Changes in arterial access site and association with mortality in the United Kingdom: observations from a national percutaneous coronary intervention database

Short title: Arterial access site for PCI and mortality

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Abstract

Background

The transradial access (TRA) site has become the default access site for PCI in the UK with randomized trials and national registry data showing reductions in mortality associated with TRA utilization. This study evaluates regional changes in access site practice in England and Wales over time and whether changes in access site practice has been uniform nationally and across different patient sub-groups, and provide national estimates for the potential number of lives 'saved' or 'lost' associated with regional differences in access site practice.

Methods and Results

Using the BCIS (British Cardiovascular Intervention Society) database, we investigated outcomes for growth of TRA in different regions in England and Wales in 448,853 patients who underwent PCI, 2005-2012. Multiple logistic regressions used to quantify the effect of TRA on 30-day mortality and quantify lives 'saved' and 'lost' by differences in TRA adoption. TRA utilization increased from 14.0% to 58.6% in 417,038 PCI patients with large variations in different parts of the country. TRA was independently associated with a decreased risk of 30-day mortality (OR=0·70; 95%CI=0·66-0·74) with significant but small differences observed across different regions. The number of estimated lives 'saved' was 450 (95%CI=275-650) and estimate that an additional 264 (95%CI=153-399) lives would have been saved if TRA adoption were uniform nationally.

Conclusions

TRA has become the dominant PCI approach in the UK with a wide variation in different parts of the country. Changes in practice have contributed to mortality reductions, whilst inequalities have resulted in missed opportunities for further improvements.

Key words: mortality, angioplasty, catheterization

Introduction

Since the introduction of the trans-radial (TRA) approach for diagnostic coronary angiography[1] and then percutaneous coronary intervention (PCI)[2] the radial artery has increasingly been adopted as the primary access site for cardiac catheterization in Europe and Asia, with growing uptake in the US.[3] Adoption of the TRA access site is associated with a reduced rate of access site related bleeding complications[4] and mortality[5-10] as well as earlier ambulation,[11] improved patient comfort and greater patient satisfaction[12] Bleeding complications are amongst the commonest complications encountered in contemporary PCI and are independently associated with a 3-fold increase in mortality[13, 14] It is widely believed that the consistently observed lower mortality risk that is associated with the choice of TRA is mediated through a reduction in major bleeding complications,[8, 15] although there may be additional mechanisms that contribute to this mortality reduction independent to decreases in major bleeding.[16] We have previously reported that the magnitude of this mortality reduction associated with TRA use is related to baseline bleeding risk[7]

Recent data from the UK has suggested that TRA utilization has grown from 16% to become the predominant access site in PCI for both elective and ACS indications[6, 17] Similarly, an increase in the radial approach has been reported in the US, albeit at a slower rate, from 1.2% in 2007 to 16% by 2012[18, 19] However, whilst previous national analyses have reported an association between radial access site choice and a reduced risk of mortality in high risk cohorts undergoing PCI[5, 6, 9, 20] estimates regarding the number of potential deaths that may have been avoided through a change in access site practice from a national perspective have not previously been reported. Additionally there have been no national estimates about potential lives 'lost' as a consequence of regional differences and/or inequalities in the rates of increased radial access use for PCI.

We studied changes in PCI access site practice from a national perspective in England and Wales over an eight-year period using the British Cardiovascular Interventional Society database. Specifically, we assessed (i) changes in the characteristics of patients undergoing PCI over this timeframe, (ii) growth of TRA amongst different patient subgroups and (iii) differences in access site utilization across different regions. Finally, we estimated the number of potential deaths that may have been avoided by a wholesale change to TRA in access site practice across different parts of the country.

Methods

The British Cardiovascular Intervention Society Database

The British Cardiovascular Intervention Society (BCIS) collects data on all PCI procedures in the UK[21, 22]. The data collection is coordinated by the National Institute of Cardiovascular Outcomes Research (http://www.ucl.ac.uk/nicor/) via the Central Cardiac Audit Database. In 2011, this dataset collected information on 99.4% of all PCI procedures performed in NHS Hospitals in England and Wales.

The BCIS-NICOR database contains a total of 113 variables, which includes information on clinical variables, procedural parameters and patient outcomes. Mortality tracking is undertaken by the Medical Research Information Service (MRIS) using patients' NHS number that provides a unique identifier for any person registered with the NHS in England and Wales.

Study inclusions

The data presented relate to all reported PCI procedures undertaken in patients in the United Kingdom between January 1, 2005, and December 31, 2012 (N=448853). PCI procedures performed via the left or right femoral artery or the left or right radial artery were included in the TFA and TRA cohorts, respectively (N=423032). Patients in whom the access site was unclear, missing or where multiple access sites were attempted / used and the primary access site that was used for the procedure could not be identified were excluded (N=25821; 5.8%).

Statistical analyses

All analyses were conducted in Stata v13.1 with an alpha level of 5% used throughout. We obtained spatial maps of England and Wales at Strategic Health Authority (SHA) level, a high level National Health Service (NHS) structure geography using the *spmap* command.

