



Angiography-derived fractional flow reserve- vs usual care-guided percutaneous coronary intervention: interim analysis of the PIONEER IV trial

Patrick W. Serruys ^{1,*†}, Tsung-Ying Tsai ^{1,†}, Joanna J. Wykrzykowska², Faisal Sharif^{3,4}, Liesbeth Rosseel⁵, Mohammad Alkhalil^{6,7}, Nick Curzen ^{8,9}, Vincent Floré¹⁰, Edouard Benit¹¹, Yoann Bataille¹¹, Mathieu Pankert¹², Clemens von Birgelen ^{13,14}, Kenneth De Wilder¹⁵, Valeria Paradies¹⁶, Giovanni Amoroso¹⁷, Lionel Mangin¹⁸, Manel Sabate ^{19,20}, Samer Somi²¹, Adel Aminian²², Sjoerd Hofma²³, Ignacio J. Amat Santos^{20,24,25}, Victor Alfonso Jimenez Diaz^{26,27}, Gilles Barone-Rochette^{28,29,30}, Anthony Mathur^{31,32,33}, Jeroen Sonck³⁴, Julien Adjedj ³⁵, Jacques Monsegu³⁶, Julien Lemoine³⁷, Michael Angioi³⁷, Carlos González Juanatey³⁸, Amer Zabalawi³⁹, Nozomu Kanehama¹, Akihiro Tobe¹, Kotaro Miyashita¹, Adrian Bednarek ^{1,40}, Asahi Oshima¹, Albert Chihenzva¹, Kanika Wadhwa¹, Scot Garg^{41,42}, Andreas Baumbach ^{43,44}, Peter Smits^{44,45}, and Yoshinobu Onuma¹

¹CORRIB Research Centre for Advanced Imaging and Core Laboratory, University of Galway, University Road, Galway H91 TK33, Ireland; ²Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands; ³Department of Cardiology, University of Galway, Galway, Ireland; ⁴SFI infrastructure Funding, University of Galway, Galway, Ireland; ⁵Department of Cardiology, Algemeen Stedelijk Ziekenhuis, Aalst, Belgium; ⁶Cardiothoracic Centre, Freeman Hospital, Newcastle-upon-Tyne, UK; ⁷Translational and Clinical Research Institute, Newcastle University, Newcastle-upon-Tyne, UK; ⁸Faculty of Medicine, University of Southampton, Southampton, UK; ⁹Department of Cardiology, University Hospital, Southampton NHS Trust, Southampton, UK; ¹⁰Department of Cardiology, AZ Maria Middelaere, Ghent, Belgium; ¹¹Department of Cardiology, Jessa Hospital, Hasselt, Belgium; ¹²Service de cardiologie, Centre Hospitalier Avignon, Avignon, France; ¹³Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands; ¹⁴Health Technology and Services Research, Faculty of Behavioural, Management and Social Sciences, Technical Medical Centre, University of Twente, Enschede, the Netherlands; ¹⁵Heart Centre, Imelda Hospital Bonheiden, Bonheiden, Belgium; ¹⁶Department of Cardiology, Maasstad Hospital, Rotterdam, the Netherlands; ¹⁷Department of Cardiology, OLVG, Amsterdam, the Netherlands; ¹⁸Cardiology Department, Hospital Ancey-Genevois, Metz-Tessy, France; ¹⁹Interventional Cardiology Department, Cardiovascular Institute, University Hospital Clinic, IDIBAPS, Barcelona, Spain; ²⁰Interventional Cardiology Department, Centro de Investigación Biomédica en red—Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain; ²¹Department of Cardiology, Haga Hospital, The Hague, The Netherlands; ²²Division of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium; ²³Department of Cardiology, FrisiusMC, Leeuwarden, the Netherlands; ²⁴Cardiology Department, University Clinic Hospital of Valladolid, Valladolid, Spain; ²⁵Cardiovascular Research Area, Instituto de Investigación Biosanitaria de Valladolid (IBioVALL), Valladolid, Spain; ²⁶Cardiology Department, Hospital Álvaro Cunqueiro, University Hospital of Vigo, Vigo, Pontevedra, Spain; ²⁷Cardiovascular Research Group, Galicia Sur Health Research Institute (IIS Galicia Sur), SERGAS-UVIGO, Vigo, Spain; ²⁸Department of Cardiology, University Hospital Grenoble France, Grenoble, France; ²⁹Clinic of Cardiology, Cardiovascular and Thoracic Department, University Grenoble Alpes, INSERM, CHU Grenoble Alpes, Grenoble, France; ³⁰French Alliance Clinical Trial, French Clinical Research Infrastructure Network, Paris, France; ³¹Barts Heart Centre, Barts Health NHS Trust, London, UK; ³²Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London, London, UK; ³³NIHR Barts Biomedical Research Centre, Queen Mary University of London, Charterhouse Square, London, UK; ³⁴Cardiovascular Center Aalst, AZorg Hospital Aalst, Aalst, Belgium; ³⁵Arnault Tzanck Institute Cardiology Department, Arnault Tzanck Institute, Saint-Laurent-du-Var, France; ³⁶Medipôle Private Hospital, GCV Cardiopôle, Grenoble, France; ³⁷Department of Cardiology, Clinique Louis Pasteur, essey les Nancy, France; ³⁸CardioHULA Research Group, Cardiology Department, Lucus Augusti University Hospital, Lugo, Spain; ³⁹Department of Cardiology, Centre Hospitalier de Saint-Brieuc, 10 rue Marcel Proust, Saint-Brieuc 22000, France; ⁴⁰First Department of Cardiology, Medical University of Warsaw, Warsaw, Poland; ⁴¹Department of Cardiology, Royal Blackburn Hospital, Blackburn, UK; ⁴²School of Medicine, University of Lancashire, Preston, UK; ⁴³Department of Cardiology, Barts Heart Centre, Barts Health NHS Trust, London, UK; ⁴⁴Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University London, London, UK; and ⁴⁵Department of Cardiology, Maasstad Ziekenhuis, Rotterdam, the Netherlands

