

# Colchicine for the prevention of peri-operative atrial fibrillation after major thoracic surgery – the COP-AF trial

David Conen MD MPH, on behalf of the COP-AF investigators

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# Background

- **Perioperative atrial fibrillation (AF) and myocardial injury after noncardiac surgery (MINS)**
  - prognostically important adverse outcomes after major thoracic surgery
- **Colchicine is an anti-inflammatory drug**
  - reduced risk of perioperative AF in small cardiac surgery trials
  - reduced major cardiovascular events in patients with coronary artery disease (LoDoCo2, COLCOT)

# Study objective

- To evaluate effect of oral colchicine on occurrence of
  - Clinically important perioperative AF
  - MINS
- In patients undergoing major noncardiac thoracic surgery

# Co-primary outcomes

- **Clinically important AF**

- AF that results in angina, heart failure, or symptomatic hypotension, or that requires treatment with rate-controlling drug, antiarrhythmic drug, or electrical cardioversion
- Definition chosen because of its prognostic relevance and to avoid adding short asymptomatic AF episodes of uncertain clinical relevance

- **MINS**

- Myocardial infarction (MI), or elevated postoperative troponin that was judged to be due to myocardial ischemia



# Patients

- **Inclusion criteria**

- Age  $\geq 55$  years
- Scheduled for noncardiac thoracic surgery with general anaesthesia
- Expected to require at least one overnight hospital stay after surgery

- **Main exclusion criteria**

- History of AF or currently taking anti-arrhythmic medication
- Minor thoracic interventions (e.g. needle biopsy, chest tube insertion)
- Contraindication for colchicine (e.g. severe renal dysfunction)
- Currently taking non-study colchicine
- Currently taking medications known to interact with colchicine metabolism

# Study procedures

- **Study medication**

- first dose of colchicine 0.5mg or matching placebo was administered within 4 hours before surgery
- Thereafter, study medication was given twice daily for total of 10 days
- Patients, healthcare providers, outcome adjudicators and all study personnel were blinded to treatment assignment

- **Outcome ascertainment**

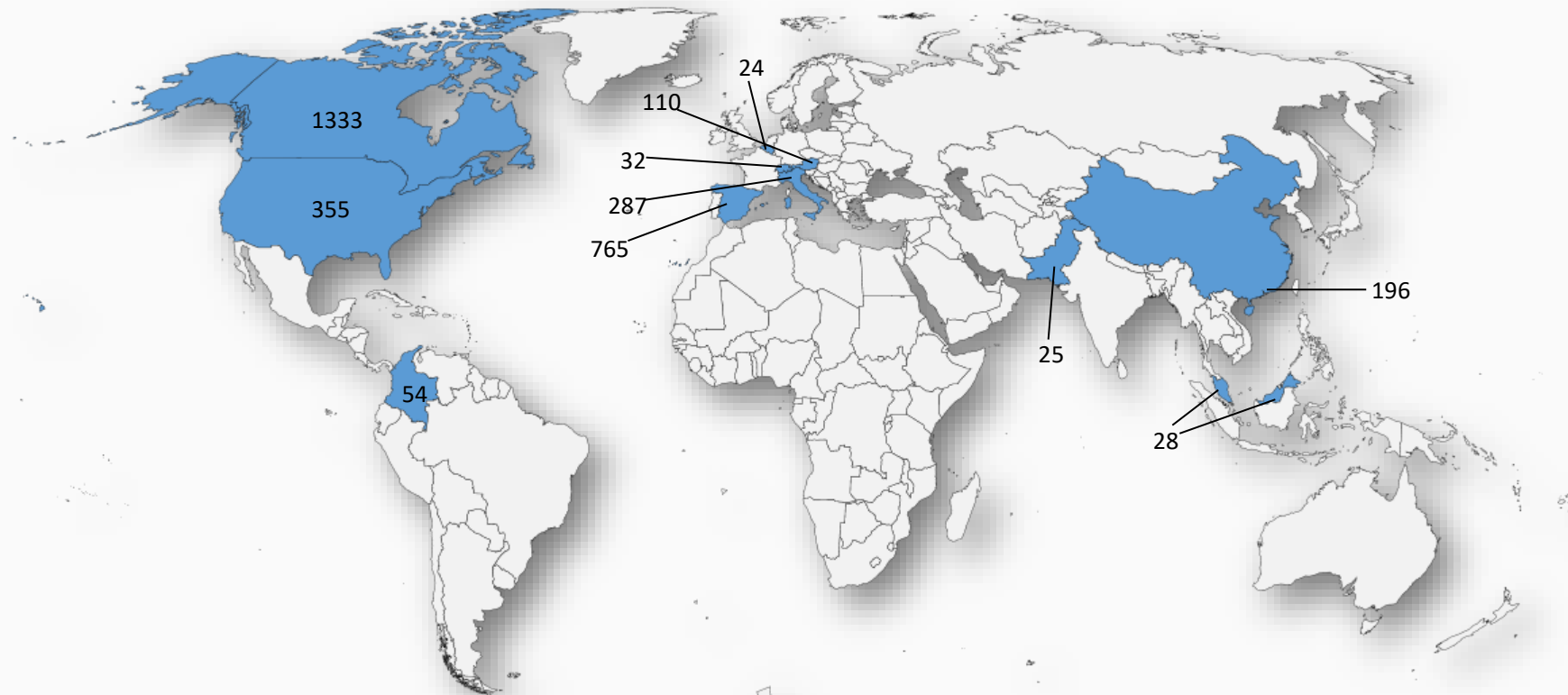
- Mandatory daily troponin measurements for 3 days after surgery
- Rhythm monitoring was as per standard care

