Olier, I, Carr, M, Curzen, N, Ludman, P, Baumbach, A, Kinnaird, T, de Belder, MA, Hildick-Smith, D, Sirker, A, Kwok, CS, Rashid, M, Nolan, J, Kontopantelis, E and Mamas, MA

Changes in Peri-procedural Bleeding Complications Following Percutaneous Coronary Intervention in The United Kingdom Between 2006-2013 (From the British Cardiovascular Interventional Society)

Changes in Peri-procedural Bleeding Complications Following Percutaneous Coronary Intervention in The United Kingdom Between 2006-2013 (From the British Cardiovascular Interventional Society)

Running title: Bleeding complications following PCI

Ivan Olier, PhD[a]; Matthew Carr, PhD[b]; Nick Curzen, BM, PhD[c]; Peter Ludman, MD[d]; Andreas Baumbach, MD[e]; Tim Kinnaird, MD[f]; Mark A. de Belder, MD[g]; Dave Hildick-Smith, MD[h]; Alex Sirker, MB BChir, PhD [i]; Chun Shing Kwok, MBBS, MSc, BSc[j]; Muhammad Rashid, MBBS [j]; Jim Nolan, MD[j]; Evangelos Kontopantelis, PhD[k]; Mamas A. Mamas, BM BCh, MA, DPhil[j]

a. Department of Applied Mathematics, Liverpool John Moores University, UK
b. Faculty of Medical and Human Sciences, University of Manchester, UK
c. University Hospital Southampton & Faculty of Medicine, University of Southampton, UK.
d. Department of Cardiology, Queen Elizabeth Hospital, Birmingham, UK.
e. Department of Cardiology, Barts Heart Centre, Queen Mary University, London, UK.
f. Department of Cardiology, University Hospital of Wales, Cardiff, UK.
g. Department of Cardiology, The James Cook University Hospital, Middlesbrough, UK.
h. Department of Cardiology, Royal Sussex County Hospital, Brighton, UK.
i. Department of Cardiology University College London Hospitals and St. Bartholomew's Hospital, London, UK.
j. Keele Cardiovascular Research Group, Keele University, Stoke on Trent, UK.
k. Health eResearch Centre, Farr Institute for Health Informatics Research, University of Manchester, UK.

Corresponding Author:

Mamas A. Mamas

Professor of Cardiology

Keele Cardiovascular Research Group, Institute of Applied Clinical Science

University of Keele, Stoke-on-Trent

E-mail: mamasmamas1@yahoo.co.uk

Abstract

Major bleeding is a common complication following percutaneous coronary intervention (PCI), although little is known about how bleeding rates have changed over time and what has driven this. We analyzed all patients undergoing PCI in England and Wales from 2006 to 2013. Multivariate analyses using logistic regression models were performed to identify predictors of bleeding in order to identify potential factors influencing bleeding trends over time. 545,604 participants who had PCI in England and Wales between 2006 and 2013 were included in the analyses. Overall bleeding rates declined from 7.0 (CI:6.2–7.8) per 1000 procedures in 2006 to 5.5 (CI:4.7–6.2) per 1000 in 2013. Increasing age, female sex, GPIIb/IIIa inhibitor use and circulatory support was independently associated with increased risk of bleeding complications whilst radial access and vascular closure device use were independently associated with decreases in risk. Decreases in bleeding rates over time were associated with radial access site, and changes in pharmacology, but this was offset by greater proportion of ACS cases and more the adverse patient clinical demographics. In conclusion, Major bleeding complications after PCI has declined due to changes in access site practice and decreased usage of GPIIb/IIIa inhibitors, but this is offset by the increase of patients with higher propensity to bleed. Changes in access site practice nationally have the potential to significantly reduce major bleeding following PCI.

Keywords: percutaneous coronary intervention, bleeding, trends

Introduction

Major bleeding is one of the most common complications following percutaneous coronary intervention (PCI), independently associated with a 3-fold increase in mortality [1]and contributing to 12% of all in-hospital PCI mortalities [2]. The average age and comorbid burden of patients undergoing PCI has increased over time with more potent pharmacotherapy and worsening patient clinical risk profiles that would tend to increase incident major bleeding[3-5], whilst changes in access site practice towards radial would reduce major bleeding[6-8]. Temporal changes in major bleeding therefore represents a complex dynamic between changes in these competing risks. Access site related bleeding complications account for half of all bleeding complications observed post PCI[9]. In the United Kingdom (UK) there has been a national change in access site practice towards radial with 80% of all PCI procedures undertaken radially[7,10]. We report changes in temporal bleeding rates in a large contemporary unselected all-comer national cohort in the UK from British Cardiovascular Intervention Society (BCIS) database studying changes in clinical and procedural demographics, pharmacotherapy and access site practice, assess associations with peri-procedural bleeding complications, and determine which factors associate most with the temporal changes in bleeding complications observed.

Methods

This is a retrospective analysis of prospectively collected national data for all patients undergoing PCI in England and Wales from January 2006 to December 2013. BCIS records information on PCI practice in the UK with data collection managed by the National Institute of Cardiovascular Outcomes Research (NICOR)[7,8,10]. In-hospital major bleeding complications were defined as a composite of reported gastrointestinal bleed, intracerebral bleed, retroperitoneal hematoma, tamponade, blood or platelet

transfusion, or an arterial access site complication requiring surgical intervention[6-8]. Procedures were divided into 2 groups, based on the indication for PCI, either elective or acute coronary syndrome (ACS). Procedures performed for unstable angina (UA), non ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI) formed the ACS group. Analyses were carried out on the whole cohort, and then in elective and ACS cohorts separately.

Procedures were excluded if in-hospital outcomes, coronary syndrome, or patient age or gender were missing from the dataset. Procedures in which the access site was unclear or missing, or where multiple access sites were recorded and the primary access site used for the procedure could not be identified were also excluded.

For basic analyses of demographics, procedural details and unadjusted outcomes, continuous variables were evaluated as median and interquartile range (IRQ), whilst categorical variables were reported using frequencies and proportions (in percentages). Chi-square tests were used to assess the significance of differences in proportions between groups for categorical variables. Kruskal-Wallis rank sum test was used for continuous variables. All statistical tests were two-tailed and an alpha of 5% (for significance) was used throughout. In the present analysis, we modified the risk score published by Mehran et al[11]. to define the baseline risk of major bleeding. Our modified Mehran score, was calculated and an integer score assigned for each category as previously reported by our group[12].

Multiple imputation methods were used in order to reduce potential bias created by missing data. To this aim, we used the *mice* R package, version 2.25[13]. Chained equations were used to impute data for all variables with missing values to generate 10 dataset instances for use in the analyses.

Unadjusted annual bleeding rates were estimated using the whole cohort and then the two groups, Elective and ACS. We used simple linear regressions to quantify the association between year of procedure and annual bleeding rates. Multivariate analyses using logistic regression model were performed to identify predictors of bleeding in order to identify potential factors influencing bleeding trends over time. We included all variables assumed clinically relevant as explanatory variables in the model: age, gender, smoking status, diabetes, peripheral vascular disease (PVD), hypertension, hypercholesterolemia, renal disease, previous coronary artery bypass graft (CABG), previous myocardial infarction (MI), previous stroke, previous PCI, left ventricular ejection fraction (LVEF), indication for PCI, access site, vascular closure device (VCD), stent, left main stem artery use, multivessel PCI, cardiogenic shock (CS), intra-aortic balloon pump (IABP) use, ventilatory support, circulatory support, glycoprotein IIb/IIIa inhibitors (GPI) use, antiplatelet drug, and bivalirudin use . We used the base *stats* R package to build the models. Odd ratios and confidence intervals were obtained after pooling the fitted model coefficients of the 10 complete dataset instances per group according to using the *mice* R package[14]. Areas under the receiver operator curves (AUCs) were estimated in order to assess model robustness for prediction.