Next, we proceeded with quantifying the effect of arterial access type (femoral only vs. radial only) on 30-day mortality, controlling for various patient characteristics: age, gender, diabetes, hypercholesterolemia, hypertension, peripheral vascular disease, cerebrovascular event, renal history, previous MI, previous PCI, previous CABG, family history of CAD, smoking (never smoked, ex-smoker and current smoker), indication for intervention (Elective, NSTEMI and STEMI), cardiogenic shock pre-procedure and ventilation pre-procedure. Area location deprivation (based on the 2007 Index of Multiple

Deprivation, or IMD) was not included in the model since it was completely missing for Wales. For 42.4% of the 423032 patients with femoral- or radial-only access type, values were missing for at least one covariate (Figure 1). Therefore, we employed chained equations multiple imputation methods (*mi impute chained* command) to impute missing values through linear, logistic or multinomial logistic regressions. We generated 50 datasets with imputed values, and through these we were able to include 98.6% of the patients (femoral only and radial only) in the logistic regression analysis. This analysis followed a mixed-effects model specification (*xtlogit* command) to account for the nested structure of the data (patients nested within geographies) through the inclusion of random effects for Primary Care Trusts (or PCTs; a medium-level NHS structure geography, abolished in 2013), and was controlled for all the covariates previously mentioned as well as SHA (as a fixed-effect). The regression model also included interaction terms between access type and SHA, allowing us to estimate a different effect for access type in each geographical areas, after controlling for other covariates. The specified model was then run with the *mi estimate* command, in order to combine estimates across the 50 imputed datasets.

Using the combined model estimates (across the 50 datasets) with the *mimrgns* command (and necessarily assuming that the random-effect of the model was zero), we calculated the probability of 30-day mortality by arterial access type, within each SHA and year while setting all covariates at their mean values within each SHA-year stratum. This allowed us to calculate the difference of these probability estimates within each strata and pool their errors to obtain the standard error of the difference. These differences in the patient-level effect of access type were then aggregated for each SHA-year stratum using the number of performed operations, allowing us to calculate the number of lives 'saved' and 'lost' at 30 days (and their 95% confidence intervals). We defined as 'saved' lives the number of 30 day deaths that were prevented with the use of radial-only access, compared to a hypothetical scenario where only femoral-only operations were performed within the stratum. Lives 'lost' (speculative) were similarly defined as the number of 30-day deaths that would have been prevented with the use of radial-only access, in hypothetical scenarios where their rate was higher than what was observed in practice. In the first scenario, the rate was set to the highest observed radial-only rate across all strata and years (82.9%), which was assumed to have been feasible for the whole of our study period. However, this overall maximum rate might have not been possible in earlier years because of inexperience, equipment inefficiencies or other factors. Therefore, we used a second scenario to calculate lives 'lost' (conservative), where the hypothetical radial-only access rate varied over time, and it was assumed to be the highest observed stratum rate within the respective year.

Using a similar modeling approach, multiple imputation multiple logistic regression with the *logit* and *mimrgns* commands, we also investigated the relationship between patient characteristics, year and region with choice of arterial access type. The same database of 50 imputed datasets was used for this purpose, but this time we encountered non-convergence issues with mixed-effects models (*xtlogit*) and we had to compromise with a simpler fixed-effects only model. All covariates previously listed for the mortality analysis were included as potential predictors, with the exception of arterial access type which was now the outcome. The *mimrgns* command was use to obtain the probability of radial-only access by year, setting all covariates to their mean levels within each year.

Finally, we also ran a propensity score matching sensitivity analysis for mortality, with the *teffects psmatch* command. Under this analysis we calculated the average treatment effect of radial- vs femoral-only access after propensity score adjustment, as a probability difference over the 50 imputed datasets. The propensity score for each patient was calculated using a logistic model, in which we included all the covariates that were included in the main analyses.

Results

A total of 448,853 patients underwent PCI from 2005 to 2012 in England and Wales, of whom 25,821 (5·8%) were excluded because access site utilized was either missing, unclear or multiple access sites were attempted and primary access site utilized could not be identified. Figure 1 illustrates the flowchart of patient inclusion and exclusion. A total of 159,425 PCI procedures (35·5%) were undertaken through the TRA. TRA utilization increased from 14% to 58·6% between 2005 and 2012. Table 1 illustrates changes in the clinical and procedural demographics in patients undergoing PCI from 2005-2012. The number of patients per year undergoing PCI increased from 37,658 in 2005 to 65,476 in 2012. Over time, mean patient age as well as diabetes and renal disease prevalence increased, and patients were more likely to undergo PCI for STEMI indications but less likely to undergo elective PCI.

Figures 2a and 2b illustrates rates of TRA utilization in Primary Care Trusts in England and Local Health Boards in Wales, between 2005-2012. It can be seen graphically that TRA utilization has increased in all regions of England and Wales over time, but that there were very large variations in TRA adoption in different parts of the country, with the greatest growth in the North East, North West, Midlands and Wales whilst adoption in the South East Coast and London has been the slowest.

