Outpatient Management of Patients with Acute Pulmonary Embolism

The Home Treatment of Pulmonary Embolism (HoT-PE) Trial

Stavros V. Konstantinides

Center for Thrombosis und Hemostasis, University of Mainz, Germany
stavros.konstantinides@unimedizin-mainz.de

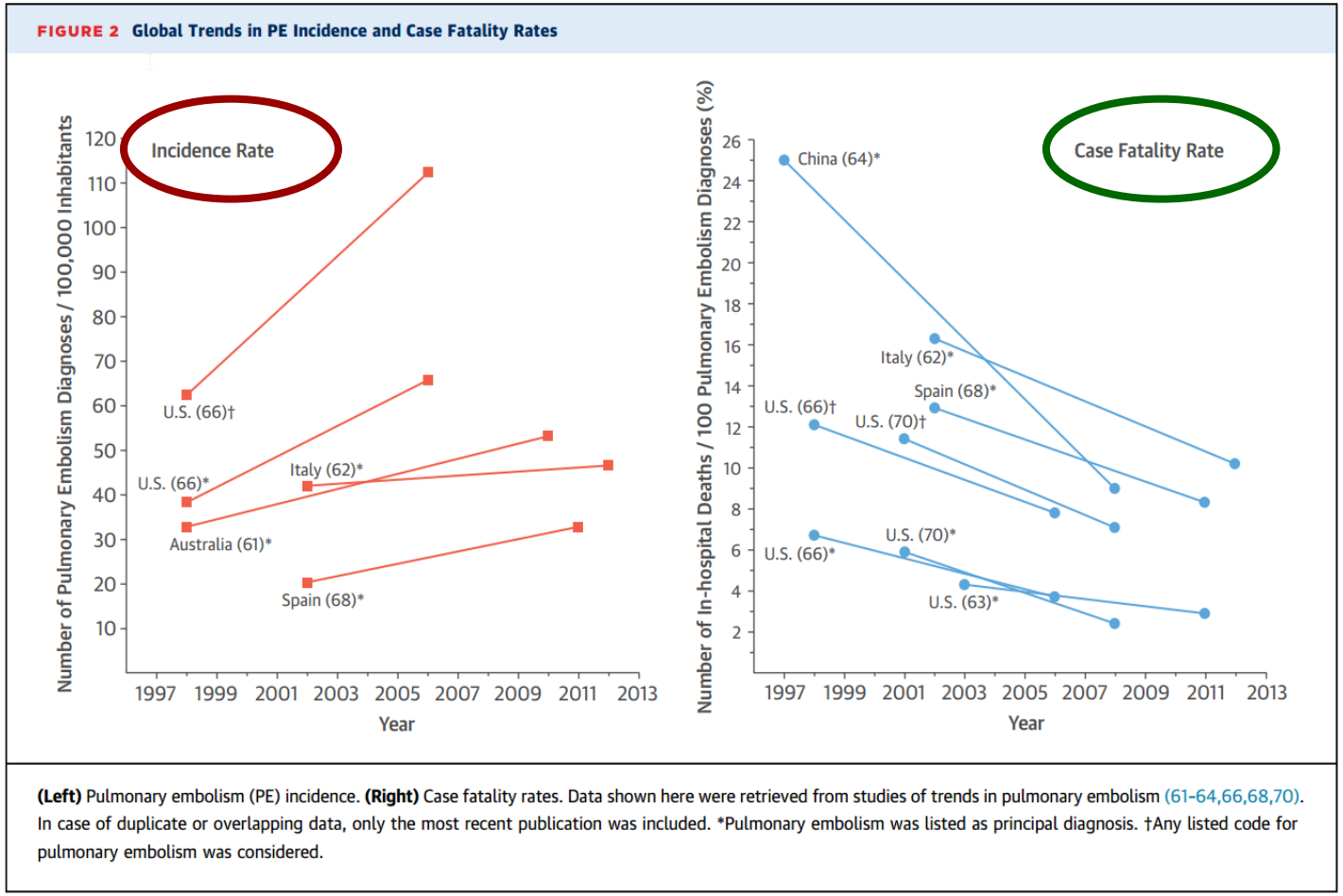
Democritus University of Thrace, Greece
skonst@med.duth.gr