Our aim was to identify possible factors influencing the changes in bleeding rates over time and to quantify their effects Firstly, we took the annual average of the predicted bleeding log odds predicted by the aforementioned logistic models and decomposed them into their additive terms, one for each explanatory variable. We grouped the terms in (functional) factors taking into account their associations with the bleeding outcome, as follows: *clinical demographics* (age, gender, smoking status, diabetes, PVD, hypertension, hypercholesterolemia, renal disease, previous CABG, previous MI, previous stroke, previous PCI, and LVEF); *indication for PCI*; *access site*;

VCD use; *CS and IABP*; *other procedural characteristics* (stent, left main stem artery, and multivessel PCI); and *pharmacology* (GPI, antiplatelets, and bivalirudin). We reported scores measuring relative factor contributions to the changes in bleeding rates over time. This approach provides a graphical representation of the relative factor contributions and allows us to explore them year-by-year. Finally, and with the aim to quantify the influence of factors on the bleeding rate trends, we started with a new simple univariate logistic regression model (Supplementary methods).

Results

A total of 577,471 procedures were undertaken in England and Wales between 2006 and 2013 of which 545,604 (94.5%) were included in the analyses (Figure 1). Changes in clinical demographics, procedural characteristics and pharmacology over this period of time are summarized in Table 1a, for the whole cohort, and Tables 1b and 1c for elective PCI and ACS groups, respectively. Supplementary Table S1 gives details of missing value levels presented in the data. We observed that PCI volume increased from 51,850 procedures in 2006 to 78,398 in 2013, mainly driven by the increase in procedures for ACS. During this period of time, the average age of patients increased; their clinical risk factor profile worsened and the proportion of PCI procedures on patients with cardiogenic shock or requiring ventilatory / circulatory support increased. The use of GPIIb/IIIa inhibitors declined during the study period, whilst bivalirudin and newer anti-platelet agent use increased. Finally radial access grew to become the default access site used for PCI in 68.5% of procedures in 2013. Bleeding risk as quantified by the Mehran risk score increased for both elective and ACS PCI indications over time (supplementary Figure 1).

Figure 2 shows the results of using simple linear regressions to estimate unadjusted bleeding rate trends over time. Overall bleeding rates declined from 7.0 (CI:

6.2 – 7.8) per 1000 procedures in 2006 to 5.5 (CI: 4.7 – 6.2) per 1000 in 2013. Decreases in the rates were observed in both groups, being more pronounced in ACS. The bleeding complication rate in the elective PCI group dropped from 4.9 (CI: 4.1 – 5.7) per 1000 in 2006 to 3.9 (CI: 3.2 – 4.7) per 1000 in 2013, whilst in the ACS group, from 8.9 (CI: 7.8 – 10.1) per 1000 to 6.2 (CI: 5.1 – 7.4) per 1000 during the same period. Results of the analyses using multivariate logistic regressions are summarized in Table 2. In both groups, elective and ACS indications for PCI, increasing age, female sex, GPIIb/IIIa inhibitor use and circulatory support was independently associated with increased risk of bleeding complications whilst radial access and VCD use were independently associated with decreases in risk.

In Figure 3, we report relative contributions to the overall bleeding change score, using 2006, the initial year, as the baseline. It can be observed in this figure that most of the decrease in bleeding rates over time was associated with the adoption of radial access site, and by changes in pharmacology, although this was offset by the changes such as changes in PCI indications towards ACS cases and more the adverse clinical demographics of the patients.Results of the quantification of influencing factors in bleeding trends as estimated using multiple multivariate regression models (*model_0* to *model_7*) are presented in Table 3. In this table, large positive attenuation values indicate a strong association of a particular factor with lower bleeding rates. We observed that the reported results in Table 4 are in the same direction as the ones using the relative score contributions (Figure 3). In the three groups, access site choice was the most influential factor associated with lower bleeding rates over time. Pharmacology was another important factor associated with lower bleeding rates. Additionally, although to a lesser extent, VCD use (in all cohorts), procedural characteristics (in both the whole cohort and ACS group) contributed to lower the

bleeding rates over time. In contrast, the indication for PCI tended towards increasing the bleeding rates over time.

Discussion

In the current analysis of over half a million PCI procedures, our data suggests that significant temporal changes in clinical and procedural demographics, access site practice and pharmacology has been accompanied by a decline in incident rates of in-hospital major bleeding. Our analysis suggests that these reductions in major bleeding relate mainly to changes in access site practice and pharmacology driven by decreased usage of glycoprotein IIb/IIIa inhibitors, although offset by the increase in PCI cases undertaken for ACS and worsening clinical demographic profiles of patients.

Temporal changes in incident major bleeding complications represent a complex dynamic between changes in pharmacological therapy, indications for PCI, co-morbid burden, clinical demographics, procedural characteristics and access site practice[1,9]. This dynamic will vary across different healthcare systems. Analysis of data from a Canadian registry of 14,111 patients with non-ST elevation myocardial infarction (NSTEMI) between 1999 and 2008 reported no significant changes in major bleeding rates over time[15] despite changes in pharmacotherapy and interventional strategies. In contrast, data derived from the US CathPCI Registry reported 20% temporal reductions in post-PCI bleeding observed in patients undergoing PCI for elective and NSTEMI indications, although adjusted bleeding rates in the STEMI cohort remained similar[16]. In national registry from Sweden in elderly patients undergoing PCI for STEMI indications, incident major bleeding rates remained similar over a decade[5]. A further analysis derived from the CathPCI registry over a 3-year period (2009-2012) showed that bleeding rates declined over the period studied, although when compared with hospitals with very low or low increase in the use of

radial access, the decline in risk-adjusted overall bleeding over time was greater at hospitals with moderate or high increase in the use of radial access (RR, 0.51; 95% CI, 0.43–0.61 versus RR, 0.69; 95% CI, 0.63–0.74; P for comparison, 0.002)[17]. Our analysis suggests that the decline in major bleeding complications observed in the UK, are mainly associated with the national change in access site practice towards radial, changes in pharmacological practices, particularly declining use of GP IIb/IIIa inhibitors and to a lesser extent VCD use. However, this effect is attenuated by the worsening bleeding risk profile of patients undergoing PCI (as evidenced by the temporal increase in Mehran bleeding risk score) and the increase in PCI procedures undertaken for ACS indications. Our analysis is the first to study this in a healthcare system where there has been a national change in access site practice towards radial and the first to study the contribution of all aspects of the PCI procedure and patient clinical characteristics that may contribute to changes in incident bleeding recorded. Interestingly, data from the CathPCI registry studying changes in national bleeding rates between 2005-2009 suggested that changes in access site practice in the US contributed minimally to the reduction in bleeding rates recorded, although only 1.5% of cases were undertaken radially during this time[16]. This is in contrast to radial rates of close to 70% reported in the current analysis.

Changes in anti-thrombotic strategies such as decreased utilization of GPIIb/IIIa inhibitors and concomitant increases in bivalirudin contributed to close to 50% of the reduction in major bleeding observed in the NCDR analysis[16]. Our analysis suggests that after changes in access site practice, changes in pharmacological practice were most closely associated with reduced major bleeding complications with similar attenuations of bleeding risk reported to those observed in the NCDR (52.8% in all PCI indications). Specifically, we observed a reduction in GPIIb/IIIa inhibitor usage from

35% to 16.7% in the whole population and 50.6% to 23.2% in the ACS population reflecting changes in contemporary anticoagulant practice in PCI. Increases in the use of newer antiplatelet agents such as Ticagrelor and Prasugrel over time were observed, although neither contributed to temporal changes in major bleeding that we observed. Our analysis shows that the average age of patients has increased, with more females undergoing PCI, and a greater prevalence of cardiovascular risk factors, with corresponding increases in the calculated bleeding risk of the patients. Similarly, our data show that the proportion of PCI cases undertaken for ACS indications has increased, thereby further contributing to worsening bleeding outcomes[18-20].