Table 2 presents the clinical and procedural demographics of patients undergoing TRA PCI between 2005-2012. Over this time period PCI undertaken through TRA were in increasingly more complex patients, who were older, more likely to have ACS, and cardiogenic shock. Table 2 also reports some of the inequalities of TRA adoption observed nationally. Uptake of TRA was slowest in the least deprived areas and greatest in those areas at highest deprivation and there was significant variation in TRA uptake amongst different SHAs, with rates between 4·9% (Yorkshire and the Humber) and 37·6% (North East) in 2005 and between 28·0 % (South East Coast) and 81·2 % (North East) in 2012.

Table 3 illustrates independent predictors for TRA adoption in England and Wales. The odds of patients undergoing PCI in 2012 were over 11 times *higher* compared to 2005 (OR=11·6; 95%CI=11·2-12·0) compared to 2005. The odds of patients undergoing PCI through the radial artery were *lower* if they were female, elderly, had previous CABG or presented with cardiogenic shock. SHA appeared to be an important independent predictor of access site choice, and patients in the South East Coast were much less likely to undergo PCI through the TRA route, than patients in the North East (OR=0·07; 95%CI=0·07-0·08). Table 4 illustrates predictors of 30-day mortality, with TRA utilization independently associated with a decreased risk of 30-day mortality (OR=0·70; 95%CI=0·66-0·74). There were no significant differences observed in the mortality benefit observed with TRA adoption in the different SHA studied once differences in baseline covariates were adjusted for. An alternative model without interaction terms, where the other covariates can be interpreted, is provided for completeness in Supplementary Table 1.

Estimated lives ‘saved’ and ‘lost’ (conservative), as a consequence of change in access site practice over time in each individual SHA, are presented in Supplementary Tables 2 and 3 and graphically in Figure 3. Over the eight-year study period, the fewest lives ‘saved’ occurred in the South East Coast with 0 (95%CI=0-9) and the greatest number in the South West with 79 lives (95%CI=56-102), while the total number of estimated lives ‘saved’ was 450 (95%CI=275-650). In terms of conservative lives ‘lost’, if TRA adoption was uniform nationally to the highest observed SHA rates within each year (which was consistently in the North-East), an additional 264 (95%CI=153-399) lives would have been saved between 2005-2012. Speculative lives ‘lost’ when compared to a hypothetical scenario where radial access percentages across all strata are 82.9%, the highest percentage observed are presented in Supplementary Table 4 and Supplementary Figure 1, and the overall estimate was 385 (95%CI=224-573), over the study period.

Results from the propensity score matching sensitivity analysis on 30-day mortality agreed with the main analysis results. The average treatment effect of radial-only vs femoral-only was estimated to be -0·0052 (95% CI: -0·0067 to -0·0036), compared to -0·0046 (95% CI: -0·0058 to -0·0034) from the main analysis. The comparative benefit of TRA appeared at least as strong in the sensitivity analyses.

Discussion

TRA has grown globally to become the predominant access site for PCI procedures although significant differences in its adoption have been reported worldwide. Our analysis has shown that the radial artery has become the predominant access site for PCI procedures in England and Wales over a period of eight years, with a rate of around 60% nationally in 2012. Adoption of TRA has been widely heterogeneous in different parts of the country, varying between 28·0% in the South coast and 81·2% in the North-East, in 2012. We report that this change in national access site practice is associated with utilization of TRA in increasingly more complex patients, such as those with ACS, the elderly and those with cardiogenic shock. We estimated that this change in access site practice nationally has contributed to 450 lives ‘saved’ whilst inequalities in these changes have contributed to over 260 lives ‘lost’, over a period of eight years.

In the current study we have evaluated temporal trends in TRA adoption nationally in England and Wales and show significant heterogeneity in TRA adoption across the country with TRA utilization varying from 28% in the South coast to 81.2% in the North East of England. Our analysis shows that even when differences in baseline clinical demographics that may influence TRA choice are accounted for, significant heterogeneity in TRA adoption exists across SHA with patients in the South East Coast 93% (OR 0.07 95% CI 0.073-0.080; P<0.001) less likely to undergo PCI through the TRA approach than those patients in the North East. Other studies derived from the NCDR have suggested significant heterogeneity across the US with rates of TRA adoption varying from 12 to 38% in the Northeast and South respectively[19]

