

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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## **Supplementary Appendix to the article**

# **Oral Rivaroxaban for the treatment of symptomatic pulmonary embolism**

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## **LEGENDS to figures for supplementary appendix**

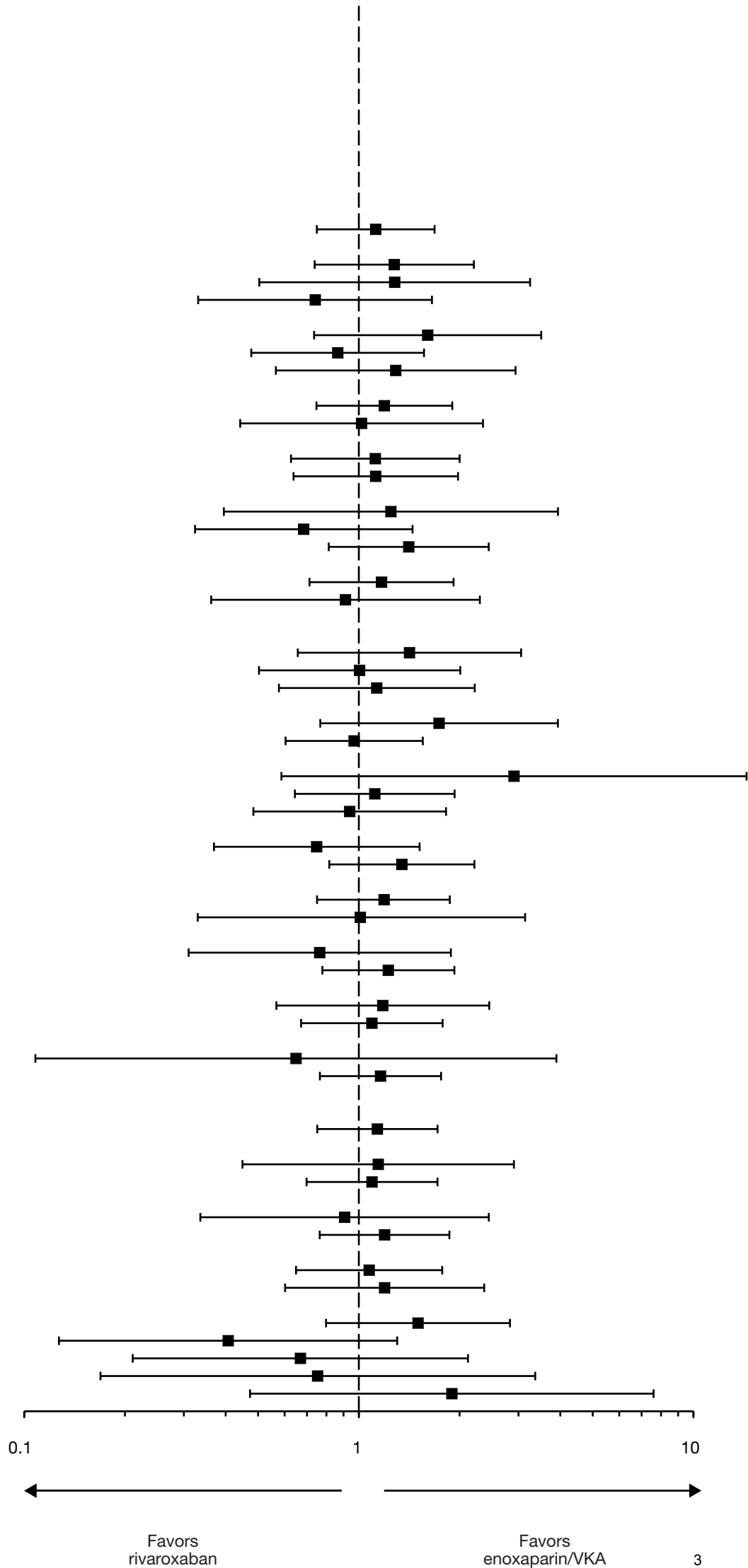
### **Appendix Figure 1. Relative efficacy in the pre-specified subgroups**

VKA, vitamin K antagonist; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low molecular weight heparin.