Disclosures

Lecture & consultancy honoraria: Bayer AG, Boehringer Ingelheim, MSD, Pfizer – Bristol-Myers Squibb, Daiichi-Sankyo, Actelion, Biocompatibles Group UK, Servier

Institutional research support: Bayer AG, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Actelion

PE and VTE: rising incidence, high costs



(Left) Pulmonary embolism (PE) incidence. **(Right)** Case fatality rates. Data shown here were retrieved from studies of trends in pulmonary embolism (61-64,66,68,70). In case of duplicate or overlapping data, only the most recent publication was included. *Pulmonary embolism was listed as principal diagnosis. †Any listed code for pulmonary embolism was considered.

Event	Cost (in €, 2014)
PE events (inpatients)	3,891-4,197
DVT events (inpatients)	1,685-2,330
DVT events (outpatients)	1,614-1,847
Direct annual VTE costs	1.3-7.1 billion

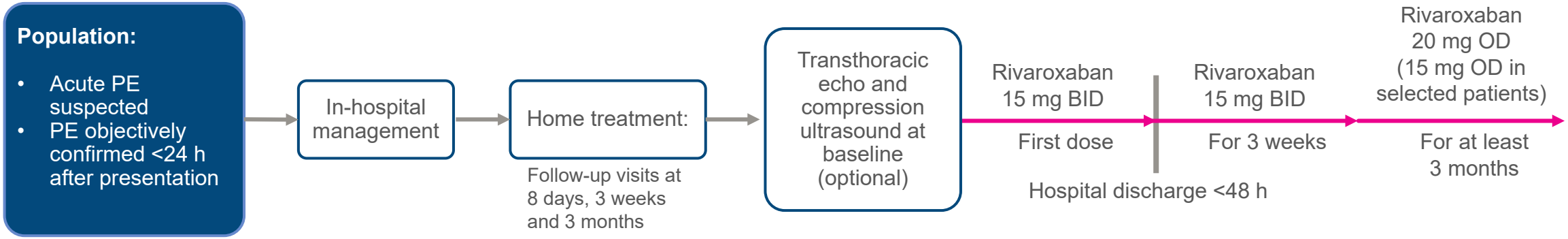
Costs per event retrieved from literature data, inflated to 2014 currency and adjusted for Purchasing Power Parity: low and high medians are presented.

Konstantinides S, et al. *J Am Coll Cardiol* 2016;67:976-990

Barco S, et al. *Thromb Haemost* 2014;116:800-808

HOT-PE Objectives and study design

- **Objective**: to determine whether early discharge and out-of-hospital treatment of patients with acute low-risk PE with the F Xa inhibitor rivaroxaban is feasible, effective and safe
- **Prospective, investigator-initiated and academically sponsored, international, multicenter, single-arm phase 4 management trial with 3-month follow-up (plus one-year follow-up for survival)**



Barco S, et al. *Thromb Haemost* 2016;116:191–197

HOT-PE Key selection criteria

- Inclusion criteria:
  - Age ≥18 years
  - Objectively confirmed PE
  - Absence of RV dysfunction and of free floating thrombi in the heart (echo or CT)

- Exclusion criteria:
  - Hemodynamic instability; need for reperfusion treatment of PE

  - Active bleeding or known bleeding risk
  - Need for oxygen or parenteral analgesics
  - Serious comorbidity requiring hospitalization; severe renal/hepatic dysfunction
  - PE diagnosed in a patient hospitalized for another reason
  - Patient on chronic treatment with any anticoagulant, or antiplatelet agent except ASA ≤100 mg/day
  - Pregnancy or lactation
  - Life expectancy < 3 months

  - Lack of compliance
  - Lack of support by family or social background

EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-001657-28/DE

HOT-PE Study flow

Hemodynamically stable patient admitted with clinically suspected PE:

☞ **Start parenteral anticoagulation**

↓

☞ **Confirm PE within 24 hours of admission**
(Chest CT, V/Q scan or pulmonary angiogram)

↓

Enrollment after eligibility criteria verified and informed consent

↓

☞ **First dose of rivaroxaban in hospital**

↓

Additional baseline tests (echocardiography, CUS of leg veins) recommended, not compulsory