The growing number of dedicated training courses and workshops have helped to expand interest in this technique worldwide[23] with many of the TRA training courses in the UK based in the areas with the greatest adoption of the TRA such as the West Midlands. This highlights the importance of such dedicated training courses and workshops and has important implications for other countries such as the United States who are still in the early stages of radial adoption nationally. Indeed, in a recent survey around barriers to TRA adoption in Veterans' Administration catheterization laboratories undertaken in the United States, important barriers such as lack of training opportunities (18%), perceived long radial learning curve for cases (43%) and lack of support from other interventional cardiologists or other catheterization staff (20%) were identified as important barriers that prevented adoption in many VA laboratories[24] It is possible that many of these findings are equally applicable to UK interventional practice. Newly appointed consultants are more likely to have received formal training in use of the TRA in PCI than established consultants who often lack such training opportunities, and are limited by operational barriers within their departments. In a recent survey amongst 204 interventional cardiologists across the UK, there was a correlation between access site preference for PCI and years since qualification, with operators whose primary access site choice was femoral having been qualified on average 5 years earlier than those in whom radial was their default choice[25] It is unclear from our current analysis whether SHAs in which the greatest adoption of TRA are also the ones in which most new interventional appointments have been undertaken. Finally, the SHA in which the greatest growth of TRA has been observed are also the SHA were the earliest adopters and pioneers of TRA practice are based, many of whom undertook periods of training in the Netherlands where use of TRA for PCI was pioneered. It is possible that the high rates of TRA adoption in these regions have been driven by these early pioneers through education and active promotion and support of TRA use in their units.

A recent meta-analysis of 42 studies in over ½ a million patients has reported that peri-procedural major bleeding complications in the PCI setting are independently associated with a 3-fold increase in mortality[13] with recent NCDR registry data suggesting that 1 in 7 of all PCI deaths in the US were related to bleeding complications[26] Access site related bleeding complications account for up to half of bleeding events recorded during PCI[14, 27] with adoption of the TRA associated with reductions in major bleeding complications and mortality in selected UK and North American cohorts[6, 9, 17] The recent MATRIX trial suggests that there is no significant interaction between pharmacology and anti-platelet usage and the mortality benefit associated with TRA[10] Recent work data derived from national registries and randomized controlled trials has suggested that TRA use in primary PCI is associated with a similar decreased mortality risk as observed in the switch from thrombolysis to primary PCI for revascularization[5, 9, 28] Previous studies have suggested that patients at highest risk of bleeding complications gain the greatest benefit from adoption of the TRA approach, but are least likely to receive it[7] Indeed our recent work suggests a mortality benefit associated with TRA use across both elective as well as ACS indications for PCI, although the mortality benefit associated with TRA use in elective cases was modest.[6] Whilst reductions in major bleeding may contribute to the mortality reductions associated with TRA, other studies have suggested that the reduction in mortality associated with TRA adoption can not be explained by the reduction in major bleeding alone.[16]

Our analysis has estimated that over the period of eight years studied, this national change in access site practice has contributed to around 450 'saved' lives with the greatest number of lives 'saved' in the South West (79 lives), West Midlands (68 Lives) and North East (65 lives). We have also shown that once differences in baseline covariates were adjusted for, the magnitude of benefit of TRA was similar across different SHAs studied, and that on average TRA is associated with a 32% reduction in the risk of mortality (OR=0·70; 95% CI=0·66-0·74) which is similar in magnitude to recent RCTs (albeit reporting outcomes in the ACS setting) including MATRIX (RR 0·72, 95% CI 0·53-0·99; p=0·045) [10], RIFLE-STEACS (43% reduction in CV mortality) [28], STEMI-RADIAL (26% reduction)[29] and RIVAL (STEMI group 0·60 OR 0·38–0·94, P=0.026) [30]. The significant heterogeneity in TRA adoption across the UK, even after adjusting for differences in clinical and procedural characteristics, has resulted in lost opportunities in optimizing PCI safety, where we have conservatively estimated that as many as 264 additional lives may have been 'lost' due to inequalities in TRA adoption.

Our analysis has suggested that even after adjustment for clinical presentation, year of procedure and strategic health authority, patients at higher risk of bleeding complications such as the elderly and females and patients presenting with hemodynamic instability are less likely to receive TRA. This is in agreement to observations recorded from North American datasets,[15, 31] despite the greatest potential benefit in limiting bleeding complications in these patients, supported by recent data derived from a radial default centre in the UK[32] Significant challenges remain in ensuring more widespread adoption of TRA in PCI particularly in those patients at highest risk of bleeding complications who derive greatest benefit. Finally, there will be a proportion of patients, by means of their clinical presentation with significant haemodynamic compromise or through anatomic reasons such as brachiocephalic disease, radial loops or hemodialysis access where a TRA procedure cannot be completed. In such patients, optimal femoral access site practice, such as micropuncture techniques using fluoroscopic or ultrasound guidance for femoral access should be considered.

