: 1341-1348
 - 33 **Villanueva C**, Martínez FJ, Torras X, Sáinz S, Soriano G, González D, Balanzó J. [Nadolol as an adjuvant to sclerotherapy of esophageal varices for prevention of recurrent hemorrhaging] *Rev Esp Enferm Dig* 1994; **86**: 499-504
 - 34 **Elsayed SS**, Shiha G, Hamid M, Farag FM, Azzam F, Awad M. Sclerotherapy versus sclerotherapy and propranolol in the prevention of rebleeding from oesophageal varices: a randomised study. *Gut* 1996; **38**: 770-774
 - 35 **Dowidar N**, Hafez A, Abdel Baki M. Endoscopic sclerotherapy of oesophageal varices due to hepatosplenic schistosomiasis. A randomized controlled trial evaluating the effect of adjuvant propranolol therapy. *J Egypt Soc Parasitol* 2005; **35**: 773-786
 - 36 **Westaby D**, Melia W, Hegarty J, Gimson AE, Stellan AJ, Williams R. Use of propranolol to reduce the rebleeding rate during injection sclerotherapy prior to variceal obliteration. *Hepatology* 1986; **6**: 673-675
 - 37 **Jensen LS**, Krarup N. Propranolol in prevention of rebleeding from oesophageal varices during the course of endoscopic sclerotherapy. *Scand J Gastroenterol* 1989; **24**: 339-345
 - 38 **Bertoni G**, Fornaciari G, Beltrami M, Conigliaro R, Grazia Mortilla M, Ricci E, Castagnetti E, Bedogni G, Plancher AC. Nadolol for prevention of variceal rebleeding during the course of endoscopic injection sclerotherapy: a randomized pilot study. *J Clin Gastroenterol* 1990; **12**: 364-365
 - 39 **Gerunda GE**, Neri D, Zangrandi F, Merenda R, Granzotto P, Ancona E, Battaglia G, Patarnello E, Antoniozzi F, Primignani M, Vitagliano P, de Franchis R. Nadolol does not reduce early rebleeding in cirrhotics undergoing endoscopic variceal sclerotherapy: a multicenter randomized controlled trial [Abstract]. *Hepatology* 1990; **12**: 988
 - 40 **Lundell L**, Leth R, Lind T, Lönnroth H, Sjövall M, Olbe L. Evaluation of propranolol for prevention of recurrent bleeding from esophageal varices between sclerotherapy sessions. *Acta Chir Scand* 1990; **156**: 711-715
 - 41 **Vinel JP**, Lamouliatte H, Cales P, Combis JM, Roux D, Desmorat H, Pradere B, Barjonet G, Quinton A. Propranolol reduces the rebleeding rate during endoscopic sclerotherapy before variceal obliteration. *Gastroenterology* 1992; **102**: 1760-1763
 - 42 **Acharya SK**, Dasarathy S, Saksena S, Pande JN. A prospective randomized study to evaluate propranolol in patients undergoing long-term endoscopic sclerotherapy. *J Hepatol* 1993; **19**: 291-300
 - 43 **Avgerinos A**, Rekoumis G, Klonis C, Papadimitriou N, Gouma P, Pournaras S, Raptis S. Propranolol in the prevention of recurrent upper gastrointestinal bleeding in patients with cirrhosis undergoing endoscopic sclerotherapy. A randomized controlled trial. *J Hepatol* 1993; **19**: 301-311
 - 44 **Vickers C**, Rhodes J, Chesner I, Hillenbrand P, Dawson J, Cockell R, Adams D, O'Connor H, Dykes P, Bradby H. Prevention of rebleeding from oesophageal varices: two-year follow up of a prospective controlled trial of propranolol in addition to sclerotherapy. *J Hepatol* 1994; **21**: 81-87
 - 45 **Benedeto-Stojanov D**, Tasic T, Bjelakovic G, Nagorni A. Prevention of recurrent upper gastrointestinal bleeding with propranolol in patients with cirrhosis undergoing endoscopic sclerotherapy. *J Hepatol* 2000; **32**: A72
 - 46 **Abdel-Rahim AY**, Abdel-Ghany MS, El-Kholy B. Band ligation alone versus band ligation and propranolol in the management of bleeding oesophageal varices [Abstract]. *Am J Gastroenterol* 2000; **95**: A2442