↓

☞ **Discharge within 48 hours of admission (max. 2 nights in hospital)**

↓

3-month follow-up

CUS, compression ultrasound

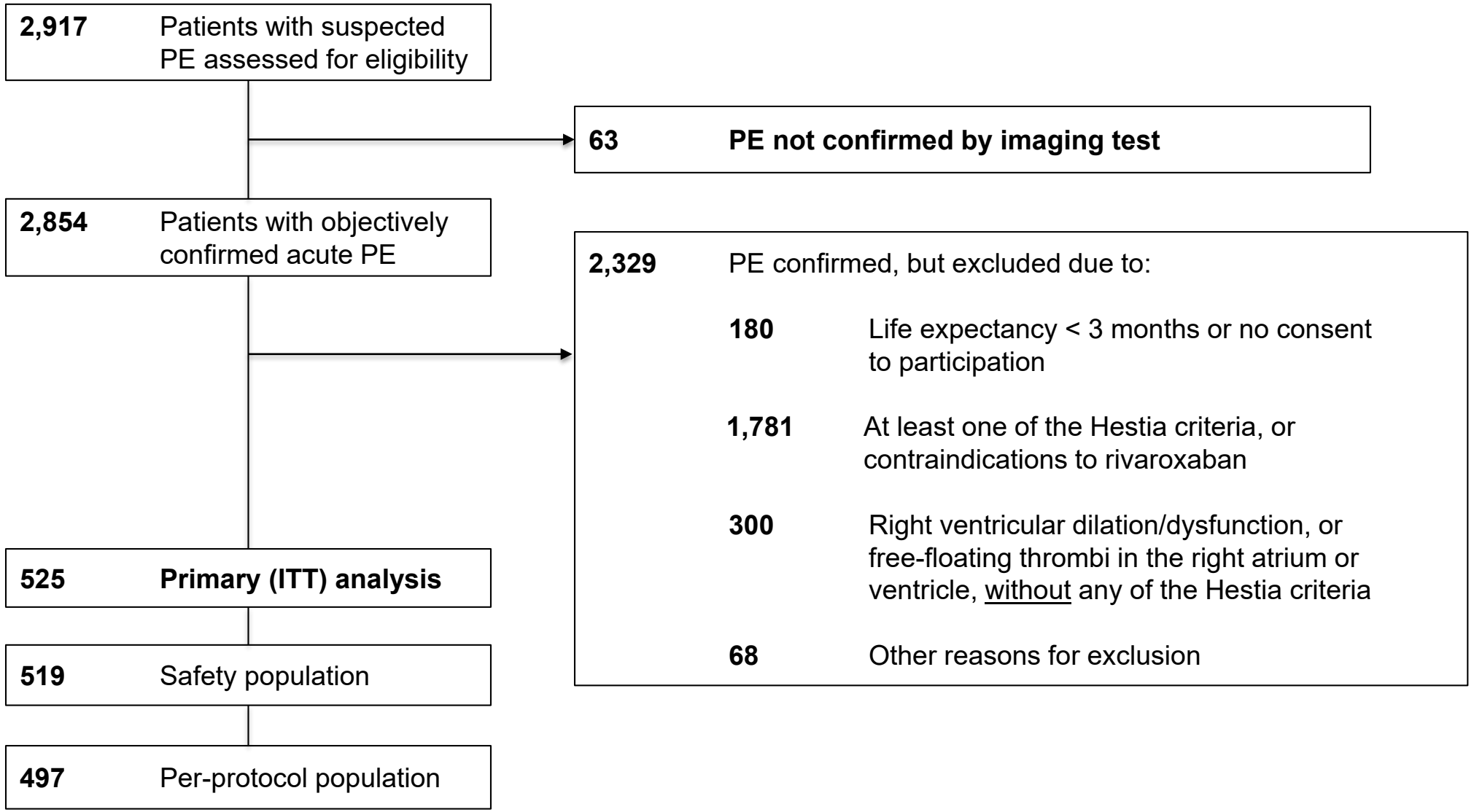
Barco S, et al. *Thromb Haemost* 2016; 116:191–197