Our analysis has a number of limitations. First and foremost, this is an observational study and the risk of confounding is real. TFA use is often the preferred access site choice for patients who are hemodynamically unstable and more complex (and consequently at higher risk of mortality)[20] To minimize the confounding risk, we used advanced multiple regression models in which we controlled for important covariates and adverse procedural and clinical characteristics; propensity score matching sensitivity analyses verified the findings from the main analyses. However, we may still be over-estimating the effectiveness of TRA. Second, missing data is a common problem for observational databases and the BCIS database is no exception. We used multiple imputation approaches, which offer excellent protection against missing completely at random (MCAR) and missing at random (MCAR) mechanisms for the data[33, 34] and managed to include 96·7% of eligible patients in the analyses. However, information for some covariates might be missing not at random (MNAR) and thus introducing bias into our estimates, although multiple imputation can still offer some protection in this case. Third, we could not control the regression models for patient residence area deprivation, since the information was completely missing for Wales. Nevertheless we expect the additional predictive power of deprivation to have been small, considering the large number of patient characteristics that were included in the models. Fourth, the BCIS dataset does not contain information on crossover between access sites due to failure for cases in which multiple access sites were used, although such cases were excluded from the analysis when the access site utilised was not clear. Most multiple access site cases are likely to represent cases in which radial was attempted and then the case was converted to femoral, however, up to 10-30% can be procedures that were initially started through a femoral approach and switched to radial[10, 28, 29]. In addition, these cases are likely to be more complicated and if classed as femoral, since they are the majority, the analyses would tend to overestimate the relative benefit of radial. Nevertheless, in a sensitivity analysis where we classed all multiple access procedures where femoral was attempted as femoral, the effect was almost identical with OR=0·69 (95%CI=0·65-0·73). Finally, as with all such observational analyses, the association of TRA choice in PCI and decreased mortality cannot infer causality, although the mortality reductions that we report are in line to those reported in contemporary RCTs.

In conclusion, our analyses have shown that TRA has grown to be the dominant access site for PCI procedures in England and Wales over a period of eight years although the adoption of TRA has not been uniform, with a wide variation in different parts of the country. Although patients who have the highest risk of bleeding complications (elderly, women) are least likely to have PCI undertaken through TRA, there has been a change in national access site with TRA utilization in increasingly more complex patients, such as those with ACS, the elderly and those with cardiogenic shock or those requiring circulatory or inotropic support. TRA was independently associated to mortality reductions and over eight years, we estimated that this change in national access site practice has contributed to over 450 lives saved, whilst inequalities in changes in access site practice have contributed to over 260 lives 'lost'. Significant challenges remain in a more uniform adoption of TRA nationally even in the UK where TRA represent the commonly used access site, particularly in those patients at highest risk of bleeding complications who have most to benefit. More uniform access to training opportunities nationally may be needed, to maximize the clinical benefit for patients undergoing PCI.

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References

1. Campeau L. Percutaneous radial artery approach for coronary angiography. *Catheterization and cardiovascular diagnosis*. 1989;16:3-7.

2. Kiemeneij F and Laarman GJ. Percutaneous transradial artery approach for coronary stent implantation. *Catheterization and cardiovascular diagnosis*. 1993;30:173-8.

3. Bertrand OF, Rao SV, Pancholy S, Jolly SS, Rodes-Cabau J, Larose E, Costerousse O, Hamon M and Mann T. Transradial approach for coronary angiography and interventions: results of the first international transradial practice survey. *JACC Cardiovascular interventions*. 2010;3:1022-31.

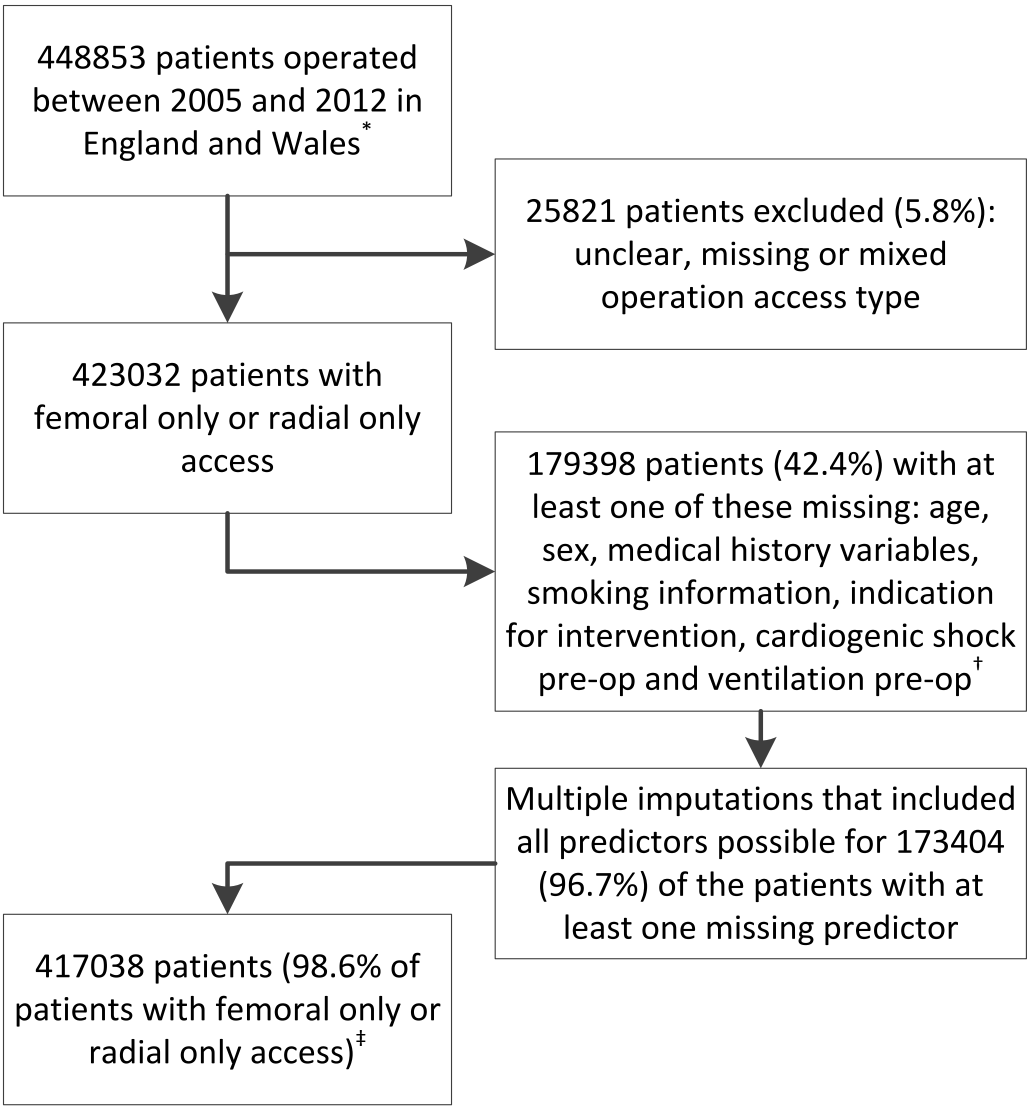
4. Bertrand OF, Belisle P, Joyal D, Costerousse O, Rao SV, Jolly SS, Meerkin D and Joseph L. Comparison of transradial and femoral approaches for percutaneous coronary