- **Total follow-up duration was 14 days**

# Protocol change and sample size increase

- COP-AF was originally designed to recruit 2800 patients, with single primary outcome of clinically important AF
- After publication of LoDoCo2 and COLCOT, MINS was added as an independent co-primary outcome
- New sample size of 3200 patients was needed:
  - Assuming a 9.0% incidence for perioperative AF, 30% relative RR, 2-sided  $\alpha=0.0324$  provided 83% power for first co-primary outcome
  - Assuming a 22% incidence for MINS, 20% relative RR, 2-sided alpha  $\alpha=0.0176$  provided 80% power for second co-primary outcome

## 3209 patients randomized at 45 sites in 11 countries



3208 (>99.9%) patients with complete 14-day follow-up

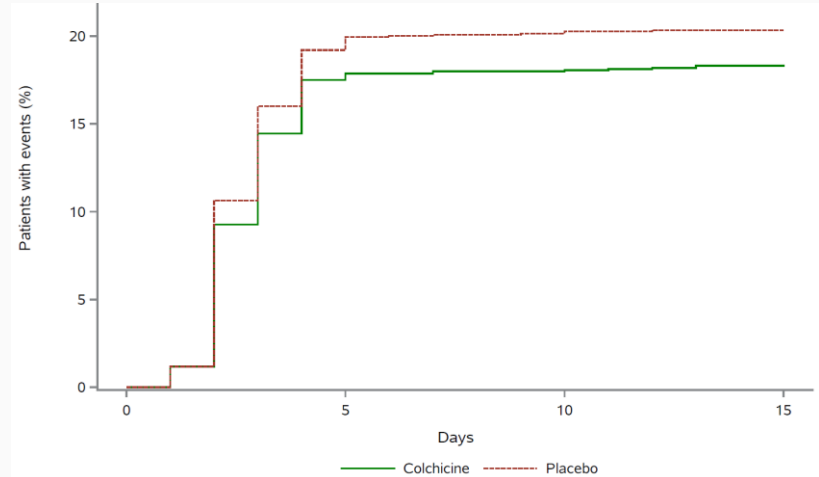
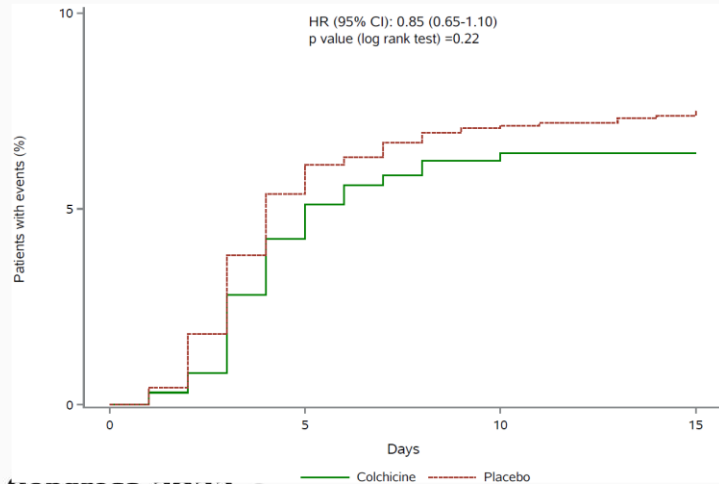