Our analysis suggests that the growth of transradial access (TRA) from 17% in 2006 to close to 70% in 2013 has been most strongly associated with the reduction in national major bleeding rates observed in both the elective and ACS settings. Both national registry[12] and randomized controlled trial data[21-23] has shown that TRA is independently associated with reduced mortality and major bleeding risk in high-risk patient groups. Temporal changes in the incidence of major bleeding complications represents a complex dynamic between changes in pharmacological practices, PCI indication, co-morbid burden, clinical demographics, procedural characteristics and access site practice, and this will change annually dependent on the annualized prevalence of each factor. Furthermore, the contribution of each of these competing "risks" to the final incident bleeding rates will vary in different countries dependent on differences in case mix, clinical and pharmacological practice, with the greatest benefit to be gained in countries that are at the earliest stages of radial adoption.

Our analysis has several limitations. Firstly, bleeding complications are self-reported and are not adjudicated / validated by BCIS potentially resulting in under-reporting. Secondly, the definition of major bleeding that is used in the BCIS dataset is

different from those frequently used in clinical trials (1) making comparisons with other studies / trials difficult, although has remained constant during the period studied. The thresholds for blood transfusions (a component of the BCIS definition for major bleeding) may have changed over time that may introduce confounding and the BCIS dataset does not differentiate between blood transfusions given for bleeding complications and those for chronic anemia. Thirdly, whilst the BCIS dataset captures CV risk factors, it does not capture other measures of co-morbid burden[24] that may have contributed to the changes in incident bleeding reported here. Finally, our observational data can only report associations and causal relationships cannot be inferred.

In conclusion, observe significant changes in clinical and procedural demographics, access site practice and pharmacology over time in patients undergoing PCI in England and Wales, accompanied by a decline in the crude incident rates of in-hospital major bleeding complications. Our analysis suggests that these national decreases in major bleeding are most strongly associated with changes in access site practice and decreased usage of glycoprotein IIb/IIIa inhibitors, although this has been offset by the increase in proportion of PCI cases undertaken for ACS indications and the treatment of patients who are at higher risk of bleeding complications. Our data suggest a change in access site practice nationally has the potential to significantly reduce major bleeding following PCI.

Funding sources: The authors acknowledge the North Staffordshire Medical Institute for supporting the study through the award of a 50th anniversary research grant.

Disclosures: There are no relationships with industry

References

1. Kwok CS, Rao SV, Myint PK, Keavney B, Nolan J, Ludman PF, de Belder MA, Loke YK, Mamas MA. Major bleeding after percutaneous coronary intervention and risk of subsequent mortality: a systematic review and meta-analysis. *Open Heart.* 2014; 1: e000021.

2. Chhatriwalla AK, Amin AP, Kennedy KF, House JA, Cohen DJ, Rao SV, Messenger JC, Marso SP, National Cardiovascular Data Registry. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA.* 2013; 309: 1022-1029.

3. Rashid M, Kwok CS, Gale CP, Doherty P, Olier I, Sperrin M, Kontopantelis E, Peat G, Mamas MA. Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: a systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes.* 2017; 3: 20-36.

4. Bangalore S, Toklu B, Kotwal A, Volodarskiy A, Sharma S, Kirtane AJ, Feit F. Anticoagulant therapy during primary percutaneous coronary intervention for acute myocardial infarction: a meta-analysis of randomized trials in the era of stents and P2Y12 inhibitors. *BMJ.* 2014; 349: g6419.

5. Velders MA, James SK, Libungan B, Sarno G, Fröbert O, Carlsson J, Schalij MJ, Albertsson P, Lagerqvist B. Prognosis of elderly patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention in 2001 to 2011: A report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) registry. *Am Heart J.* 2014; 167: 666-673.

6. Ratib K, Mamas MA, Anderson SG, Bhatia G, Routledge H, De Belder M, Ludman PF, Fraser D, Nolan J, British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research. Access site practice and procedural outcomes in relation to clinical presentation in 439,947 patients undergoing percutaneous coronary intervention in the United kingdom. *JACC Cardiovasc Interv.* 2015; 8: 20-29.

7. Mamas MA, Nolan J, de Belder MA, Zaman A, Kinnaird T, Curzen N, Kwok CS, Buchan I, Ludman P, Kontopantelis E, British Cardiovascular Intervention Society (BCIS) and the National Institute for Clinical Outcomes Research (NICOR). Changes in Arterial Access Site and Association With Mortality in the United Kingdom: Observations From a National Percutaneous Coronary Intervention Database. *Circulation.* 2016; 133: 1655-1667.

8. Rashid M, Rushton CA, Kwok CS, Kinnaird T, Kontopantelis E, Olier I, Ludman P, De Belder MA, Nolan J, Mamas MA. Impact of Access Site Practice on Clinical Outcomes in Patients Undergoing Percutaneous Coronary Intervention Following Thrombolysis for ST-Segment Elevation Myocardial Infarction in the United Kingdom: An Insight From the British Cardiovascular Intervention Society Dataset. *JACC Cardiovasc Interv.* 2017; 10: 2258-2265.

9. Kwok CS, Khan MA, Rao SV, Kinnaird T, Sperrin M, Buchan I, de Belder MA, Ludman PF, Nolan J, Loke YK, Mamas MA. Access and non-access site bleeding after percutaneous coronary intervention and risk of subsequent mortality and major adverse cardiovascular events: systematic review and meta-analysis. *Circ Cardiovasc Interv.* 2015; 8(4).

10. Ludman PF, British Cardiovascular Intervention Society. British Cardiovascular Intervention Society Registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. *Heart.* 2011; 97: 1293-1297.

11. Mehran R, Pocock S, Nikolsky E, Dangas GD, Clayton T, Claessen BE, Caixeta A, Feit F, Manoukian SV, White H. Impact of bleeding on mortality after percutaneous coronary intervention: results from a patient-level pooled analysis of the REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events), ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy), and HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trials. *JACC: Cardiovascular Interventions.* 2011; 4: 654-664.

12. Mamas MA, Anderson SG, Carr M, Ratib K, Buchan I, Sirker A, Fraser DG, Hildick-Smith D, de Belder M, Ludman PF, Nolan J, British Cardiovascular Intervention Society, National Institute for Cardiovascular Outcomes Research. Baseline bleeding risk and arterial access site practice in relation to procedural outcomes after percutaneous coronary intervention. *J Am Coll Cardiol.* 2014; 64: 1554-1564.

13. Rubin D. Multiple Imputation for Nonresponse in Surveys 1987 Wiley New York. 1987.

14. Meng X, Rubin DB. Performing likelihood ratio tests with multiply-imputed data sets. *Biometrika.* 1992; 103-111.

15. Elbarouni B, Elmanfud O, Yan RT, Fox KA, Kornder JM, Rose B, Spencer FA, Welsh RC, Wong GC, Goodman SG. Temporal trend of in-hospital major bleeding

among patients with non ST-elevation acute coronary syndromes. *Am Heart J.* 2010; 160: 420-427.

16. Subherwal S, Peterson ED, Dai D, Thomas L, Messenger JC, Xian Y, Brindis RG, Feldman DN, Senter S, Klein LW, Marso SP, Roe MT, Rao SV. Temporal Trends in and Factors Associated With Bleeding Complications Among Patients Undergoing Percutaneous Coronary Intervention: A Report From the National Cardiovascular Data CathPCI Registry. *J Am Coll Cardiol.* 2012; 59: 1861-1869.