interventions: a systematic review and hierarchical Bayesian meta-analysis. *American heart journal*. 2012;163:632-48.
5. Khan MA, Ahmed F, Neyses L and Mamas MA. Atrial fibrillation in heart failure: The sword of Damocles revisited. *World J Cardiol*. 2013;5:215-27.
6. Ratib K, Mamas MA, Anderson SG, Bhatia G, Routledge H, De Belder M, Ludman PF, Fraser D, Nolan J, British Cardiovascular Intervention S and the National Institute for Cardiovascular Outcomes R. Access site practice and procedural outcomes in relation to clinical presentation in 439,947 patients undergoing percutaneous coronary intervention in the United kingdom. *JACC Cardiovascular interventions*. 2015;8:20-9.
7. 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 S and the National Institute for Cardiovascular Outcomes R. Baseline bleeding risk and arterial access site practice in relation to procedural outcomes after percutaneous coronary intervention. *Journal of the American College of Cardiology*. 2014;64:1554-64.
8. Chase AJ, Fretz EB, Warburton WP, Klinke WP, Carere RG, Pi D, Berry B and Hilton JD. Association of the arterial access site at angioplasty with transfusion and mortality: the M.O.R.T.A.L study (Mortality benefit Of Reduced Transfusion after percutaneous coronary intervention via the Arm or Leg). *Heart*. 2008;94:1019-25.
9. Baklanov DV, Kaltenbach LA, Marso SP, Subherwal SS, Feldman DN, Garratt KN, Curtis JP, Messenger JC and Rao SV. The prevalence and outcomes of transradial percutaneous coronary intervention for ST-segment elevation myocardial infarction: analysis from the National Cardiovascular Data Registry (2007 to 2011). *Journal of the American College of Cardiology*. 2013;61:420-6.
10. 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 and Investigators M. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet*. 2015.
11. Brasselet C, Tassan S, Nazeyrollas P, Hamon M and Metz D. Randomised comparison of femoral versus radial approach for percutaneous coronary intervention using abciximab in acute myocardial infarction: results of the FARMI trial. *Heart*. 2007;93:1556-61.
12. Nathan S and Rao SV. Radial versus femoral access for percutaneous coronary intervention: implications for vascular complications and bleeding. *Current cardiology reports*. 2012;14:502-9.
13. Kwok CS, Rao SV, Myint PK, Keavney B, Nolan J, Ludman PF, de Belder MA, Loke YK and Mamas MA. Major bleeding after percutaneous coronary intervention and risk of subsequent mortality: a systematic review and meta-analysis. *Open heart*. 2014;1:e000021.
14. Kwok CS, Khan MA, Rao SV, Kinnaird T, Sperrin M, Buchan I, de Belder MA, Ludman PF, Nolan J, Loke YK and 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. *Circulation Cardiovascular interventions*. 2015;8.
15. Rao SV, Ou FS, Wang TY, Roe MT, Brindis R, Rumsfeld JS and Peterson ED. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. *JACC Cardiovascular interventions*. 2008;1:379-86.