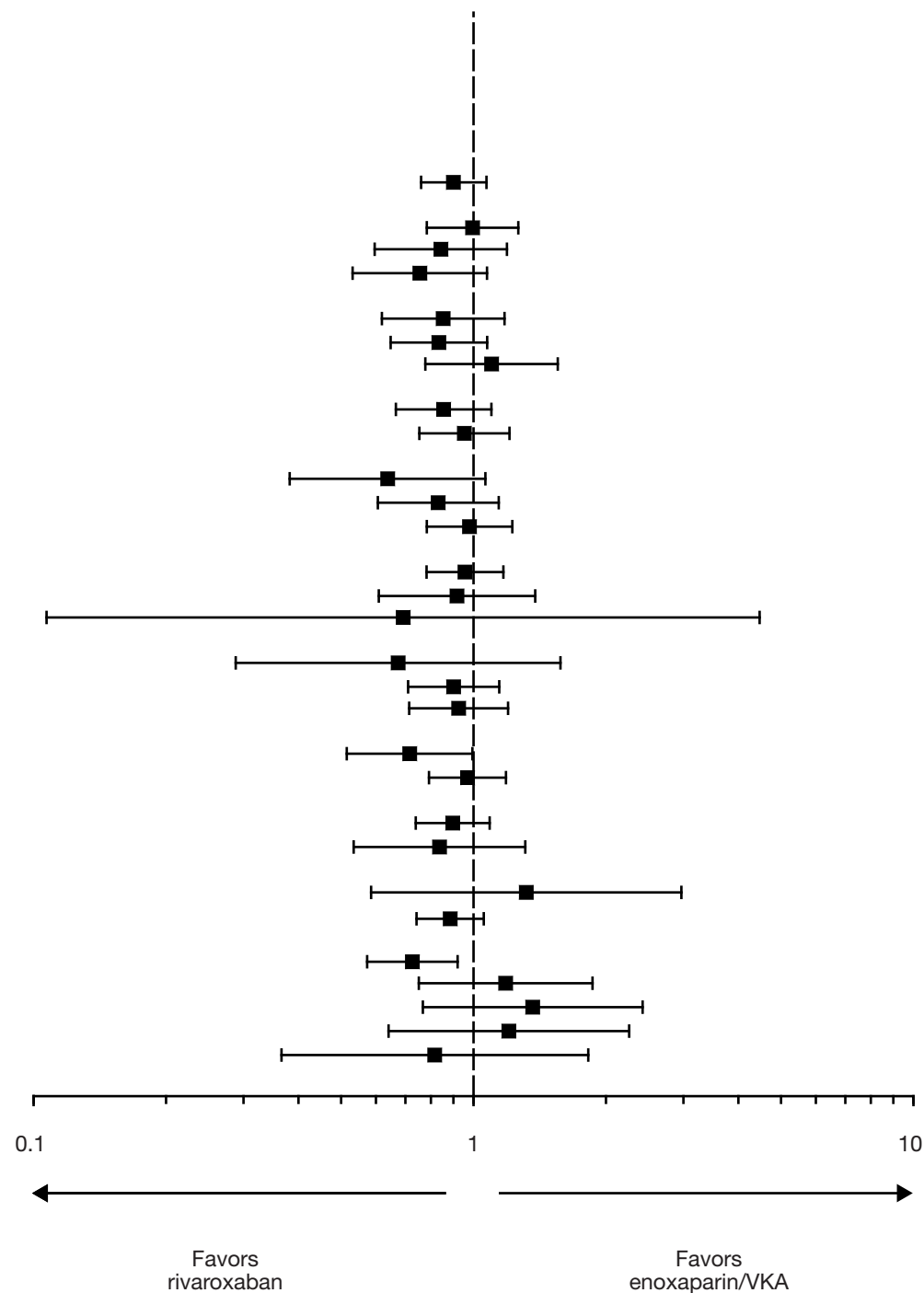
### **Appendix Figure 2: Relative safety in the pre-specified subgroups (major and clinically relevant non-major bleeding)**

VKA, vitamin K antagonist; LMWH, low molecular weight heparin.