17. Bradley SM, Rao SV, Curtis JP, Parzynski CS, Messenger JC, Daugherty SL, Rumsfeld JS, Gurm HS. Change in hospital-level use of transradial percutaneous coronary intervention and periprocedural outcomes: insights from the national cardiovascular data registry. *Circ Cardiovasc Qual Outcomes.* 2014; 7: 550-559.

18. Mehta SK, Frutkin AD, Lindsey JB, House JA, Spertus JA, Rao SV, Ou FS, Roe MT, Peterson ED, Marso SP, National Cardiovascular Data Registry. Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the National Cardiovascular Data Registry. *Circ Cardiovasc Interv.* 2009; 2: 222-229.

19. Kinnaird TD, Stabile E, Mintz GS, Lee CW, Canos DA, Gevorkian N, Pinnow EE, Kent KM, Pichard AD, Satler LF. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol.* 2003; 92: 930-935.

20. Anderson SG, Ratib K, Myint PK, Keavney B, Kwok CS, Zaman A, Ludman PF, de Belder MA, Nolan J, Mamas MA. Impact of age on access site-related outcomes in 469,983 percutaneous coronary intervention procedures: insights from the British

Cardiovascular Intervention Society. *Catheterization and Cardiovascular Interventions.* 2015; 86: 965-972.

21. Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Ando G, Repetto A, Limbruno U, Cortese B, Sganzerla P, Lupi A, Galli M, Colangelo S, Ierna S, Ausiello A, Presbitero P, Sardella G, Varbella F, Esposito G, Santarelli A, Tresoldi S, Nazzaro M, Zingarelli A, de Cesare N, Rigattieri S, Tosi P, Palmieri C, Brugaletta S, Rao SV, Heg D, Rothenbuhler M, Vranckx P, Juni P, MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet.* 2015; 385: 2465-2476.

22. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, Summaria F, Patrizi R, Borghi A, Di Russo C, Moretti C, Agostoni P, Loschiavo P, Lioy E, Sheiban I, Sangiorgi G. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol.* 2012; 60: 2481-2489.

23. Ando G, Capodanno D. Radial Access Reduces Mortality in Patients With Acute Coronary Syndromes: Results From an Updated Trial Sequential Analysis of Randomized Trials. *JACC Cardiovasc Interv.* 2016; 9: 660-670.

24. Mamas MA, Fath-Ordoubadi F, Danzi GB, Spaepen E, Kwok CS, Buchan I, Peek N, de Belder MA, Ludman PF, Paunovic D. Prevalence and impact of co-morbidity burden as defined by the Charlson co-morbidity index on 30-day and 1-and 5-year

outcomes after coronary stent implantation (from the Nobori-2 study). *Am J Cardiol.* 2015; 116: 364-371.

List of Figures and Tables

Table 1a: Baseline patient demographics, procedural details, and pharmacology (whole cohort)

Variable	2006 (51,850)	2009 (69,094)	2011 (75,016)	2013 (78,398)	P-value
Age (years)	64.5 (56.6 - 72.4)	65.1 (56.6 - 73.6)	65.3 (56.4 - 74.1)	65.0 (56.0 - 74.0)	< 0.0001
Gender (Men)	38,133 (73.5%)	51,120 (74.0%)	55,544 (74.0%)	58,173 (74.2%)	0.30
Smoking status					< 0.0001
Never	12,135 (34.6%)	20,615 (33.3%)	24,346 (36.1%)	26,258 (36.8%)	
Ex-smoker	14,968 (42.7%)	25,829 (41.8%)	26,107 (38.7%)	27,822 (39.0%)	
Current	7,989 (22.8%)	15,386 (24.9%)	17,038 (25.2%)	17,332 (24.3%)	
Diabetes Mellitus	7,115 (17.2%)	12,415 (18.5%)	13,937 (19.3%)	15,749 (21.2%)	< 0.0001
Peripheral vascular disease	1,725 (3.7%)	3,171 (4.7%)	3,676 (5.0%)	3,728 (4.9%)	< 0.0001
Hypertension	19,818 (42.2%)	37,000 (54.6%)	39,386 (53.7%)	41,730 (54.7%)	< 0.0001
Hypercholesterolemia	21,514 (45.8%)	40,466 (59.7%)	39,913 (54.4%)	41,137 (53.9%)	< 0.0001
Renal disease	913 (2.3%)	1,762 (2.6%)	1,814 (2.5%)	2,152 (2.9%)	< 0.0001
Previous CABG	3,440 (14.3%)	4,777 (9.7%)	5,264 (9.1%)	5,682 (9.3%)	< 0.0001
Previous myocardial infarction	11,820 (30.1%)	17,464 (28.5%)	18,747 (27.1%)	19,811 (26.8%)	< 0.0001
Previous stroke	1,183 (2.5%)	2,786 (4.1%)	3,090 (4.2%)	3,164 (4.2%)	< 0.0001
Previous Percutaneous coronary intervention	7,759 (18.2%)	14,824 (22.2%)	16,847 (23.0%)	19,052 (24.8%)	< 0.0001
Left ventricular ejection fraction					< 0.0001
>50%	14,835 (74.7%)	25,320 (69.3%)	25,260 (70.8%)	28,081 (70.0%)	
30%-50%	4,036 (20.3%)	8,659 (23.7%)	8,516 (23.9%)	9,468 (23.6%)	
<30%	981 (4.9%)	2,537 (6.9%)	1,924 (5.4%)	2,568 (6.4%)	
Indication for Percutaneous coronary intervention					< 0.0001
Elective	26,853 (53.6%)	29,088 (42.2%)	27,530 (36.8%)	27,426 (35.1%)	
Unstable angina/Non ST-elevation acute myocardial infarction	18,112 (36.1%)	26,226 (38.1%)	27,707 (37.0%)	29,608 (37.8%)	
ST-elevation acute myocardial infarction	5,043 (10.1%)	13,428 (19.5%)	19,490 (26.0%)	21,081 (26.9%)	
Stent thrombosis	104 (0.2%)	121 (0.2%)	123 (0.2%)	120 (0.2%)	
Access site (Radial)	9,123 (17.6%)	27,199 (39.4%)	41,143 (54.8%)	53,703 (68.5%)	< 0.0001

Variable	2006 (51,850)	2009 (69,094)	2011 (75,016)	2013 (78,398)	P-value
Vascular closure device use	17,410 (33.6%)	23,719 (34.3%)	19,668 (26.2%)	15,141 (19.3%)	< 0.0001
Stent					< 0.0001
None	2,768 (6.0%)	6,708 (10.2%)	7,214 (10.0%)	7,856 (10.4%)	
Drug eluting	29,599 (63.7%)	41,010 (62.6%)	51,108 (70.9%)	60,569 (80.2%)	
Bare metal	14,097 (30.3%)	17,815 (27.2%)	13,767 (19.1%)	7,099 (9.4%)	
Left main stem artery	1,270 (2.7%)	2,139 (3.1%)	2,501 (3.4%)	3,651 (4.7%)	< 0.0001
Multivessel Percutaneous coronary intervention	12,107 (23.8%)	12,821 (19.0%)	13,603 (18.3%)	14,209 (18.2%)	< 0.0001
Cardiogenic shock	463 (1.0%)	1,145 (1.7%)	1,635 (2.2%)	2,205 (2.8%)	< 0.0001
Intra-aortic balloon pump use	587 (1.1%)	1,073 (1.6%)	1,217 (1.6%)	1,064 (1.4%)	< 0.0001
Ventilatory support	221 (0.6%)	648 (1.1%)	1,112 (1.7%)	1,411 (2.0%)	< 0.0001
Circulatory support	628 (1.6%)	1,239 (1.9%)	1,491 (2.1%)	1,521 (2.0%)	< 0.0001
Glycoprotein inhibitor use	15,706 (35.7%)	17,376 (27.3%)	14,880 (21.6%)	11,720 (16.4%)	< 0.0001
Antiplatelet drug					< 0.0001
Clopidogrel	51,850 (100.0%)	69,027 (99.9%)	58,873 (92.0%)	53,228 (78.8%)	
Prasugrel	0 (0.0%)	67 (0.1%)	5,122 (8.0%)	4,718 (7.0%)	
Ticagrelor	0 (0.0%)	0 (0.0%)	26 (0.0%)	9,597 (14.2%)	
Bivalirudin	440 (0.8%)	452 (0.7%)	3,349 (4.5%)	4,957 (6.3%)	< 0.0001
Bleeding	328 (0.6%)	417 (0.6%)	469 (0.6%)	435 (0.5%)	< 0.0001