# Baseline characteristics

Characteristics	Colchicine (N=1608)	Placebo (N=1601)
Age, mean (SD)	68 (7)	68 (7)
Male, N (%)	831 (52)	825 (52)
<b>Medical History</b>		
Coronary artery disease, N (%)	142 (9)	144 (9)
Diabetes mellitus, N (%)	301 (19)	294 (18)
Hypertension, N (%)	836 (52)	832 (52)
Current tobacco use, N (%)	351 (22)	336 (21)
<b>Type of surgery</b>		
Lobe resection, N (%)	1029 (64)	1013 (63)
Wedge resection, N (%)	314 (20)	337 (21)
Segment resection, N (%)	245 (15)	242 (15)
<b>Surgical approach</b>		
Thoracoscopic, N (%)	1219 (76)	1178 (74)
Thoracoscopic converted to open, N (%)	98 (6)	106 (7)
Open (Non-thoracoscopic), N (%)	276 (17)	304 (19)

# Co-primary outcomes

	Colchicine (N=1608)	Placebo (N=1601)	Hazard Ratio (95% CI)	P Value
<b>Clinically important perioperative AF</b>	103 (6.4)	120 (7.5)	0.85 (0.65-1.10)	0.22
<b>Myocardial injury after noncardiac surgery</b>	295 (18.3)	325 (20.3)	0.89 (0.76-1.05)	0.16



# Main secondary and safety outcomes

	Colchicine (N=1608)	Placebo (N=1601)	Hazard Ratio (95% CI)	P Value
<b>Secondary outcomes – N (%)</b>				
Composite of all-cause mortality, nonfatal MINS and nonfatal stroke	300 (18.7)	335 (20.9)	0.88 (0.75-1.03)	0.11
Composite of all-cause mortality, nonfatal MI and nonfatal stroke	21 (1.3)	31 (1.9)	0.67 (0.39-1.17)	0.16
MINS not fulfilling the fourth universal definition of MI	285 (17.7)	311 (19.4)	0.90 (0.76-1.06)	0.22
Myocardial infarction	13 (0.8)	15 (0.9)	0.86 (0.41-1.81)	0.69
<b>Safety outcomes – N (%)</b>				
Composite of sepsis and infection	103 (6.4)	83 (5.2)	1.24 (0.93-1.66)	0.14
Non-infectious diarrhoea*	134 (8.3)	38 (2.4)	3.64 (2.54-5.22)	<0.001