	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Overall	50/2419	(2.1)	44/2413	(1.8)
Age				
<65 years	29/1461	(2.0)	23/1479	(1.6)
65–75 years	10/517	(1.9)	8/532	(1.5)
>75 years	11/441	(2.5)	13/402	(3.2)
Weight				
≤70 kg	17/653	(2.6)	10/621	(1.6)
>70–90 kg	20/1081	(1.9)	24/1119	(2.1)
>90 kg	13/683	(1.9)	10/672	(1.5)
Body mass index				
<30 kg/m <sup>2</sup>	39/1668	(2.3)	32/1643	(1.9)
≥30 kg/m <sup>2</sup>	11/741	(1.5)	11/755	(1.5)
Gender				
Male	25/1309	(1.9)	21/1247	(1.7)
Female	25/1110	(2.3)	23/1166	(2.0)
Creatinine clearance				
<50 ml/min	7/211	(3.3)	5/193	(2.6)
50 – <80 ml/min	12/637	(1.9)	16/593	(2.7)
≥80 ml/min	30/1555	(1.9)	22/1617	(1.4)
Prerandomization LMWH				
1 day	34/1754	(1.9)	29/1760	(1.6)
2 days	9/460	(2.0)	9/443	(2.0)
>2 days	0/23	(0.0)	0/20	(0.0)
Severity of PE				
1st tercile	16/751	(2.1)	11/723	(1.5)
2nd tercile	16/737	(2.2)	16/756	(2.1)
3rd tercile	18/810	(2.2)	16/820	(2.0)
Index PE				
With DVT	16/603	(2.7)	9/587	(1.5)
Without DVT	34/1793	(1.9)	35/1803	(1.9)
Intended treatment duration				
3 months	6/127	(4.7)	2/122	(1.6)
6 months	27/1387	(1.9)	24/1387	(1.7)
12 months	17/905	(1.9)	18/904	(2.0)
Fragility				
Yes	14/510	(2.7)	17/477	(3.6)
No	36/1909	(1.9)	27/1936	(1.4)
VKA received (by site)				
Warfarin	40/1801	(2.2)	34/1841	(1.8)
Acenocoumarol	6/359	(1.7)	6/359	(1.7)
Cardiac disease				
Yes	9/428	(2.1)	10/374	(2.7)
No	41/1991	(2.1)	34/2039	(1.7)
Pulmonary disease				
Yes	16/627	(2.6)	13/608	(2.1)
No	34/1792	(1.9)	31/1805	(1.7)
Active cancer				
Yes	2/114	(1.8)	3/109	(2.8)
No	48/2305	(2.1)	41/2304	(1.8)
Thrombophilic condition				
Yes	2/138	(1.4)	2/121	(1.7)
No	48/2281	(2.1)	42/2292	(1.8)
Immobilization				
Yes	10/384	(2.6)	8/380	(2.1)
No	40/2035	(2.0)	36/2033	(1.8)
Prior DVT/PE				
Yes	7/455	(1.5)	9/489	(1.8)
No	43/1964	(2.2)	35/1924	(1.8)
Idiopathic index PE				
Yes	32/1566	(2.0)	29/1551	(1.9)
No	18/853	(2.1)	15/862	(1.7)
Region				
Western Europe	24/1309	(1.8)	16/1311	(1.2)
Australia & New Zealand	4/306	(1.3)	10/307	(3.3)
North America	5/244	(2.0)	7/242	(2.9)
Eastern Europe	3/208	(1.4)	4/209	(1.9)
Asia	6/145	(4.1)	3/142	(2.1)



	<b>Rivaroxaban</b>		<b>Enoxaparin/VKA</b>	
	n/N	(%)	n/N	(%)
Overall	249/2412	(10.3)	274/2405	(11.4)
Age				
<65 years	132/1458	(9.1)	136/1472	(9.2)
65–75 years	59/514	(11.5)	71/532	(13.3)
>75 years	58/440	(13.2)	67/401	(16.7)
Weight				
≤70 kg	71/649	(10.9)	79/618	(12.8)
>70–90 kg	110/1078	(10.2)	134/1116	(12.0)
>90 kg	68/683	(10.0)	61/670	(9.1)
Gender				
Male	117/1307	(9.0)	129/1243	(10.4)
Female	132/1105	(11.9)	145/1162	(12.5)
Creatinine clearance				
<50 ml/min	26/209	(12.4)	34/192	(17.7)
50 – <80 ml/min	73/634	(11.5)	81/593	(13.7)
≥80 ml/min	149/1553	(9.6)	159/1610	(9.9)
Prerandomization LMWH				
1 day	186/1749	(10.6)	195/1757	(11.1)
2 days	45/460	(9.8)	47/441	(10.7)
>2 days	3/23	(13.0)	2/19	(10.5)
Intended treatment duration				
3 months	9/125	(7.2)	13/122	(10.7)
6 months	129/1383	(9.3)	142/1382	(10.3)
12 months	111/904	(12.3)	119/901	(13.2)
Fragility				
Yes	64/508	(12.6)	80/476	(16.8)
No	185/1904	(9.7)	194/1929	(10.1)
VKA received (by site)				
Warfarin	194/1796	(10.8)	219/1834	(11.9)
Acenocoumarol	35/359	(9.7)	42/359	(11.7)
Active cancer				
Yes	14/114	(12.3)	10/108	(9.3)
No	235/2298	(10.2)	264/2297	(11.5)
Region				
Western Europe	119/1306	(9.1)	161/1308	(12.3)
Australia & New Zealand	41/305	(13.4)	34/307	(11.1)
North America	28/244	(11.5)	20/239	(8.4)
Eastern Europe	21/207	(10.1)	18/209	(8.6)
Asia	11/143	(7.7)	13/140	(9.3)