Received 20 September 2025; revised 28 November 2025; accepted 18 February 2026

† Equally contributed.

* Corresponding author. Tel: +353 91 524411, Email: patrick.w.j.c.serruys@gmail.com

© The Author(s) 2026. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

Keywords

Quantitative flow ratio guidance • Usual care guidance • Non-inferiority trial • All comers percutaneous coronary intervention • Healing-Targeted Supreme sirolimus-eluting stent • Ticagrelor monotherapy

Quantitative flow ratio (QFR), an angiography-based method for estimating fractional flow reserve (FFR) without pressure wire, can be integrated into percutaneous coronary intervention (PCI) workflows to guide lesion treatment selection and stent optimization.¹ The FAVOR III China trial demonstrated superior clinical outcomes with QFR vs visual angiographic guidance, while the FAVOR III Europe trial failed to demonstrate clinical non-inferiority of QFR-guided PCI to FFR-guided PCI, raising concerns with increased rate of spontaneous myocardial infarction (MI), potentially impacting the Class I(B) guideline endorsement.²⁻⁴ To address these safety concerns, the PIONEER IV steering committee, consultatively advised by the Data Safety Monitoring Board (DSMB), decided to report an interim analysis of the first 1270 patients (60%) in the trial to offer timely insights for the community.

PIONEER IV (NCT04923191) is a multicentre, 1:1 randomized, open-label, all-comer, non-inferiority trial comparing clinical outcomes of PCI guided by QFR vs usual care, enrolling patients irrespective of clinical presentation or lesion complexity with unrestricted use in both arms of the Healing-Targeted Supreme sirolimus-eluting stent (HT Supreme, SINOMED, Tianjin, China), followed by a 1-month dual-antiplatelet therapy and ticagrelor monotherapy up to 1 year.⁵ In the QFR arm, lesions were functionally assessed by investigators with QFR, with stenting indicated in lesions with a QFR ≤ 0.80 . Post-stenting, QFR was repeated in the stented vessel(s), with post-dilatation or additional stenting recommended if vessel QFR < 0.91 , or if the delta QFR (across the stent) was > 0.05 , with the use of intravascular imaging at investigator's discretion. Usual care PCI was performed according to standard clinical practice, with pressure wire, angiographic physiology, and intravascular imaging use, left to the investigator's discretion.²