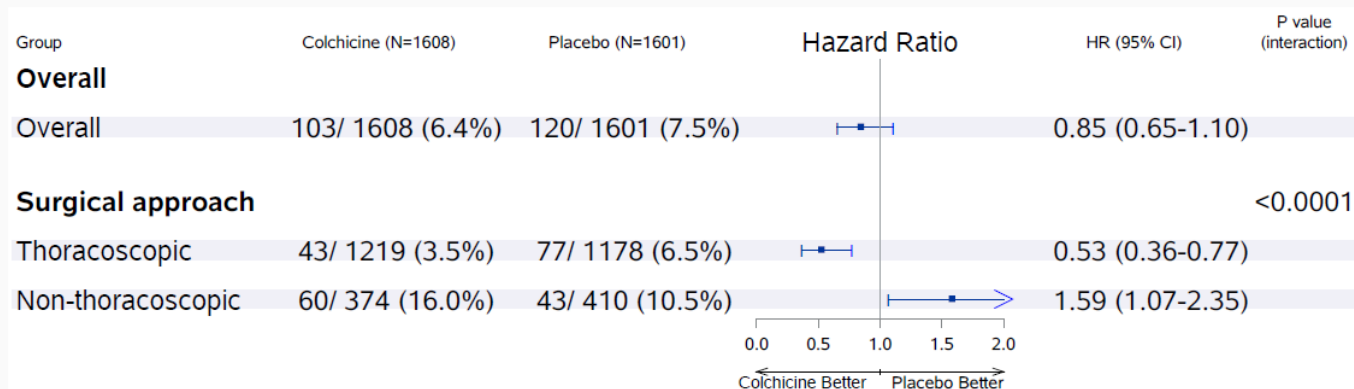
\* Diarrhoea did not prolong median length of hospital stay and led to only one readmission.

# Post-hoc analyses

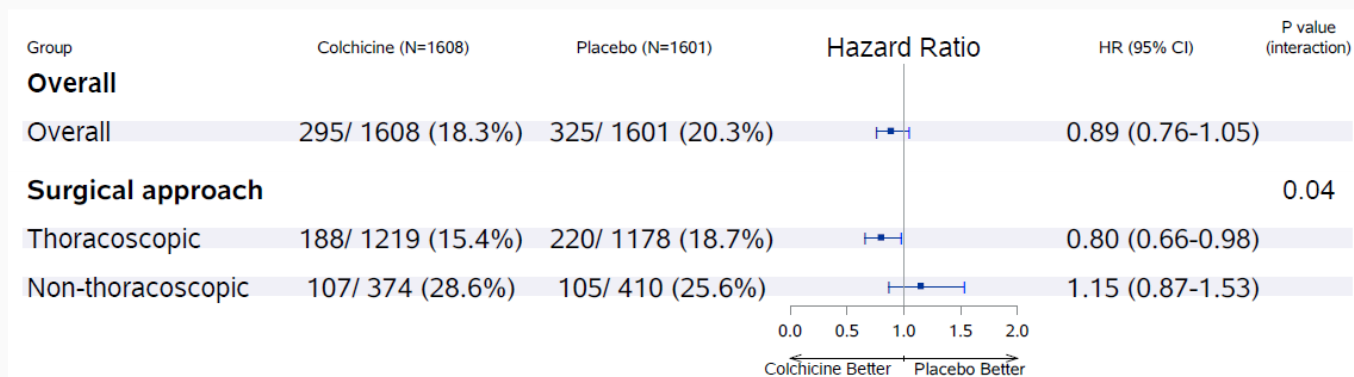
	Colchicine (N=1608)	Placebo (N=1601)	Hazard Ratio (95% CI)	P Value
<b>Post-hoc outcomes – N (%)</b>				
Composite of MINS and clinically important AF	360 (22.4)	415 (25.9)	0.84 (0.73-0.97)	0.02
Composite of vascular mortality, nonfatal MINS, nonfatal stroke and clinically important AF	364 (22.6)	422 (26.4)	0.83 (0.72-0.96)	0.01

# Subgroup analyses

## Clinically important AF



## MINS



# Conclusion

- In patients undergoing major noncardiac thoracic surgery administration of colchicine did not significantly reduce incidence of co-primary outcomes clinically important AF or MINS
- Colchicine increased risk of mostly benign non-infectious diarrhoea
- Encouraging and consistent trend of fewer cardiovascular events with colchicine that requires further research