Supplementary Appendix Table 1

Cardiovascular events

On treatment population	<b>Rivaroxaban (N = 2412)</b>	<b>Standard-therapy (N = 2405)</b>
Acute coronary event	15 (0.6)	21 (0.9)
Cerebrovascular event	12 (0.5)	13 (0.5)
Systemic embolism	5 (0.2)	3 (0.1)
30 day post study treatment period	<b>Rivaroxaban (N = 2206)</b>	<b>Standard-therapy (N = 2197)</b>
Acute coronary event	3 (0.1)	2 (0.09)
Cerebrovascular event	2 (0.09)	1 (0.05)
Systemic embolism	1 (0.05)	0

## **Supplementary Appendix**

A) Study committees and B) Investigators- Study centers participating in the EINSTEIN-PE Study

A) Study committees

### **Steering Committee (consists of 2 committees)**

#### **1) Executive Committee:**

Giancarlo Agnelli  
Scott Berkowitz  
Henri Bounameaux  
Harry R. Büller (Chair)  
Alexander Cohen  
Alexander Gallus  
Anthonie W.A. Lensing  
Frank Misselwitz  
Lloyd Haskell  
Martin H. Prins  
Gary Raskob  
Sebastian Schellong

#### **2) Study Management and Coordination Committee:**

Rupert Bauersachs  
Bonno van Bellen  
Zoltán Boda  
Lars Borris  
Benjamin Brenner  
Tim Brighton  
Jaromir Chlumsky  
Bruce Davidson  
Herve Decousus  
Henry Eriksson  
Barry Jacobson  
Ajay Kakkar  
Yok-Lam Kwong  
Lai Heng Lee  
Karina Meijer (Jan van der Meer<sup>†</sup>)  
Erich Minar  
Manuel Monreal  
Franco Piovella  
Per Morten Sandset  
Mark Smith

Witold Tomkowski  
Peter Verhamme  
Yuqi Wang  
Phil Wells

**Central Independent Adjudication Committee:**

Dees Brandjes  
Melvin Mac Gillavry  
Hans-Martin Otten  
Martin H. Prins (Chair)

**Data Safety Monitoring Board:**

Anders Carlsson  
Silvy Laporte  
Sam Schulman (Chair)

**Dose Confirmation Committee**

Michael Gent  
Alexander Turpie

**24 hours medical support line**

Ida Martinelli  
Annelise Segers  
Bruce Davidson

**Study management of Bayer HealthCare:**

Global clinical lead: Anthonie W. Lensing  
Eva Muhlhofer  
Miriam Tewes  
Mila Trajanovic  
Karin Muller  
Calvin Kim  
Martin Gebel  
Alice Benson  
Akos Ferenc Pap  
Juliette Godrie  
Andrea Horvat-Broecker  
Giovanni Spadari  
Cornelia Peters-Wulf