The primary non-inferiority endpoint is 12-month patient-oriented composite endpoint (POCE) of all-cause death, any stroke, any MI, or any Academic Research Consortium-2 clinically and physiologically driven revascularization with a non-inferiority margin of 3.2%.⁶

Clinical events were adjudicated by blinded clinical event committee and angiographic Syntax Score was assessed by an imaging corelab (CORRIB CORELAB, Galway, Ireland).⁷ MI was defined using the SCAI consensus for peri-procedure MI, and the Fourth Universal Definition of MI > 48 h after the index procedure.⁸ Secondary endpoints included the individual components of POCE and bleeding academic research consortium (BARC) bleedings.^{6,9}

The protocol was amended to accommodate an interim analysis with a modest reduction in the sample size from 2540 to 2130 patients lowering the statistical power from 90% to 85%. Considering the additional look, a one-sided *P*-value threshold of .035 was applied, based on the Lan-DeMets boundaries with Pocock alpha spending functions.¹⁰ Event rate was

estimated by the Kaplan–Meier method. The primary analysis was performed in the intention-to-treat population.

Among the first 1270 patients, 631 were randomized to the QFR arm and 639 to the usual care arm, with 1-year follow-up data available for 622 (98.6%) patients and 618 (96.7%) patients in the QFR and the usual care arms, respectively, while vital status was available for all patients (Figure 1). The median age was 66.0 years (IQR 59.0–74.0), with 304 (23.9%) female participants, 405 (31.8%) presenting with ACS, 298 (23.5%) having diabetes mellitus and 258 (20.3%) classified as high bleeding risk. Mean anatomic SYNTAX scores in the QFR arm was 9.7 (6.9) vs 9.6 (6.8) in the usual care arm.

In the QFR arm, QFR was performed by investigators in 883 (90.8%) lesions and QFR guidance was followed in 862 (97.6%) lesions. In the usual care arm, pressure-wire-derived or angiography-derived physiological assessments in the cath lab were performed in 395 (41.0%) of the total 963 study lesions.

Overall, a similar proportion of lesions in both arms were deferred (QFR $n = 343/973$, 35.3% vs Usual care $n = 319/963$, 33.1%, $P = .368$).

The mean number of implanted stents and the total stent length per patient were 1.6 stents and 34.0 mm in the QFR arm and 1.6 stents and 34.8 mm in the usual care arm. Intravascular imaging was used in 4.6% and 5.3% of the QFR and usual care patients, respectively. Post-PCI physiology was assessed in 76.5% of the QFR arm patients, with 17.9% (56/313) having an angio-FFR < 0.91 , leading to additional treatment in 19.6% (11/56) of cases. After PCI, patients who were not on anticoagulant therapy were on DAPT at 1 month, with P2Y12 monotherapy used in 83.0% at 6 months.

The 1-year POCE rates were 6.9% in the QFR arm and 6.8% in the usual care arm. With a risk difference of 0.11% (95% CI: -2.70% to 2.92% , one-sided $P_{\text{noninferiority}} = .015$, Figure 1), non-inferiority was declared. The individual components of POCE were similar between the two arms. Importantly, there were no between-group differences in the rates of all-MI, periprocedural MI or spontaneous MI. Furthermore, only one MI and two revascularizations occurring in deferred vessels. One acute definite stent thrombosis was observed in the usual care arm, and one late probable stent thrombosis was observed in the QFR arm. The BARC 3 or 5 bleeding rates were 1.8% and 1.3% in the QFR and usual care arms, respectively ($P = .482$).