# COP-AF investigators

David Conen (Principal Investigator), PJ Devereaux (Chair), Jeff S. Healey, Giovanni Landoni, William F. McIntyre, Ekaterine Popova, Daniel I. Sessler, Sadeesh K. Srinathan, Jessica Vincent, Michael Ke Wang, Jennifer R. Wells. Mohammed Amir, Shrikant I. Bangdiwala, Matthias Bossard, Matthew TV Chan, John W. Eikelboom, Edith Fleischmann, Jeff S. Healey, Sanjit Jolly, Giovanni Landoni, William F. McIntyre, Felix Ramón Montes, Ekaterine Popova, Cara Reimer, Denis Schartz, Daniel I. Sessler, Sadeesh K. Srinathan, Jessica Vincent, Chew Yin Wang, Michael Ke Wang, Jennifer R. Wells. William F. McIntyre (Chair), Michael Ke Wang, Sandra N. Ofori, Steffen Blum, Jesus Alvarez-Garcia, Giuliana Lo Bianco, Hugh Traquair, Fernando Andres Guerrero-Pinedo, Christopher Oleynick, Pascal B. Meyre, Francisco Méndez-Zurita, Helene Chiarella-Redfern, Maura Marucci, Francesco Donati, Aranzazu Gonzalez-Osuna, Fabrizio Minervini, Zoraida Moreno Weidmann, Jose M. Guerra-Ramos, Gabriel Dion, Anna Ramos-Pachón, Flavia K. Borges, Danielle de Sa Boasquevisque, Maria Giulia Mosconi, Pierre Amarenco. L. Brent Mitchell (Chair), George Wyse (Past Chair), Davy Cheng, Finlay A. McAlister, George A. Wells. Geethan Baskaran, Andrew T. Burns, Julia Gennaccaro, Rosemary Howe, Louise Mastrangelo, Shirley Pettit, Michelle Popovic, Subana Shahbaz, Makayla Tosh, Jessica Vincent, Jennifer R. Wells, Simona J. Zucchetto. Shrikant I. Bangdiwala, Laura Heenan, Shun Fu Lee, Zhuoru Li, Lizhen Xu. Mohammed Amir (Pakistan), Matthias Bossard (Switzerland), Matthew TV Chan (China), David Conen (Canada), Edith Fleischmann (Austria), Giovanni Landoni (Italy), Felix Ramón Montes (Colombia), Ekaterine Popova (Spain), Denis Schartz (Belgium), Daniel I. Sessler (United States), Chew Yin Wang (Malaysia).

AUSTRIA (110) – Medical University of Vienna (110): Barbara Kabon, Edith Fleischmann, Konrad Hoetzenecker, Thomas Schweiger, Christian Reiterer, Oliver Zotti, Paul Bsuehner, Beatrix Hochreiter, Alexander Taschner, Nikolas Adamowitsch, Katharina Horvath, Nicole Hantáková.

BELGIUM (24) – CHU Brugmann, Université libre de Bruxelles (10): Denis Schartz, Javad Bidgoli; CUB Hôpital Erasme, Université libre de Bruxelles (8): Isabelle Huybrechts; University Hospital of Charleroi (6): Serge Cappeliez.

CANADA (1,333) – St. Joseph's Healthcare Hamilton (525): John D. Neary, Yaron Shargall, Vikas Tandon, David Conen, Christian Finley, John Agzarian, Waël Hanna, Muammar Abdulrahman, Kelly Lawrence, Krysten Gregus, Faraaz Quraishi, Spencer Wikkerink, Christine Wallace, Merissa Prine, Emily Gregus, Jacqueline Hare, Kristen Lombardo, Behashta Fezia, Teresa Columbus, Jacob Rushton; Kingston Health Sciences Centre (197): Cara Reimer, Deborah DuMerton, Ken Reid, Joel Parlow, Wiley Chung, Maria Karzhenskaia, Aftab Malik, Rob Tanzola, Andrew Giles; Vancouver General Hospital (186): Sean R. McLean, Anna McGuire, Jens Lohser, Shirley Lim, Rebecca Grey, John Yee, Kyle Grant, Alex L. Lee, James J. Choi, Leith R. Dewar, Christopher Durkin, Travis Schisler, Patrick Hecht, Bevan Hughes; Health Sciences Centre, Winnipeg (181): Sadeesh K. Srinathan, Biniam Kidane, Richard Liu, Lawrence Tan, Stephen Gowing, Gordon Buduhan, Stephanie Enns, Emma Poole, Kristin Graham, Niina Dubik, Andrew Giles, Alex Chin; The Ottawa Hospital (81): Donna E. Maziak, Andrew JE Seely, Sebastien Gilbert, P. James Villeneuve, Sudhir Sundaresan, Molly Gingrich, Anna Fazekas, Kirby Bucciero; London Health Sciences Centre (52): Richard A. Malthaner, Deb Lewis, Dalilah Fortin, Mehdi Qiabi, Rahul Nayak; Victoria General Hospital (44): Madelaine Marie Plourde, Tehmina Haider, Rowan Murphy; Toronto General Hospital (26): Daniel Sellers, Laura Donahoe; CIUSSS de l'Estrie – CHUS (17): Marco Lefebvre, Luc Lanthier; St. Joseph's Health Centre – Unity Health Toronto (11): Michael Augustine Ko, David Parente, Victoria Cheung; Foothills Medical Centre (8): Colin Schieman; Montreal General Hospital (5): Amal Bessisow.