Sample size calculation, interim analysis, early termination

- H_0 that $p \geq 0.03$[a] (probability of recurrent VTE or PE-related death within 3 months) tested against H_1 that $p < 0.03$, using a binomial test (2-stage adaptive design based on O'Brien Fleming design)
- Point estimate for 3-month symptomatic VTE recurrence rate, 1.7%[b]
- A total of 1,050 patients required for 80% power to reject H_0 with $\alpha \leq 0.05$
- Interim analysis planned after enrollment and 3-month evaluation of the first 525 patients in ITT population, with the objective of early termination of the study if H_0 could be rejected at the level of $\alpha=0.004$ (<6 events)

[a] Based on the largest RCT on home treatment of PE (Aujesky D, et al. *Lancet* 2011;378:41-48)
[b] Based on a meta-analysis of home treatment studies (Zondag W, et al. *Eur Respir J* 2013;42:134-144), and the EINSTEIN PE trial (Büller HR, et al. *N Engl J Med* 2012;366:1287-1297)

HOT-PE Screened – enrolled – analyzed patients



HOT-PE Baseline characteristics

Patient Demographics	
Age, mean (SD; range)	**56.7 (16.6; 18-90) y**
Women	240/525 (45.7%)
Caucasian	517/525 (98.5%)
Functional Parameters and Biochemical Markers	
Body mass index, mean (SD)	27.8 (5.0) kg/m²
Systolic/diastolic BP, mean (SD)	137/80 (19/12) mm Hg
Heart rate, mean (SD)	78 (13) b.p.m.
Oxygen saturation, mean (SD)	97% (2)
Creatinine clearance < 30 mL/min	2/525 (0.4%)
Creatinine clearance 30 to 50 mL/min	**27/525 (5.1%)**
Hs troponin T , median (IQR)	8 (5-13) pg/mL
NT-proBNP, median (IQR)	88 (49-188)

Risk Factors for Pulmonary Embolism and Comorbidities	
Estrogen use	81/520 (15.6%)
Immobilization (for at least 3 days)	54/520 (10.4%)
Previous deep vein thrombosis	82/515 (15.9%)
Previous pulmonary embolism	39/521 (7.5%)
Recent major surgery (within past 30 days)	37/523 (7.1%)
Recent major trauma (within past 30 days)	23/524 (4.4%)
Long travel (> 4 hours, within past 30 days)	66/517 (12.8%)
Active cancer	**32/518 (6.2%)**
Chronic obstructive pulmonary disease	26/518 (5.0%)
Chronic heart failure	7/524 (1.3%)
Simplified PESI ≥ 1	**106/525 (20.2%)**

HOT-PE Primary efficacy outcome

Primary Efficacy Outcome[a]	
Recurrent venous thromboembolism or fatal PE (ITT population)	**3/525 (0.6%)**
One-sided upper 99.6% CI & p-value	**2.1%; p<0.0001**
Recurrent PE (95% CI)	**3/525 (0.6%; 0.1-1.7%)**
Recurrent deep vein thrombosis	**0**
Death related to PE	**0**
Recurrent venous thromboembolism or fatal PE (PP population)	2/497 (0.4%)
One-sided upper 99.6% CI & p-value	1.3%; p<0.0001
Recurrent venous thromboembolism or fatal PE (worst case scenario)	5/525 (0.95%)
One-sided upper 99.6% CI & p-value	1.99%; p<0.0015

[a] Adjudicated by an independent clinical events committee.

HOT-PE Safety outcomes

Safety Outcomes[a]	
Major bleeding[b] (95% CI)	6/519 (1.2%; 0.4-2.5%)
Any clinically relevant bleeding (95% CI)	31/519 (6.0%; 4.1-8.4%)
At least one serious adverse event (SAE; with 95% CI)	58/519 (11.2%; 8.6-14.2%)

[a] Adjudicated by an independent clinical events committee.
[b] As defined by the criteria of the International Society of Thrombosis and Haemostasis (ISTH).