The favourable outcomes relative to FAVOR III Europe likely reflect key design differences: PIONEER IV compared a QFR-guided strategy with usual care, whereas FAVOR III Europe mandated systematic FFR guidance. Consequently, PIONEER IV occupies an intermediate position on the 'physiology spectrum', with 41% invasive physiology use in the control arm, contrasting with the 100% FFR use in FAVOR III Europe

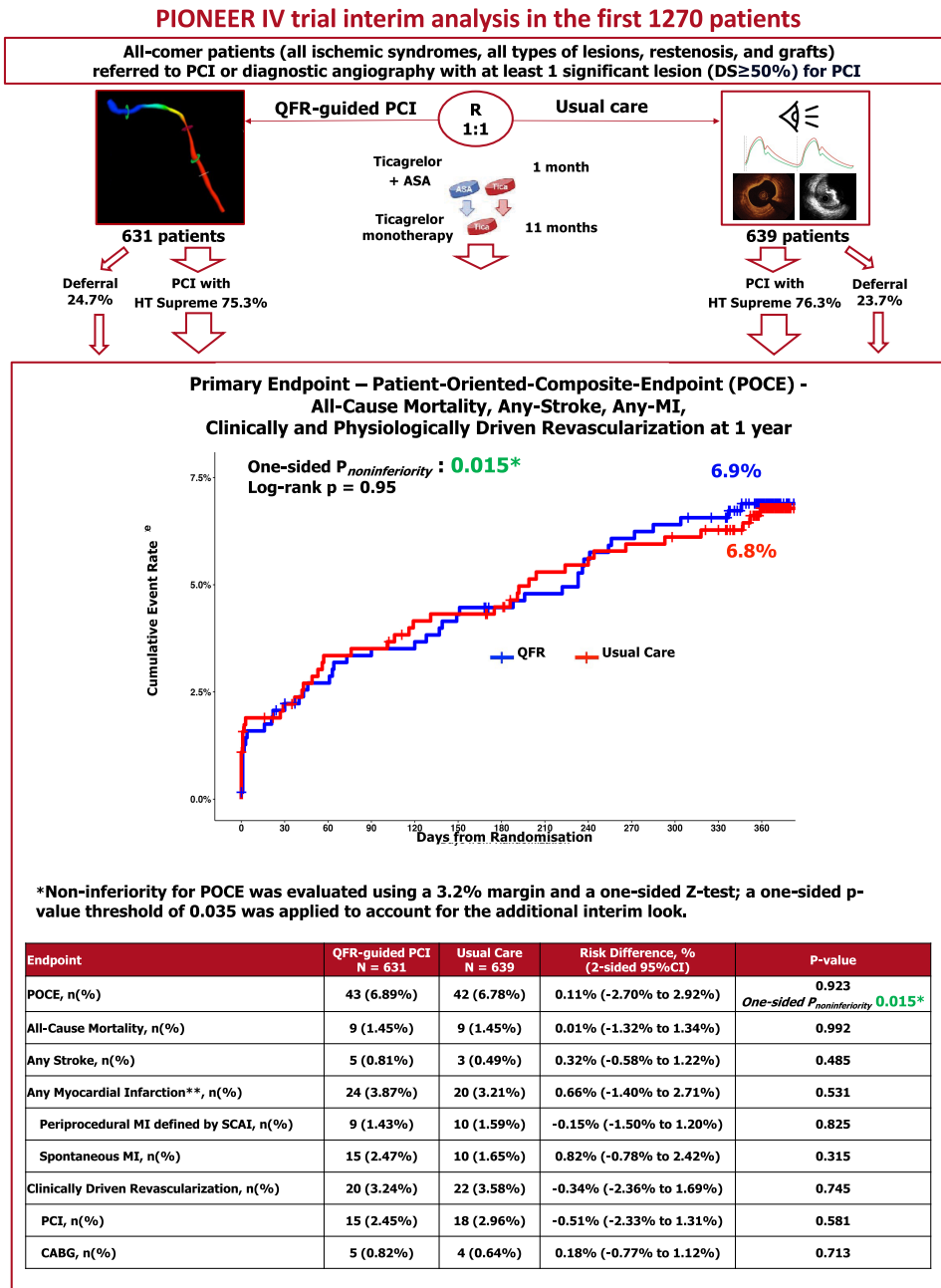


Figure 1 (Top) Trial design of the PIONEER IV study, a multicentre, open-label, randomized control trial comparing angiography-derived fractional flow reserve (QFR)-guided PCI vs usual care in an all-comer population. Patients received the Healing-Targeted Supreme sirolimus-eluting stent followed by 1 month of dual antiplatelet therapy and ticagrelor monotherapy up to 1 year. (Bottom) Kaplan-Meier cumulative event curves and event rates for the primary endpoint, the patient-oriented composite endpoint (POCE), at 1 year. The table details the individual components of POCE and key secondary endpoints, showing risk differences and P-values. *Non-inferiority for POCE was assessed using a one-sided Z-test with a threshold of 0.035. **Spontaneous Myocardial Infarction defined according to the Fourth Universal Definition while periprocedural MI defined according to the SCAI definition. ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