 - 47 **Laine L**, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. *Ann Intern Med* 1995; **123**: 280-287
 - 48 **Hou MC**, Lin HC, Kuo BI, Chen CH, Lee FY, Lee SD. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: a prospective randomized trial. *Hepatology* 1995; **21**: 1517-1522
 - 49 **Lo GH**, Lai KH, Cheng JS, Lin CK, Huang JS, Hsu PI, Chiang

- HT. Emergency banding ligation versus sclerotherapy for the control of active bleeding from esophageal varices. *Hepatology* 1997; **25**: 1101-1104
- 50 **Laosebikan AO**, Thomson SR, Naidoo NM. Schistosomal portal hypertension. *J Am Coll Surg* 2005; **200**: 795-806
- 51 **Gonzalez R**, Zamora J, Gomez-Camarero J, Molinero LM, Bañares R, Albillos A. Meta-analysis: Combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. *Ann Intern Med* 2008; **149**: 109-122
- 52 **Ayoub WS**, Nguyen MH. Combination of pharmacologic and endoscopic therapy for the secondary prevention of esophageal variceal bleeding. *Gastrointest Endosc* 2009; **70**: 665-667
- 53 **Abrales JG**, Tarantino I, Turnes J, Garcia-Pagan JC, Rodés J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. *Hepatology* 2003; **37**: 902-908
- 54 **Pérez-Ayuso RM**, Piqué JM, Bosch J, Panés J, González A, Pérez R, Rigau J, Quintero E, Valderrama R, Viver J. Propranolol in prevention of recurrent bleeding from severe portal hypertensive gastropathy in cirrhosis. *Lancet* 1991; **337**: 1431-1434
- 55 **Cholongitas E**, Papatheodoridis GV, Manesis EK, Burroughs AK, Archimandritis AJ. Spontaneous bacterial peritonitis in cirrhotic patients: Is prophylactic propranolol therapy beneficial? *J Gastroenterol Hepatol* 2006; **21**: 581-587
- 56 **Hoshino S**, Shinoura S, Akamine H, Kikuchi K, Keida Y. Effect of propranolol for the prevention of spontaneous bacterial peritonitis. *Am J Gastroenterol* 2000; **95**: A349
- 57 **Ravipati M**, Katragadda S, Swaminathan PD, Molnar J, Zarling E. Pharmacotherapy plus endoscopic intervention is more effective than pharmacotherapy or endoscopy alone in the secondary prevention of esophageal variceal bleeding: a meta-analysis of randomized, controlled trials. *Gastrointest Endosc* 2009; **70**: 658-664.e5
- 58 **Cheung J**, Zeman M, van Zanten SV, Tandon P. Systematic review: secondary prevention with band ligation, pharmacotherapy or combination therapy after bleeding from oesophageal varices. *Aliment Pharmacol Ther* 2009; **30**: 577-588
- 59 **Merkel C**, Marin R, Enzo E, Donada C, Cavallarin G, Torboli P, Amodio P, Sebastianelli G, Sacerdoti D, Felder M, Mazzaro C, Beltrame P, Gatta A. Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. Gruppo-Triveneto per L'ipertensione portale (GTIP). *Lancet* 1996; **348**: 1677-1681
- 60 **García-Pagán JC**, Morillas R, Bañares R, Albillos A, Villanueva C, Vila C, Genescà J, Jimenez M, Rodriguez M, Calleja JL, Balanzó J, García-Durán F, Planas R, Bosch J. Propranolol plus placebo versus propranolol plus isosorbide-5-mononitrate in the prevention of a first variceal bleed: a double-blind RCT. *Hepatology* 2003; **37**: 1260-1266
- 61 **D'Amico G**, Pasta L, Politi F, Vizzini G, Traina M, Caltagirone M, Patti R, Madonia S, Pagliaro L. Isosorbide mononitrate with nadolol compared to nadolol alone for prevention of the first bleeding in cirrhosis. A double-blind placebo-controlled randomized trial. *Gastroenterol Int* 2002; **15**: 40-50

S- Editor Shi ZF L- Editor O'Neill M E- Editor Ma WH