## **B) the Investigators- Study centers participating in the EINSTEIN-PE Study**

*Andorra* (2 patients, 1 center) – J. Roig, Andorra (2). *Australia* (499 patients, 23 centers) – R. Baker, Perth (31); A. Bianchi, Sydney (11); P. Blombery, Melbourne (3); T. Brighton, Sydney (18); P. Campbell, Geelong (1); P. Carroll, R. Geraghty, Redcliffe (62); B. Chong, S. Ramanathan, C. Archis, Sydney (49 patients, 3 centers); P. Coughlin, H. Salem, Box Hill (51); P. Crispin, Garran (4); M. Dean, R. Soni, Gosford (24); C. Denaro, P. Kubler, Brisbane (28); D. Coghlan, A. Gallus, Adelaide (20); T. Eng Gan, H. Tran, C. Coleman, Melbourne (51); D. Jackson, Lismore (19); A. Khalafallah, Launceston (14); M. Leahy, Fremantle (16); M. Leyden, D. Leyden, C. Sturtz, Ringwood (46); A. McCann, Brisbane, H. Gibbs, Melbourne (24); S. McRae, Adelaide (1); B. Richards, Gold Coast (1); C. Ward, J. Curnow, Sydney (25). *Austria* (229 patients, 6 centers) – M. Baghestanian, B. Erdogmus, E. Samaha, M. Nikoupayan-Mofrad, Vienna (110); M. Hirschl, Vienna (21); W. Sturm, R. Kirchmair, P. Marschang, Innsbruck (43); H. Drexel, R. Mathies, Feldkirch (28); E. Pilger, M. Brodmann, Graz (24); A. Weltermann, Linz (3). *Belgium* (194 patients, 12 centers) – M. Buche, Yvoir (1); J. Demelenne, Namur (3); M. Gustin, Luik (9); P. Hainaut, L. Pothén, Brussels (51); J. de Leersnyder, Duffel (1); S. Motte, Bruxelles (32); H. Schroë, Genk (1); M. Sprynger, Liege (3); P. Verhamme, K. Peerlinck, M. Delcroix, Leuven (67); F. Vermassen, Gent (1); P. Verstraeten, V. Smet, Aalst (23); R. Vossaert, Zottegem (2). *Brazil* (18 patients, 2 centers) – B. van Bellen, São Paulo (14); M. Panico C. Porto, São Paulo (4). *Canada* (137 patients, 4 centers) – J. Blondal, Toronto (1); M. Kovacs, A. LazoLangner, London (74); P. Wells, M. Rodger, M. Carrier, Ottawa (48); T. Wong, Winnipeg (14). *China* (228 patients, 15 centers) – J. Bi, Wuhan (1); Z. Chen, Beijing (6); R. Chen, Guangzhou (12); Z-C Jing, J. He, Shanghai (17); C. Liu, Beijing (2); S. Liu, Beijing (20); S. Long (19); Y. Ma, Beijing (12); Y. Shao, Harbin (27); Y. Wang, Shanghai (4); C. Wang, YH Yang, Beijing (40); C. Xie, Guangzhou (5); J. Xu, Beijing (6); K. Ying, Hangzhou (25); L. Zhihong, Beijing (32). *Czech Republic* (221 patients, 7 centers) – J. Chlumsky, D. Hola, Prague (21); S. Jirat, M. Vitovec, Prague (18); K. Kovářová, J. Gilík, J. Dosál, Ostrava (89); E. Mandakova, Rakovník (2); P. Matoška, Ostrava (5); I. Podpera, M. Podperova, Kladno (55); R. Spacek, R. Urbanova, Prague (31). *Denmark* (2 patients, 1 center) – C. Tuxen, Copenhagen (2). *Estonia* (8 patients, 1 center) – K. Sukles, Tallinn (8). *Finland* (10 patients, 2 centers) – K. Pietila, Tampere (7); M. Vesanen, Turku (3). *France* (1171 patients, 34 centers) – A. Achkar, Vernon (22); B. Agraou, Valenciennes (12); S. Aquilanti, A. Rifaï, Arras (95); T. Berremili, Annecy (10); D. Brisot, C. Brousse, P. Tarodo, Castelnau le Lez (69); A. Bura, C. Amid-Lacombe, J. Malloizel, Toulouse (49); C. Boulon, Bordeaux (7); L. Alavoine, B. Crestani, Bichat Paris (33); P. Mismetti, A. Buchmuller, S. Accassat, Saint-Etienne (74); A. Elias, M. Elias, Toulon (33); J. Emmerich, HEGP Paris (6); E. Ferrari, Nice (164); T. Guérin, P. Beaka, Roanne (21); P. Lacroix, Limoges (11); T.A. Szwebel, Hotel Dieu, Paris (13); Y.