Table 1b: Baseline patient demographics, procedural details, and pharmacology (Elective procedures only)

Variable	2006 (26,853)	2009 (29,088)	2011 (27,530)	2013 (27,426)	P-value
Age (years)	64.9 (57.7 - 72.2)	65.7 (58.3 - 73.3)	66.0 (58.3 - 73.7)	66.0 (58.0 - 74.0)	< 0.0001
Gender (Men)	19,870 (74.0%)	21,651 (74.4%)	20,774 (75.5%)	20,813 (75.9%)	< 0.0001
Smoking status					< 0.0001
Never	6,916 (38.5%)	9,699 (37.3%)	9,840 (39.8%)	9,987 (40.2%)	
Ex-smoker	8,561 (47.6%)	12,775 (49.1%)	11,713 (47.4%)	11,752 (47.4%)	
Current	2,494 (13.9%)	3,550 (13.6%)	3,184 (12.9%)	3,079 (12.4%)	
Diabetes Mellitus	3,819 (17.9%)	6,012 (21.2%)	5,778 (21.8%)	6,217 (23.9%)	< 0.0001
Peripheral vascular disease	924 (3.8%)	1,446 (5.1%)	1,487 (5.5%)	1,306 (4.9%)	< 0.0001
Hypertension	10,748 (44.4%)	17,235 (60.3%)	16,451 (60.8%)	16,620 (62.0%)	< 0.0001
Hypercholesterolemia	11,844 (49.0%)	19,119 (66.9%)	16,983 (62.8%)	17,048 (63.6%)	< 0.0001
Renal disease	392 (2.0%)	684 (2.4%)	597 (2.2%)	704 (2.6%)	< 0.0001
Previous coronary artery bypass graft	1,864 (15.8%)	2,563 (12.3%)	2,563 (11.9%)	2,647 (12.2%)	< 0.0001
Previous myocardial infarction	6,139 (30.5%)	9,024 (34.7%)	8,696 (34.5%)	9,072 (34.8%)	< 0.0001
Previous stroke	554 (2.3%)	1,099 (3.9%)	1,015 (3.8%)	1,024 (3.8%)	< 0.0001
Previous Percutaneous coronary intervention	5,101 (23.3%)	9,141 (32.5%)	9,609 (35.8%)	10,649 (39.5%)	< 0.0001
Left ventricular ejection fraction					< 0.0001
>50%	8,820 (82.3%)	13,755 (79.3%)	12,925 (80.7%)	13,709 (80.6%)	
30%-50%	1,571 (14.7%)	2,769 (16.0%)	2,592 (16.2%)	2,711 (15.9%)	
<30%	322 (3.0%)	829 (4.8%)	497 (3.1%)	586 (3.4%)	
Access site (Radial)	4,325 (16.1%)	10,822 (37.2%)	14,187 (51.5%)	17,902 (65.3%)	< 0.0001
Vascular closure device use	8,990 (33.5%)	10,521 (36.2%)	7,926 (28.8%)	6,100 (22.2%)	< 0.0001
Stent					< 0.0001
None	1,624 (6.8%)	3,792 (13.8%)	3,474 (13.2%)	3,562 (13.6%)	
Drug eluting	16,295 (68.1%)	18,522 (67.4%)	19,708 (75.0%)	21,117 (80.9%)	
Bare metal	5,996 (25.1%)	5,186 (18.9%)	3,080 (11.7%)	1,430 (5.5%)	
Left main stem artery	651 (2.7%)	1,031 (3.6%)	1,024 (3.8%)	1,454 (5.4%)	< 0.0001
Multivessel Percutaneous coronary intervention	6,750 (25.7%)	6,156 (21.8%)	5,991 (21.9%)	5,898 (21.6%)	< 0.0001
Cardiogenic shock	3 (0.0%)	5 (0.0%)	4 (0.0%)	15 (0.1%)	0.022

Variable	2006 (26,853)	2009 (29,088)	2011 (27,530)	2013 (27,426)	P-value
Intra-aortic balloon pump use	71 (0.3%)	70 (0.2%)	52 (0.2%)	40 (0.1%)	< 0.0001
Ventilatory support	33 (0.2%)	54 (0.2%)	93 (0.4%)	75 (0.3%)	< 0.0001
Circulatory support	79 (0.4%)	85 (0.3%)	89 (0.3%)	70 (0.3%)	0.0008
Glycoprotein inhibitor use	4,745 (21.2%)	2,347 (8.9%)	1,397 (5.5%)	989 (3.9%)	< 0.0001
Antiplatelet use					< 0.0001
Clopidogrel	26,853 (100.0%)	29,076 (100.0%)	27,120 (98.5%)	25,950 (94.6%)	
Prasugrel	0 (0.0%)	12 (0.0%)	407 (1.5%)	618 (2.3%)	
Ticagrelor	0 (0.0%)	0 (0.0%)	3 (0.0%)	858 (3.1%)	
Bivalirudin	150 (0.6%)	34 (0.1%)	62 (0.2%)	92 (0.3%)	< 0.0001
Bleeding	132 (0.5%)	118 (0.4%)	119 (0.4%)	126 (0.5%)	0.052

Table 1c: Baseline patient demographics, procedural details, and pharmacology (ACS only)