16. Mehta SR, Jolly SS, Cairns J, Niemela K, Rao SV, Cheema AN, Steg PG, Cantor WJ, Dzavik V, Budaj A, Rokoss M, Valentin V, Gao P, Yusuf S and Investigators R. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *Journal of the American College of Cardiology*. 2012;60:2490-9.
17. Anderson SG, Ratib K, Myint PK, Keavney B, Kwok CS, Zaman A, Ludman PF, de Belder MA, Nolan J, Mamas MA, on behalf of the British Cardiovascular Intervention S and the National Institute for Cardiovascular Outcomes R. 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 : official journal of the Society for Cardiac Angiography & Interventions*. 2015.
18. Feldman DN, Swaminathan RV, Kaltenbach LA, Baklanov DV, Kim LK, Wong SC, Minutello RM, Messenger JC, Moussa I, Garratt KN, Piana RN, Hillegass WB, Cohen MG, Gilchrist IC and Rao SV. Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: an updated report from the national cardiovascular data registry (2007-2012). *Circulation*. 2013;127:2295-306.
19. Bradley SM, Rao SV, Curtis JP, Parzynski CS, Messenger JC, Daugherty SL, Rumsfeld JS and Gurm HS. Change in hospital-level use of transradial percutaneous coronary intervention and periprocedural outcomes: insights from the national cardiovascular data registry. *Circulation Cardiovascular quality and outcomes*. 2014;7:550-9.
20. Mamas MA, Anderson SG, Ratib K, Routledge H, Neyses L, Fraser DG, Buchan I, de Belder MA, Ludman P, Nolan J, British Cardiovascular Intervention S and National Institute for Cardiovascular Outcomes R. Arterial access site utilization in cardiogenic shock in the United Kingdom: is radial access feasible? *American heart journal*. 2014;167:900-8 e1.
21. Ludman PF and British Cardiovascular Intervention S. British Cardiovascular Intervention Society Registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. *Heart*. 2011;97:1293-7.
22. Mamas MA, Anderson SG, O'Kane PD, Keavney B, Nolan J, Oldroyd KG, Perera D, Redwood S, Zaman A, Ludman PF, de Belder MA, British Cardiovascular Intervention S and the National Institute for Cardiovascular Outcomes R. Impact of left ventricular function in relation to procedural outcomes following percutaneous coronary intervention: insights from the British Cardiovascular Intervention Society. *European heart journal*. 2014;35:3004-12.
23. Hamon M, Pristipino C, Di Mario C, Nolan J, Ludwig J, Tubaro M, Sabate M, Mauri-Ferre J, Huber K, Niemela K, Haude M, Wijns W, Dudek D, Fajadet J, Kiemeneij F, European Association of Percutaneous Cardiovascular I, Working Group on Acute Cardiac Care of the European Society of C and Working Group on Thrombosis on the European Society of C. Consensus document on the radial approach in percutaneous cardiovascular interventions: position paper by the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care** and Thrombosis of the European Society of Cardiology. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2013;8:1242-51.
24. Helfrich CD, Tsai TT, Rao SV, Lemon JM, Eugenio EC, Vidovich MI, Shroff AR, Speiser BS and Bryson CL. Perceptions of advantages and barriers to radial-access percutaneous coronary intervention (PCI) in VA cardiac catheterization laboratories. *Cardiovascular revascularization medicine : including molecular interventions*. 2014.
25. Kinnaird TD, Ossei-Gerning N, Mitra R and Anderson RA. Interaction between access choice and pharmacotherapy for coronary intervention: the results of a UK survey. *Open heart*. 2014;1:e000094.
26. Chhatriwalla AK, Amin AP, Kennedy KF, House JA, Cohen DJ, Rao SV, Messenger JC, Marso SP and National Cardiovascular Data R. Association between bleeding events and

in-hospital mortality after percutaneous coronary intervention. *JAMA : the journal of the American Medical Association*. 2013;309:1022-9.
27. Verheugt FW, Steinhubl SR, Hamon M, Darius H, Steg PG, Valgimigli M, Marso SP, Rao SV, Gershlick AH, Lincoff AM, Mehran R and Stone GW. Incidence, prognostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary intervention. *JACC Cardiovascular interventions*. 2011;4:191-7.
28. 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 and 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. *Journal of the American College of Cardiology*. 2012;60:2481-9.
29. Bernat I, Horak D, Stasek J, Mates M, Pesek J, Ostadal P, Hrabos V, Dusek J, Koza J, Sembera Z, Brtko M, Aschermann O, Smid M, Polansky P, Al Mawiri A, Vojacek J, Bis J, Costerousse O, Bertrand OF and Rokyta R. ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: the STEMI-RADIAL trial. *Journal of the American College of Cardiology*. 2014;63:964-72.
30. Jolly SS, Yusuf S, Cairns J, Niemela K, Xavier D, Widimsky P, Budaj A, Niemela M, Valentin V, Lewis BS, Avezum A, Steg PG, Rao SV, Gao P, Afzal R, Joyner CD, Chrolavicius S, Mehta SR and group Rt. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. 2011;377:1409-20.
31. Daugherty SL, Thompson LE, Kim S, Rao SV, Subherwal S, Tsai TT, Messenger JC and Masoudi FA. Patterns of use and comparative effectiveness of bleeding avoidance strategies in men and women following percutaneous coronary interventions: an observational study from the National Cardiovascular Data Registry. *Journal of the American College of Cardiology*. 2013;61:2070-8.
32. Rafie IM, Uddin MM, Ossei-Gerning N, Anderson RA and Kinnaird TD. Patients undergoing PCI from the femoral route by default radial operators are at high risk of vascular access-site complications. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2014;9:1189-94.
33. Rubin DB. Multiple imputation after 18+ years. *Journal of the American Statistical Association*. 1996;91:473-489.
34. Groenwold RH, Donders AR, Roes KC, Harrell FE, Jr. and Moons KG. Dealing with missing outcome data in randomized trials and observational studies. *American journal of epidemiology*. 2012;175:210-7.