CHINA (196) – The Chinese University of Hong Kong (186): Matthew TV Chan, Randolph HL Wong, Gavin M. Joynt, Carmen KM Lam, Rainbow WH Lau, Innes YP Wan, Malcolm J. Underwood, William KK Wu, Wai Tat Wong, Gordon YS Choi, Eva Lee, Ka Yan Hui, Beaker Fung, Chee Sam Chan; Tuen Mun Hospital (10): Fung Kei Ng, Kin Hoi Thung.

COLOMBIA (54) – Fundación Cardioinfantil – Instituto de Cardiología (54): Laura Gutiérrez-Soriano, Felix Ramón Montes, Laura Carmenza Castañeda, Luis Jaime Téllez, Lina Marcela Ortiz-Ramirez.

ITALY (287) – IRCCS San Raffaele Scientific Institute (111): Giovanni Landoni, Martina Baiardo-Redaelli, Alessandro Belletti, Elisa Dieci, Fabrizio Monaco, Piergiorgio Muriana, Cristina Nakhnouch, Pierluigi Novellis, Stefano Turi, Stefano Viscardi, Giulia Veronesi; Careggi University Hospital (87): Luca Voltolini, Stefano Bongiolatti, Alberto Salvicchi, Lavinia Gatteschi, Rossella Indino, Simone Tombelli, Alice Ravasin, Ottavia Salimbene; A.O.U. Città della Salute e della Scienza di Torino (42): Giulio Luca Rosboch, Eleonora Balzani, Edoardo Ceraolo, Luca Neitzert, Luca Brazzi; S. Maria della Misericordia University Hospital (27): Francesco Londero, William Gossi; Sant'Andrea Hospital (14): Domenico Massullo, Silvia Fiorelli; Policlinico Universitario Agostino Gemelli (6): Stefano Margaritara.

MALAYSIA (28) – University Malaya Medical Centre (25): Chew Yin Wang, Shahrul Amry Hashim, Sivakumar Krishnasamy; Serdang Hospital (3): Woan Shiang See.

PAKISTAN (25) – Shifa International Hospital (25): Mohammed Amir, Mohammed Asghar Nawaz, Haris Bilal.