and 0% in FAVOR III China. Furthermore, PIONEER IV mandated post-PCI QFR optimization. This strategy was found to be impactful in the FLAVOUR II trial, although that trial utilized a different technology (μ FR) compared with the QFR used in PIONEER IV. Finally, rigorous site credentialing and

centralized oversight ensured high protocol adherence (97.6%). Consequently, no alarming safety signals regarding spontaneous MI were observed. Limitations include the interim nature of the analysis with a limited statistical power and the open-label design.

In conclusion, QFR-guided PCI was non-inferior to usual care with no alarming safety signal in the interim analysis of the PIONEER IV trial. These results must be confirmed in the whole population.

Author Contributions

P.W.S. and Y.O. conceptualized and supervised the study and were responsible for project administration. T.T., A.C., Y.O., and P.W.S. designed the methodology, validated the data, performed formal analysis, and were responsible for resources. J.W., F.S., L.R., M.A., N.C., V.F., E.B., Y.B., M.P., Cv.B., Kd.W., V.P., G.A., L.M., M.S., S.S., A.A., S.H., I.A.S., V.J.D., G.B.R., A.M., J.S., J.A., J.M., J.L., M.A., R.O., and A.Z. conducted the investigation. T.T., A.C., Y.O., N.K., A.T., K.M., A.B., and P.W.S. curated the data. P.W.S. was responsible for funding acquisition. T.T., N.K., A.T., K.M., A.B., A.C., Y.O., and P.W.S. were responsible for the software. T.T., A.C., A.O., and K.W. visualized the data. T.T., Y.O., and P.W.S. wrote the original draft. All authors reviewed and edited the manuscript. Y.O., T.T., and P.W.S. and the trial statistician (AC) had full access to all study data and had final responsibility for the decision to submit for publication.

Permission information

The authors declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

Acknowledgement

The PIONEER IV trial was sponsored by the University of Galway. We thank the members of the DSMB (Prof. Pedro Lemos, Prof. Dominick Angiolillo, and Dr. Alberto Alvarez-Iglesias) and the Clinical Events Committee (Prof. Scot Garg, Dr. Maik Grundeken, and Dr. Javid Iqbal) for their contributions to ensuring the safe conduct of the trial and adjudication of events. We are grateful to Medis Medical Imaging for technical support to the sites and the central core laboratory. We also deeply appreciate the intellectual contributions of our visiting scholars, Dr. Gonçalo Costa and Dr. Jacopo Farina, and the guidance of our steering committee members, Prof. William Wijns and Prof. Andrew Smith. Finally, we thank the PIONEER IV coordination, data management, and trial safety teams for their dedication, and we are indebted to the participating patients and investigators.

Declarations

Disclosure of Interest

P.W.S. reports consultancy agreements from SMT, Novartis, and Meril Life Sciences; JW reports research grants or consultancy agreements to UMCG but no personal payments from Sinomed or Medis in relation to this paper; N.C. reports grants from Haemonetics, HeartFlow, Boston Scientific and Beckman Coulter, speaker fees/consultancy from HeartFlow, Abbott, Shockwave, Boston Scientific and Edwards, and travel sponsorship from HeartFlow, Abbott, and Shockwave; Cv.B. reports an institutional research grant from Abbott Vascular for the COASTLINE study (all payments to the research department of Medisch Spectrum Twente); M.S. reports consultant fees