HOT-PE Further trial outcomes

Secondary Efficacy Outcomes[a]	
SAE requiring prolonged initial hospitalization, or rehospitalization	**54/525 (10.3%)**
Time between initial presentation and first rehospitalization, median (IQR)	29 (7-56) days
Duration of hospital stay due to SAE, median (IQR)	6 (3-8) days
Rehospitalized due to suspected recurrent PE or bleeding	**12/525 (2.3%)**
Final diagnosis:	
Pneumonia	4/525 (0.8%)
Recurrent PE	2/525 (0.4%)
Major bleeding	4/525 (0.8%)
Clinically-relevant-non-major bleeding	1/525 (0.2%)
Other	1/525 (0.2%)
Death from any cause within 3 months (95% CI)	**2/525 (0.4%; 0.1-1.4%)**
Advanced cancer as cause of death	2

[a] Adjudicated by an independent clinical events committee.

Conclusions

- In patients with acute low-risk PE (including absence of RV dysfunction and intracardiac thrombi), early discharge and home treatment with rivaroxaban was feasible, effective, and safe.
- The results of HoT-PE support the selection of appropriate PE patients for ambulatory treatment with a direct oral anticoagulant, possibly helping to reduce hospital-related complications and rationalize the use of healthcare resources.

HoT-PE The Team

HoT-PE Trial Investigators

Germany: Stavros V. Konstantinides, Stefano Barco, Mareike Lankeit, Christine Espinola-Klein, Philipp Wild, Kurt Quitzau, Nadine Martin, Dorothea Becker, *Mainz;* Michael Christ, Joachim Ficker, *Nürnberg*; Klaus Empen, *Greifswald*; Sebastian Schellong, *Dresden*; Sabine Genth-Zotz, *Mainz*; Ursula Rauch-Kröhnert, *Berlin*; Daniel Duerschmied, *Freiburg*; Jan Beyer-Westendorf, *Dresden*; Matthias Held, *Würzburg*; Martin Schwaiblmair, *Augsburg*; Andreas Meyer, *Mönchengladbach*; Johannes Brachmann, *Coburg*; Ibrahim Akin, *Mannheim*; Sabine Blaschke, *Göttingen*; Rupert Martin Bauersachs, *Darmstadt*; Tobias Geisler, *Tübingen*; Ulrich Hoffman, *München*; Evangelos Giannitsis, *Heidelberg*; Martin Möckel, *Berlin*; Marius M. Hoeper, *Hannover*; Rainer Schmiedel, *Kaiserslautern*

Italy: Cecilia Becattini, *Perugia*; Rodolfo Sbrojavacca, *Udine*; Giuseppe Bettoni, *Milano*; Walter Ageno, *Varese*; Enrico Bernardi, *Treviso*; Cinzia Nitti, *Ancona*; Roberto Cosentini, *Bergamo*; Maria Pazzaglia, *Ravenna*; Paolo Moscatelli, *Genova*; Raffaele Pesavento, *Padua*; Alessandra Ascani, *Terni*; Francesca Cortellaro, Nicola Montano, *Milano*

The Netherlands: Peter E. Westerweel, *Dordrecht*

Spain: David Jiménez, Pedro Ruiz-Artacho, *Madrid*; Remedios Otero, *Sevilla*; Raquel Lopez Reyes, *Valencia*; Aitor Ballaz-Quincoces, *Bizkaia*

Portugal: Candida Fonseca, Inês Araujo, Sergio Batista, *Lisbon*; Tiago Judas, *Almada*; Fabienne Goncalves, *Porto*

Finland: Veli-Pekka Harjola, *Helsinki*; Pirjo Mustonen, *Jyväskylä*

Greece: Athanasios Manolis, Athanassios Manginas, *Athens*; Georgios Hahalis, *Patras*; Konstantinos Gougoulianis; *Larissa*

Trial Statisticians

Irene Schmidtmann, Harald Binder, Toni Anusic

Clinical Events (Adjudication) Committee

Tobias J. Lange (Chair), Michael Czihal, Raoul Stahrenberg

Data Safety Monitoring Board

Thomas Meinertz, Menno V. Huisman, Paolo Prandoni, Walter Lehmacher

Academic Sponsor

University Medical Center of the Johannes Gutenberg University, Mainz, Germany

Academic Research Organization of the Sponsor

Interdisciplinary Center for Clinical Studies (IZKS) Mainz: Kai, Kronfeld, Stanislav Gorbulev

Study medication and grant to the sponsor by

Bayer AG

Special thanks

Luigi Visani, Chiara Colombo, EXOM Group, Milan, Italy

Sabrina Rump, Center for Thrombosis and Hemostasis, Mainz, Germany