Benhamou, Rouen (10); E. de Maistre, N. Falvo, Dijon (17); I. Mahe, Colombes (4); N. Meneveau, F. Schiele, Besançon (36); G. Meyer, O. Sanchez, B. Planquette, Est Paris (94); D. Mottier, E. Le Moigne, F. Couturaud, Brest (56); F. Parent, Clamart (4); G. Pernod, B. Imbert, Grenoble (38); D. Elkouri, M. Dary, Nantes (34); A. Queguiner, Orthez (9); I. Quere, JP Galanaud, Montpellier (31); P.M. Roy, J.M. de Boisjolly-Bonnefoi, Angers (18); J. Schmidt, N. Breuil, S. Heuser, Clermont-Ferrand (91); M.A. Sevestre, Amiens (6); G. Simoneau, JF Bergamnn, Lariboisiere Paris (29); D. Stephan, Strasbourg (10); A. Trinh-Duc, A. Gaillardou, Agen (16); C. Grange, T. Fassier, Lyon (37); D. Wahl, Nancy (12). *Germany* (351 patients, 25 centers) – P. Baron Von Bilderling, München (3); R. Bauersachs, Darmstadt (10); P. Kuhlencordt, Würzburg (1); J. Beyer-Westendorf, K. Halbritter, S. Werth, Dresden (41); C. Diehm, H. Lawall, Karlsbad (31); B. Eifrig, Hamburg (1); C. Espinola-Klein, G. Weisser, Mainz (25); E. Giannitsis, Heidelberg (5); H.U. Haering, Tübingen (12); C. Hasslacher, Heidelberg (3); T. Herrmann, Bruchsal (22); U. Hoffmann, M. Czihal, Munich (20); Th. Horacek, Witten (2); M. Ibe, A. Bauer, Nordhausen (18); A. Kieback, Hamburg (11); H. Landgraf, Berlin (9); E. Lindhoff-Last, Frankfurt (6); N. Malyar, Essen (2); W. Petermann, Paderborn (28); J. Potratz, Rotenburg (9); J. Ranft, Bottrop (12); M. Röcken, Tübingen (1); S. Schellong, L. Pomper, R. Frommhold, Dresden (54); M. Schwaiblmair, Th. Berghaus, Augsburg (20); B. Taute, Halle (5). *Hong Kong* (6 patients, 2 centers) – Y.K. Lau, Hong Kong (3); E. Tse, Hong Kong (3). *Hungary* (117 patients, 10 centers) – Z. Boda, Zs. Olah, Debrecen (35); K. Farkas, E. Kolossváry, Budapest (15); M. Gurzó, Kecskemét (7); E. Kis, Szekszárd (2); A. Kovács, Szentés (24); A. Landi, Budapest (4); G. Lupkovics, Zalaegerszeg (8); Zs. Pecsvarady, Kistarcsa (5); M. Riba, Szombathely (4); Gy. Sipos, Miskolc (13). *India* (2 patients, 1 center) – R. Parakh, New Delhi (2). *Indonesia* (3 patients, 1 center) – R. Sembiring, Medan (3). *Ireland* (2 patients, 1 center) – J. Barton, Ballinasloe (2). *Israel* (155 patients, 10 centers) – M. Elias, L. Goldstein, Afula (26); D. Gavish, Holon (3); R. Hoffman, Haifa (33); O. Hussein, Safed (7); A. Inbal, Petah Tikva (2); M. Lishner, A. Elis, Kfar Saba (15); G. Lugassy, Ashkelon (9); D. Varon, Jerusalem (1); D. Zeltser, O. Rogowski, A. Steinvil, Tel Aviv (54); D. Zisman, Haifa (5). *Italy* (106 patients, 13 centers) – W. Ageno, Varese (4); G. Ambrosio, Venezia (3); M. Cattaneo, Milano (7); A. D’Angelo, Milano (1); A. Ghirarduzzi, M. Iotti, Reggio Emilia (15); M. Giorgi Pierfranceschi, Piacenza (9); C. Lodigiani, Rozzano (2); I. Martinelli, Milan (1); G. Palareti, Bologna (4); M. Barone, C. Beltrametti, Pavia (16); E. Porreca, Francavilla Chieti (6); P. Prandoni, L. Spiezia, Padua (29); R. Quintavalla, Parma (9). *Korea* (11 patients, 4 centers) – W.H. Cho, Daegu (1); J.W. Ha, Seoul (1); H.S. Kim, Seoul (8); K. Park, Daegu (1). *Latvia* (4 patients, 1 center) – I. Sime, Liepaja (4). *Lithuania* (10 patients, 2 centers) – S. Miliauskas, Kaunas (9); R. Petrauskiene, Vilnius (1). *Malaysia* (2 patients, 1 center) – J. Sathar, Ampang (2). *Netherlands* (264 patients, 6 centers) – A. Beeker, Hoofddorp (12); H. Ten Cate, Maastricht (9); M. De Groot, Enschede (6); P. Kamphuisen, R. Douma, Amsterdam (19); M. van Marwijk Kooy, J. Coenen, Zwolle (32); K. Meijer, A. Mäkelburg, M. Knol, V. Tichelaar, Groningen (186). *New Zealand* (114 patients, 5 centers) – P.