from Abbott Vascular and iVascular; I.A.S. reports serving as procedure proctor for Abbott, Boston Scientific, Medtronic, Meril Life, and MicroPort; B.R.G. reports research grants from Merck Sharp & Dohme, Abbott Vascular, and Pfizer, and consulting fees from Bayer, General Electric, Boehringer Ingelheim, MEDIS Medical Imaging, Abbott Vascular, Novo Nordisk, Sanofi, Novartis, ZOLL and Amgen; J.S. reports consulting and speaker fees from Abbott, a license agreement with Coroventis Research AB, and patent ownership related to P.P.G. (EP3956904B1, JP7539604B2; pending US20220175260A1, CN113711317A, CA3135134A1); J.A. reports consulting fees from Abbott and Medis; J.M. reports proctoring and a research grant with Abbott and consulting for Terumo and AlchiMedics; S.G. reports honoraria or consultancy fees from Biosensors. All other authors declare no competing interests.

Data Availability

The study protocol and statistical analysis plan are available in the supplementary material. Other data, including study participant data and informed consent, will not be shared.

Funding

This study was sponsored by the University of Galway with a research grant from Sino Medical Sciences Technology Inc.

Ethical Approval

The study protocol, informed consent documents, and other relevant study documents were approved by the ethics committees of the respective study centres (Supplemental Materials). Written informed consent was obtained from all the study participants and the study was conducted in compliance with the declaration of Helsinki.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is NCT04923191.

References

- Papafaklis MI, Muramatsu T, Ishibashi Y, Lakkas LS, Nakatani S, Bourantas CV, et al. Fast virtual functional assessment of intermediate coronary lesions using routine angiographic data and blood flow simulation in humans: comparison with pressure wire—fractional flow reserve. *EuroIntervention* 2014;**10**: 574–83. https://doi.org/10.4244/EIJY14M07_01
- Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes: Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2024;**45**:3415–537. <https://doi.org/10.1093/eurheartj/ehae177>
- Andersen BK, Sejr-Hansen M, Maillard L, Campo G, Råmunddal T, Ståhli BE, et al. Quantitative flow ratio versus fractional flow reserve for coronary revascularisation guidance (FAVOR III Europe): a multicentre, randomised, non-inferiority trial. *The Lancet* 2024;**404**:1835–46. [https://doi.org/10.1016/S0140-6736\(24\)02175-5](https://doi.org/10.1016/S0140-6736(24)02175-5)
- Xu B, Tu S, Song L, Jin Z, Yu B, Fu G, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. *Lancet* 2021;**398**:2149–59. [https://doi.org/10.1016/S0140-6736\(21\)02248-0](https://doi.org/10.1016/S0140-6736(21)02248-0)
- Hara H, Serruys PW, O'Leary N, Gao C, Murray A, Breslin E, et al. Angiography-derived physiology guidance vs usual care in an all-comers PCI population treated with the healing-targeted supreme stent and Ticagrelor monotherapy: PIONEER IV trial design. *Am Heart J* 2022;**246**:32–43. <https://doi.org/10.1016/J.AHJ.2021.12.018>
- Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, et al. Standardized End point definitions for coronary intervention trials: the

- academic research consortium-2 consensus document. *Circulation* 2018;**137**: 2635–50. <https://doi.org/10.1161/CIRCULATIONAHA.117.029289>
7. Wang R, Kawashima H, Hara H, Gao C, Ono M, Takahashi K, *et al*. Comparison of clinically adjudicated versus flow-based adjudication of revascularization events in randomized controlled trials. *Circ Cardiovasc Qual Outcomes* 2021;**14**:e008055. <https://doi.org/10.1161/CIRCOUTCOMES.121.008055>
 8. Revaiah PC, Tsai T-Y, Wang B, Renkens M, Kageyama S, Wlodarczak A, *et al*. Frequency of periprocedural myocardial injury and infarction stratified by cardiac troponin I and cardiac troponin T. *Cardiovasc Revasc Med* 2025;**70**: 12–9. <https://doi.org/10.1016/j.carrev.2024.05.022>
 9. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, *et al*. Standardized bleeding definitions for cardiovascular clinical trials. *Circulation* 2011;**123**:2736–47. <https://doi.org/10.1161/CIRCULATIONAHA.110.009449>
 10. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med* 1994;**13**:1341–52; discussion 1353–1356. <https://doi.org/10.1002/sim.4780131308>