Variable	2006 (24,997)	2009 (40,006)	2011 (47,486)	2013 (50,972)	P-value
Age (years)	64.0 (55.1 - 72.6)	64.5 (55.3 - 73.9)	65.0 (55.3 - 74.6)	65.0 (55.0 - 74.0)	< 0.0001
Gender (Men)	18,263 (73.1%)	29,469 (73.7%)	34,770 (73.2%)	37,360 (73.3%)	0.49
Smoking status					< 0.0001
Never	5,219 (30.5%)	10,916 (30.5%)	14,506 (33.9%)	16,271 (34.9%)	
Ex-smoker	6,407 (37.4%)	13,054 (36.5%)	14,394 (33.7%)	16,070 (34.5%)	
Current	5,495 (32.1%)	11,836 (33.1%)	13,854 (32.4%)	14,253 (30.6%)	
Diabetes Mellitus	3,296 (16.5%)	6,403 (16.5%)	8,159 (17.9%)	9,532 (19.7%)	< 0.0001
Peripheral vascular disease	801 (3.5%)	1,725 (4.4%)	2,189 (4.7%)	2,422 (4.9%)	< 0.0001
Hypertension	9,070 (39.7%)	19,765 (50.4%)	22,935 (49.5%)	25,110 (50.7%)	< 0.0001
Hypercholesterolemia	9,670 (42.3%)	21,347 (54.5%)	22,930 (49.5%)	24,089 (48.7%)	< 0.0001
Renal disease	521 (2.7%)	1,078 (2.8%)	1,217 (2.7%)	1,448 (3.0%)	0.0006
Previous Coronary artery bypass graft	1,576 (12.9%)	2,214 (7.8%)	2,701 (7.5%)	3,035 (7.7%)	< 0.0001
Previous myocardial infarction	5,681 (29.7%)	8,440 (24.0%)	10,051 (22.9%)	10,739 (22.4%)	< 0.0001
Previous stroke	629 (2.8%)	1,687 (4.3%)	2,075 (4.5%)	2,140 (4.3%)	< 0.0001
Previous Percutaneous coronary intervention	2,658 (12.8%)	5,683 (14.7%)	7,238 (15.6%)	8,403 (16.8%)	< 0.0001
Left ventricular ejection fraction					
>50%	6,015 (65.8%)	11,565 (60.4%)	12,335 (62.7%)	14,372 (62.2%)	
30%-50%	2,465 (27.0%)	5,890 (30.7%)	5,924 (30.1%)	6,757 (29.2%)	
<30%	659 (7.2%)	1,708 (8.9%)	1,427 (7.2%)	1,982 (8.6%)	
Indication for Percutaneous coronary intervention					< 0.0001
Elective	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unstable angina/Non ST-elevation acute myocardial infarction	18,112 (77.9%)	26,226 (65.9%)	27,707 (58.5%)	29,608 (58.3%)	
ST-elevation acute myocardial infarction	5,043 (21.7%)	13,428 (33.7%)	19,490 (41.2%)	21,081 (41.5%)	
Stent thrombosis	104 (0.4%)	121 (0.3%)	123 (0.3%)	120 (0.2%)	
Access site (Radial)	4,798 (19.2%)	16,377 (40.9%)	26,956 (56.8%)	35,801 (70.2%)	< 0.0001
Vascular closure device use	8,420 (33.7%)	13,198 (33.0%)	11,742 (24.7%)	9,041 (17.7%)	< 0.0001
Stents					< 0.0001
None	1,144 (5.1%)	2,916 (7.7%)	3,740 (8.2%)	4,294 (8.7%)	
Drug eluting	13,304 (59.0%)	22,488 (59.1%)	31,400 (68.5%)	39,452 (79.8%)	
Bare metal	8,101 (35.9%)	12,629 (33.2%)	10,687 (23.3%)	5,669 (11.5%)	

Variable	2006 (24,997)	2009 (40,006)	2011 (47,486)	2013 (50,972)	P-value
Left main stem artery	619 (2.6%)	1,108 (2.8%)	1,477 (3.1%)	2,197 (4.4%)	< 0.0001
Multivessel Percutaneous coronary intervention	5,357 (21.8%)	6,665 (17.0%)	7,612 (16.1%)	8,311 (16.4%)	< 0.0001
Cardiogenic shock	460 (2.2%)	1,140 (2.9%)	1,631 (3.5%)	2,190 (4.3%)	< 0.0001
Intra-aortic balloon pump use	516 (2.1%)	1,003 (2.5%)	1,165 (2.5%)	1,024 (2.0%)	< 0.0001
Ventilatory support	188 (1.0%)	594 (1.7%)	1,019 (2.4%)	1,336 (2.9%)	< 0.0001
Circulatory support	549 (2.8%)	1,154 (3.1%)	1,402 (3.1%)	1,451 (3.0%)	0.007
Glycoprotein inhibitor use	10,961 (50.6%)	15,029 (40.4%)	13,483 (31.0%)	10,731 (23.1%)	< 0.0001
Antiplatelet use					< 0.0001
Clopidogrel	24,997 (100.0%)	39,951 (99.9%)	31,753 (87.0%)	27,278 (68.0%)	
Prasugrel	0 (0.0%)	55 (0.1%)	4,715 (12.9%)	4,100 (10.2%)	
Ticagrelor	0 (0.0%)	0 (0.0%)	23 (0.1%)	8,739 (21.8%)	
Bivalirudin	290 (1.2%)	418 (1.0%)	3,287 (6.9%)	4,865 (9.5%)	< 0.0001
Bleeding	196 (0.8%)	299 (0.8%)	350 (0.7%)	309 (0.6%)	< 0.0001

Table 2: Summary results after fitting multivariate logistic regression models on the whole cohort and the two subsets.

(a) Explanatory variables, their coefficients expressed in odd ratios (OR), and their confidence intervals (in brackets).

	All	Elective PCI	ACS
(Intercept)	0.001 (0.000-0.001)	0.001 (0.000-0.001)	0.001 (0.001-0.001)
Year	1.023 (1.005-1.041)	1.049 (1.018-1.082)	1.011 (0.989-1.033)
Age	1.028 (1.024-1.031)	1.027 (1.020-1.034)	1.028 (1.024-1.032)
Gender (Men)			
Female	2.041 (1.898-2.194)	2.223 (1.946-2.540)	1.961 (1.799-2.138)
Smoking status (Never)			
Ex-smoker	1.091 (1.003-1.187)	1.133 (0.983-1.307)	1.067 (0.963-1.183)
Current	1.046 (0.941-1.162)	1.022 (0.797-1.310)	1.044 (0.928-1.174)
Diabetes	0.923 (0.843-1.012)	0.989 (0.844-1.159)	0.896 (0.802-1.001)
Peripheral vascular disease	1.316 (1.147-1.509)	1.362 (1.054-1.760)	1.302 (1.106-1.531)
Hypertension	1.141 (1.055-1.234)	1.206 (1.043-1.395)	1.116 (1.016-1.225)
Hypercholesterolemia	1.184 (1.096-1.279)	1.120 (0.969-1.294)	1.207 (1.101-1.322)
Renal disease	1.425 (1.214-1.673)	0.904 (0.603-1.354)	1.596 (1.338-1.903)
Previous coronary artery bypass graft	0.804 (0.681-0.950)	0.797 (0.598-1.063)	0.820 (0.690-0.975)
Previous myocardial infarction	0.901 (0.818-0.992)	0.969 (0.827-1.136)	0.865 (0.770-0.971)
Previous stroke	1.280 (1.107-1.481)	1.353 (1.015-1.804)	1.255 (1.060-1.486)
Previous Percutaneous coronary intervention	1.015 (0.918-1.122)	0.976 (0.838-1.137)	1.033 (0.905-1.178)
Left ventricular ejection fraction (Good)			
30%-50%	1.009 (0.916-1.112)	0.892 (0.700-1.137)	1.050 (0.935-1.179)
<30%	1.054 (0.907-1.226)	0.855 (0.575-1.270)	1.113 (0.950-1.303)
Indication for Percutaneous coronary intervention (Elective)			
Unstable angina/Non ST elevation acute myocardial infarction	1.191 (1.089-1.302)		
ST elevation acute myocardial infarction	1.427 (1.272-1.600)		1.210 (1.096-1.336)*
Stent thrombosis	2.380 (1.564-3.622)		2.027 (1.331-3.087)*
Access site (Femoral)			
Radial	0.363 (0.330-0.399)	0.258 (0.213-0.312)	0.409 (0.366-0.457)
Vascular disclosure device use	0.878 (0.810-0.951)	0.866 (0.752-0.996)	0.880 (0.798-0.970)
Stent (None)			
Drug eluting	0.820 (0.728-0.925)	0.951 (0.771-1.174)	0.748 (0.648-0.865)
Bare metal	0.857 (0.753-0.975)	0.866 (0.671-1.119)	0.816 (0.701-0.950)
Left main stem artery	1.210 (1.039-1.410)	1.035 (0.757-1.416)	1.281 (1.075-1.526)
Multivessel Percutaneous coronary intervention	1.093 (1.000-1.195)	1.209 (1.041-1.405)	1.035 (0.926-1.156)
Cardiogenic shock	1.208 (1.019-1.432)		1.275 (1.071-1.518)
Intra-aortic balloon pump use	1.129 (0.859-1.486)	0.453 (0.220-0.931)	1.331 (0.984-1.802)
Ventilatory support	1.092 (0.892-1.336)	0.892 (0.327-2.435)	1.133 (0.922-1.392)
Circulatory support	3.308 (2.522-4.339)	15.438 (8.721-27.328)	2.581 (1.906-3.494)
Glycoprotein inhibitor use	1.953 (1.795-2.126)	2.134 (1.787-2.550)	1.877 (1.709-2.063)
Antiplatelet drug (Clopidogrel)			
Prasugrel	0.787 (0.645-0.961)	1.818 (0.961-3.438)	0.736 (0.597-0.908)
Ticagrelor	0.599 (0.435-0.826)	0.894 (0.284-2.815)	0.585 (0.418-0.818)
Bivalirudin	1.684 (1.417-2.001)	1.440 (0.588-3.523)	1.704 (1.428-2.033)

(b) Estimated average area under the receiver operator curves (AUC)

(a) Explanatory variables, their coefficients expressed in odd ratios (OR), and their confidence intervals (in brackets).