SPAIN (765) – Hospital de la Santa Creu i Sant Pau (275): Juan Carlos Trujillo Reyes, Elisabeth Martínez-Téllez, Ekaterine Popova, Josep Belda Sanchis, Georgina Planas Canovas, Alejandra Libreros Niño, Ana Parera Ruiz, Esther Cladellas Gutierrez, Mauro Guarino, Gerard Urrutia Cuchi, Marta Argilaga Nogue, Anna Rovira Juan, Melixa Medina-Aedo, M<sup>a</sup> Asunción Turró Castillo, Josep M<sup>a</sup> Gil Sanchez, Ibell Araúz-Sarmiento, Gracia Herranz Perez, Stephanie Chavarria Murillo, Alvaro Garcia-Osuna, Ainhoa Rodriguez-Arias, Nuria Berga Garrote; Hospital Universitario Ramón y Cajal (179): Ascension Martín Grande, Diego Parise Roux, Luis Gajate Martín, Angélica De Pablo Pajares, Angel Manuel Candela Toha, Nicolás Moreno Mata, Oema Muñoz Molina, Usue Caballero Silva, Alberto Cabañero, Sara Fra Fernandez, Cristina Cavestany García-Matres, Luisa Simón, Cristina Montenegro, Sergio Pozo; Vall d'Hebron Hospital Universitari (159): Anna González-Tallada, Susana González Suarez, Montserrat Ribas Ball, Miriam De Nadal Clanchet, Javier Pérez Vélez; Hospital Universitari Gregorio Marañón (82): Patricia Cruz, Guillermo Sánchez-Pedrosa, Patricia Duque, Guillermo González, Luis Huerta, Laura Rodríguez, Ignacio Garutti; Hospital Universitari Sagrat Cor, Grupo Quironsalud (48): Laura Ruiz-Villa, Maria del Mar Martí-Ejarque, Mireia Gili-Bueno, Ricardo Matias Máncho Vieyra, Juan J. Fibla, Núria Durán, Marina de Temple Pla; Hospital del Mar (14): Alberto Rodríguez-Fuster, Silvia Bermejo-Martínez; Hospital Clínic, Barcelona (8): Albert Carramiñana.

SWITZERLAND (32) – Luzerner Kantonsspital (17): Matthias Bossard, Fabrizio Minervini; University Hospital Zurich (15): Isabelle Opitz, Harry Etienne.

UNITED STATES (355) – The University of Texas MD Anderson Cancer Center (200): Juan P. Cata, Juan Jose Guerra-Londono, Ravi Rajaram, German Corrales, Ara Vaporciyan, Reza Mehran, Boris Sepesi, Garrett Walsh, David Rice, Daniel S. Cukierman, Stephen Swisher; Atrium Health Wake Forest Baptist (56): Bryan E. Marchant, Lynne C. Harris, Bruce D. Cusson, Scott A. Miller; Fairview Hospital, Cleveland Clinic (30): Sabry Ayad, Jorge Araujo, Leonardo Marquez-Roa, Richard L. Hofs, Sean M. Wudl, Jesse Cleveland (29): Steven C. Minear, Camila Teixeira, Mario Pimentel; Henry Ford Health (27): Andrew M. Popoff, Kelly Marsack, Sarah Meehan; Rhode Island Hospital (7): Tzonghuei H. Chen; The Ohio State University Wexner Medical Center (4): Michael Essandoh; Stony Brook University Hospital (2): Jeremy S. Poppers.

# Publication

- **The full publication will be available tonight 11.30pm (UK time) at <https://www.thelancet.com>**

## Effect of colchicine on perioperative atrial fibrillation and myocardial injury after non-cardiac surgery in patients undergoing major thoracic surgery (COP-AF): an international randomised trial

*David Conen, Michael Ke Wang, Ekaterine Popova, Matthew TV Chan, Giovanni Landoni, Juan P Cata, Cara Reimer, Sean R McLean, Sadeesh K Srinathan, Juan Carlos Trujillo Reyes, Ascension Martín Grande, Anna Gonzalez Tallada, Daniel I Sessler, Edith Fleischmann, Barbara Kabon, Luca Voltolini, Patricia Cruz, Donna E Maziak, Laura Gutiérrez-Soriano, William F McIntyre, Vikas Tandon, Elisabeth Martínez-Téllez, Juan Jose Guerra-Londono, Deborah DuMerton, Randolph H L Wong, Anna L McGuire, Biniam Kidane, Diego Parise Roux, Yaron Shargall, Jennifer R Wells, Sandra N Ofori, Jessica Vincent, Lizhen Xu, Zhuoru Li, John W Eikelboom, Sanjit S Jolly, Jeff S Healey, P J Devereaux, on behalf of the COP-AF Investigators\**