Harper, E. Knottenbelt, Palmerston North (25); P. Ockelford, L. Young, Auckland (33); G. Royle, Otahuhu (29); D. Simpson, S. Chunilal, Auckland (20); M. Smith, Christchurch (7). *Norway* (43 patients, 3 centers) – W. Ghanima, S. Foyn, Fredrikstad (26); P.M. Sandset, Oslo (11); A. Tveit, Rud (6). *Philippines* (7 patients, 1 center) – M.T. Abola, Quezon City (7). *Poland* (58 patients, 7 centers) – R. Adamiec, Wroclaw (1); P. Gorski, Lodz (1); J. Kloczko, Bialystok (1); J. Lewczuk, M. Nowak, Wroclaw (33); J. Musial, Kraków (8); W. Tomkowski, Warsaw (13); J. Wronski, Lublin (1). *Singapore* (2 patients, 1 center) – H.J. Ng, Singapore (2). *South Africa* (239 patients, 10 centers) – D. Adler, Johannesburg (7); J.H.R. Becker, Pretoria (3); G. Ellis, Somerset West (28); R. Isaacs, B. Bloy, R. Allie, F. Eckstein, Johannesburg (107); B. Jacobson, Johannesburg (22 patients, 2 centers); J.H. Jansen van Rensburg, Centurion (23); S. Schmidt, Goodwood (1); H. Siebert, Pretoria (35); L. Zyl, Worcester (13). *Spain* (78 patients, 8 centers) – M. Carrera, Palma de Mallorca (6); F. Del Campo, Valladolid (5); I. Diego, Terrassa (2); F. Garcia-Bragado, Girona (11); D. Jiménez, Madrid (4); J. Sánchez-Álvarez, M. Redondo, Pamplona (35); P. Roman Sanchez, Requena (2); J. Villalta, Barcelona (13). *Sweden* (77 patients, 5 centers) – H. Eriksson, M. Villegas-Scivetti, Göteborg (30); T. Jonson, H. Tygesen, Borås (25); L. Lapidus, Göteborg (7); E. Ottosson, Stockholm (9); A. Sjölander, Sundsvall (6). *Switzerland* (75 patients, 6 centers) – L. Asmis, Zurich (1); M. Banyai, M. Heidemann, Lucerne (19); I. Baumgartner, Bern (7); H. Bounameaux, M. Righini, Geneva (27); U. Frank, Chur (6); D. Hayoz, D. Periard, Fribourg (15). *Taiwan* (11 patients, 4 centers) – W.T. Chang, Taipei (4); K. Chiu, New Taipei City (5); K.Y. Wang, Taichung (1); Z-C Weng, Taipei City (1). *Thailand* (18 patients, 3 centers) – P. Angchaisuksiri, Bangkok (13); C. Pothirat, Chiang Mai (4); P. Rojnuckarin, Bangkok (1). *United Kingdom* (21 patients, 3 centers) – A. Cohen, J. Solis, London (15); B. J. Hunt, London (5); J. Luckit, London (1). *United States* (350 patients, 23 centers) – C. Albrecht, Baltimore (7); D. Banish, Covington (2); D. Feinbloom, Boston (4); W. Botnick, Decatur (2); D. Chen, Tacoma (38); J. Dexter, Redlands (15); N. Ettinger, Chesterfield (13); J. Gleeson, Albuquerque (1); A. Jaffer, Miami (2 patients, 2 centers); S. Joseph, Spokane (10); M. Kennedy, Pittsburgh (7); K. Krell, Idaho Falls (53); R. Lavender, Little Rock (8); R. M. Lyons, San Antonio (14); S. Moll, Chapel Hill (6); V. Nadar, K. Darrow, V. Hardman, Harrisburg (45); S. Rathbun, Oklahoma City (7); J. Rehm, Fredericksburg (42); W. Rodriguez-Cintron, San Juan (7); K. Stevens, Troy (12); P. Wright, M. Ramaswamy, Greensboro (55 patients, 2 centers).