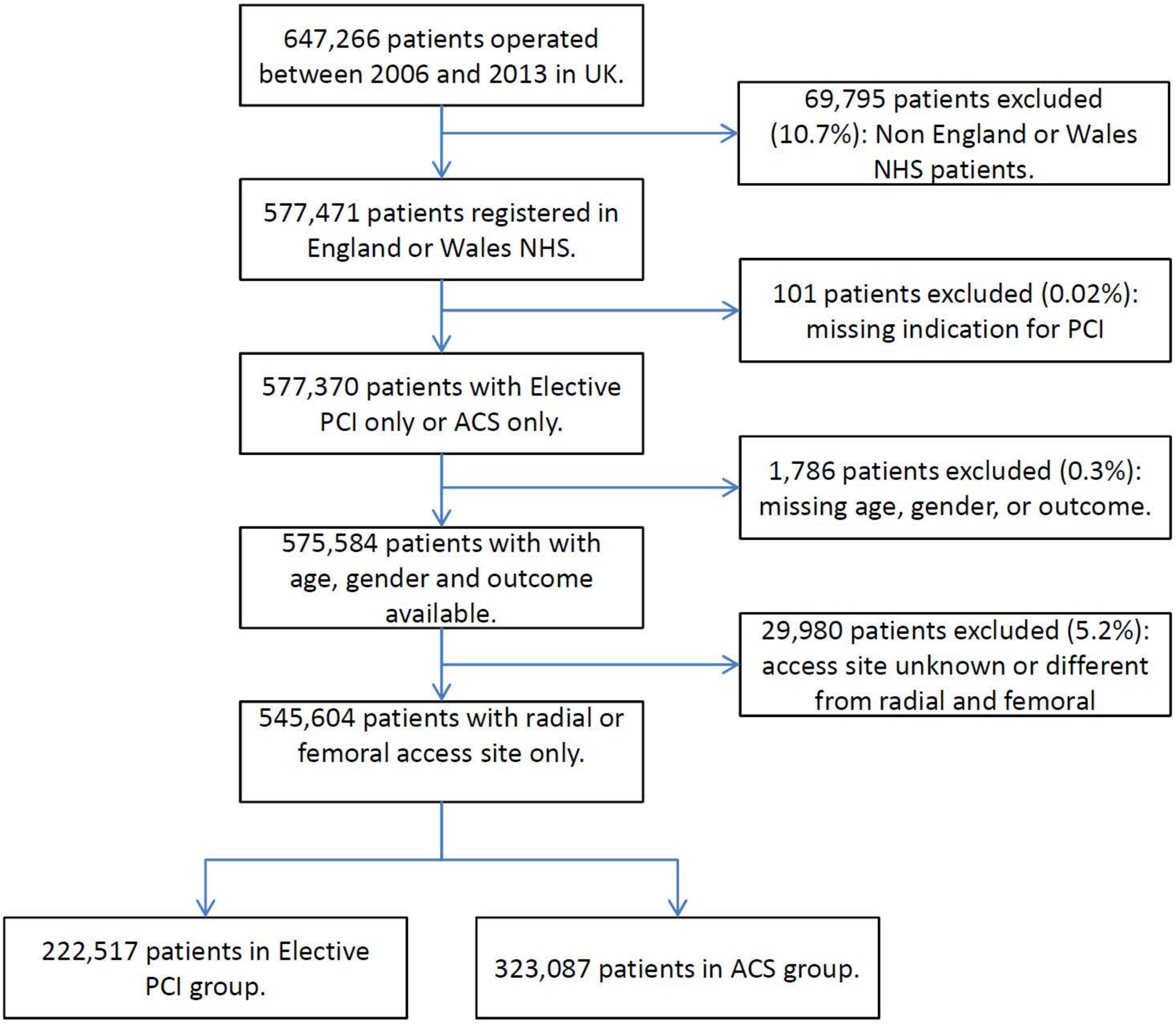
	All	**Elective PCI**	**ACS**
	All	**Elective PCI**	**ACS**
AUC	0.755	0.730	0.763

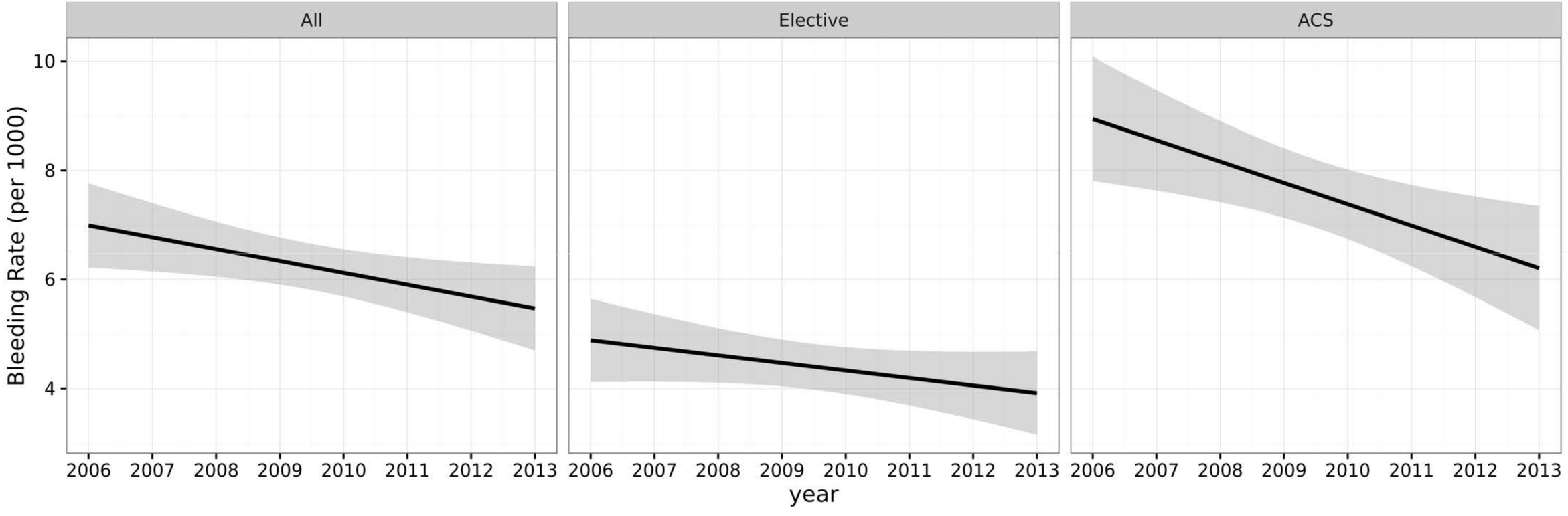
*UA/NSTEMI was used as baseline for the estimation of these ORs since there is no "Elective" category in the variable "Indication for PCI" within the ACS group.

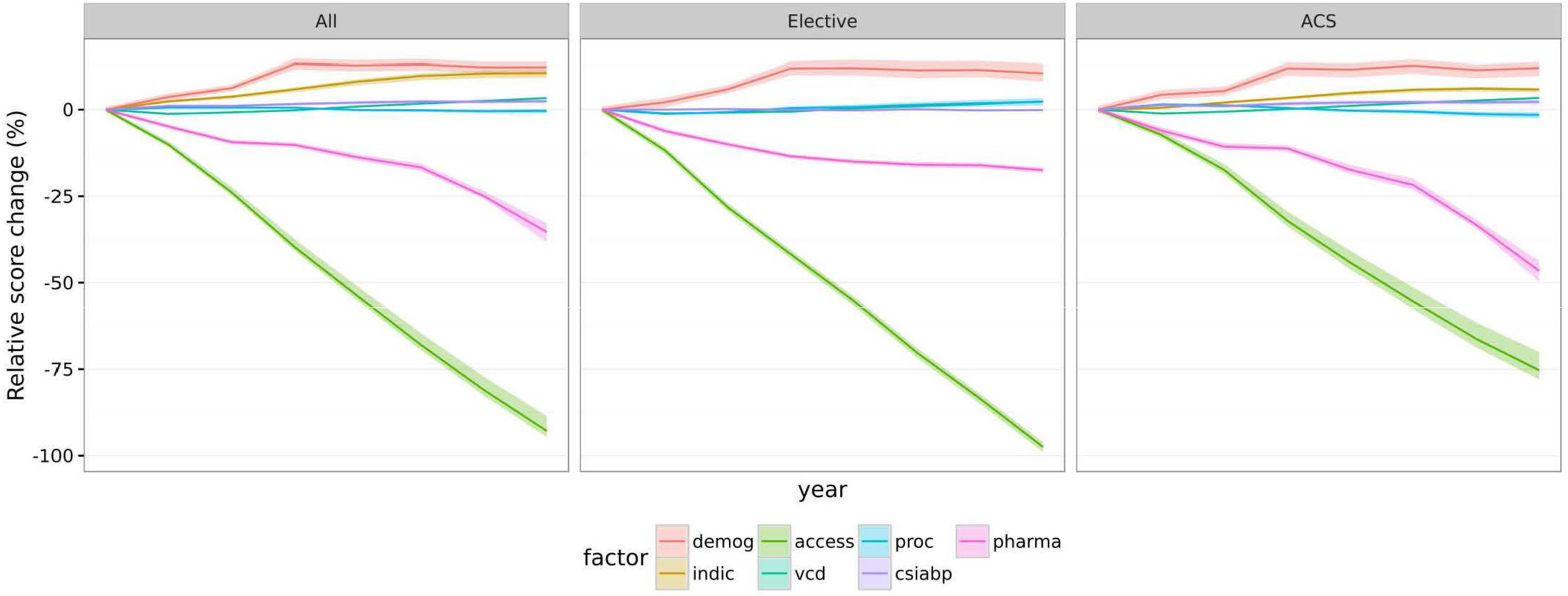
Table 3: Influence of changes in factors on temporal trends in bleeding rates.

			Comparison with Model 0		Comparison with Model 1	
Group	**Model†**	**OR (95% CI)***	**Attenuation (%)**	**P-value‡**	**Attenuation (%)**	**P-value‡**
All	0	0.964 (0.950-0.979)				
	1	0.952 (0.937-0.966)	-34.08%	<0.001		
	2	0.931 (0.916-0.945)	-92.58%	<0.001	-43.63%	<0.001
	3	1.015 (0.999-1.031)	141.52%	<0.001	130.97%	<0.001
	4	0.958 (0.944-0.973)	-15.47%	<0.001	13.88%	<0.001
	5	0.955 (0.940-0.970)	-25.42%	<0.001	6.46%	<0.001
	6	0.945 (0.931-0.960)	-51.88%	<0.001	-13.27%	<0.001
	7	0.981 (0.965-0.998)	48.26%	<0.001	61.41%	<0.001
Elective	0	0.969 (0.942-0.996)				
	1	0.959 (0.932-0.986)	-32.94%	<0.001		
	-					
	3	1.028 (0.998-1.059)	189.74%	<0.001	167.50%	<0.001
	4	0.966 (0.939-0.994)	-8.05%	<0.001	18.72%	<0.001
	5	0.954 (0.927-0.982)	-46.61%	<0.001	-10.29%	<0.001
	6	0.959 (0.932-0.987)	-31.61%	<0.001	1.00%	<0.001
	7	0.981 (0.953-1.010)	39.75%	<0.001	54.68%	<0.001
ACS	0	0.945 (0.928-0.963)				
	1	0.934 (0.917-0.951)	-20.91%	<0.001		
	2	0.919 (0.902-0.936)	-48.38%	<0.001	-22.72%	<0.001
	3	0.994 (0.975-1.013)	88.93%	<0.001	90.85%	<0.001
	4	0.940 (0.923-0.958)	-9.83%	<0.001	9.16%	<0.001
	5	0.938 (0.920-0.956)	-13.16%	<0.001	6.41%	<0.001
	6	0.929 (0.912-0.947)	-29.63%	<0.001	-7.21%	<0.001
	7	0.972 (0.953-0.992)	49.43%	<0.001	58.18%	<0.001

†Logistic regression models for Bleeding: model 0: univariate model with explanatory variable Year; models 1 to 7: multivariate models with variable Year and adjusted for: 1) demographics; 2) demographics + indication for PCI; 3) demographics + access site; 4) demographics + VCD; 5) demographics + procedural characteristics (stent, left main stem artery, multivessel PCI); 6) demographics + CS/IABP; and 7) demographics + pharmacology. *Odd ratios between time variable (in years) and bleeding outcome (95% confidence interval in brackets). ‡P-values of comparing models 0 and 1 with the others using likelihood test.


647,266 patients operated between 2006 and 2013 in UK.
69,795 patients excluded (10.7%): Non England or Wales NHS patients.
577,471 patients registered in England or Wales NHS.
101 patients excluded (0.02%): missing indication for PCI
577,370 patients with Elective PCI only or ACS only.
1,786 patients excluded (0.3%): missing age, gender, or outcome.
575,584 patients with with age, gender and outcome available.
29,980 patients excluded (5.2%): access site unknown or different from radial and femoral
545,604 patients with radial or femoral access site only.
222,517 patients in Elective PCI group.
323,087 patients in ACS group.


All
Elective
ACS
Bleeding Rate (per 1000)
10
8
6
4
2006
2007
2008
2009
2010
2011
2012
2013
year


All
Elective
ACS
Relative score change (%)
0
-25
-50
-75
-100
year
factor
demog
indic
access
vcd
proc
csiabp
pharma

Supplementary Methods

To quantify the influence of factors on the bleeding rate trends, we started with a new simple univariate logistic regression model (Supplementary methods). using time as an ordered categorical explanatory variable (henceforth, *model_0*). Then, a more complex multivariate model containing model 0 and the clinical demographics covariates was created (*model_1*). Subsequent models containing *model_1* were created, one for each factor influencing the trends, as follows: *model_2* = *model_1* + indication for PCI; *model_3* = *model_1* + access site; *model_4* = *model_1* + VCD use; *model_5* = *model_1* + procedural characteristics; *model_6* = *model_1* + CS/IABP; *model_7* = *model_1* + pharmacology. All models were fitted on multiply imputed data and pooled results were assessed against *model_1* using likelihood ratio tests (A3) [23], which take the between-imputation variability into account. As null hypothesis, we assumed no statistical difference between *model_1* and models *model_2* to *model_7*. Influences of factors over temporal trends in bleeding were quantified by comparing the estimates for 1-year increases in time for *model_1* against the corresponding estimates for time in the more complex models. If the added factor explained some of the temporal trends, we would expect the odds ratio for a 1-year increase in the time variable to attenuate towards 1. We reported the level of attenuation in odd ratios for the time variable after adding the covariates corresponding to a particular factor to the *model_1*.