Figure 1: Flowchart of patient inclusion/exclusion



* Population used in tables and graphs
† Medical history variables included: diabetes, hypercholesterolaemia, hypertension, peripheral vascular disease, cerebrovascular event, renal history, previous MI, previous PCI, previous CABG and family history of CAD.
‡ Subsample used in logistic regression analyses

Figure 2a: Change in radial access site adoption in Primary Care Trusts in England and Local Health Boards in Wales, 2005-2008

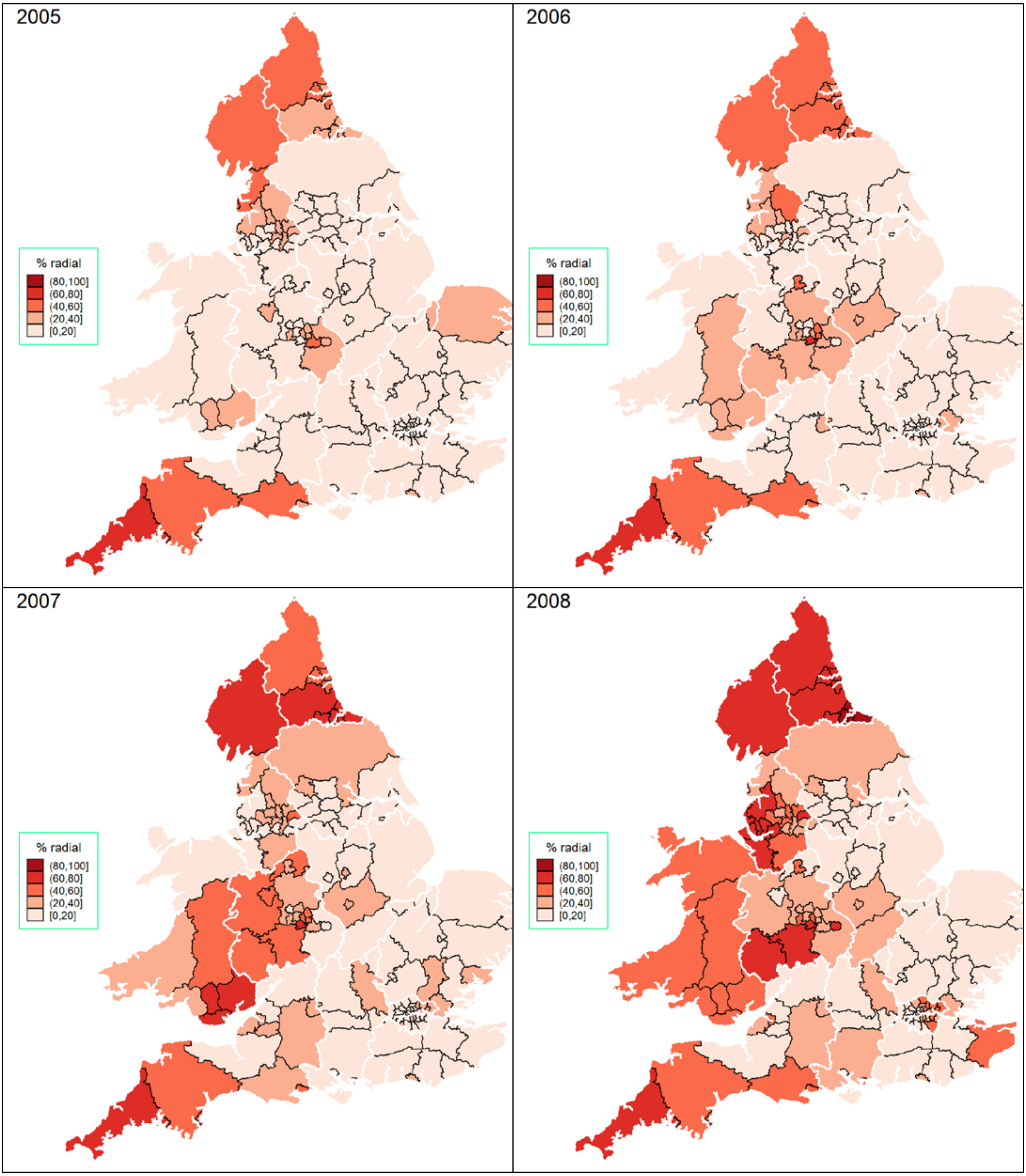


Figure 2b: Change in radial access site adoption in Primary Care Trusts in England and Local Health Boards in Wales, 2009-2012

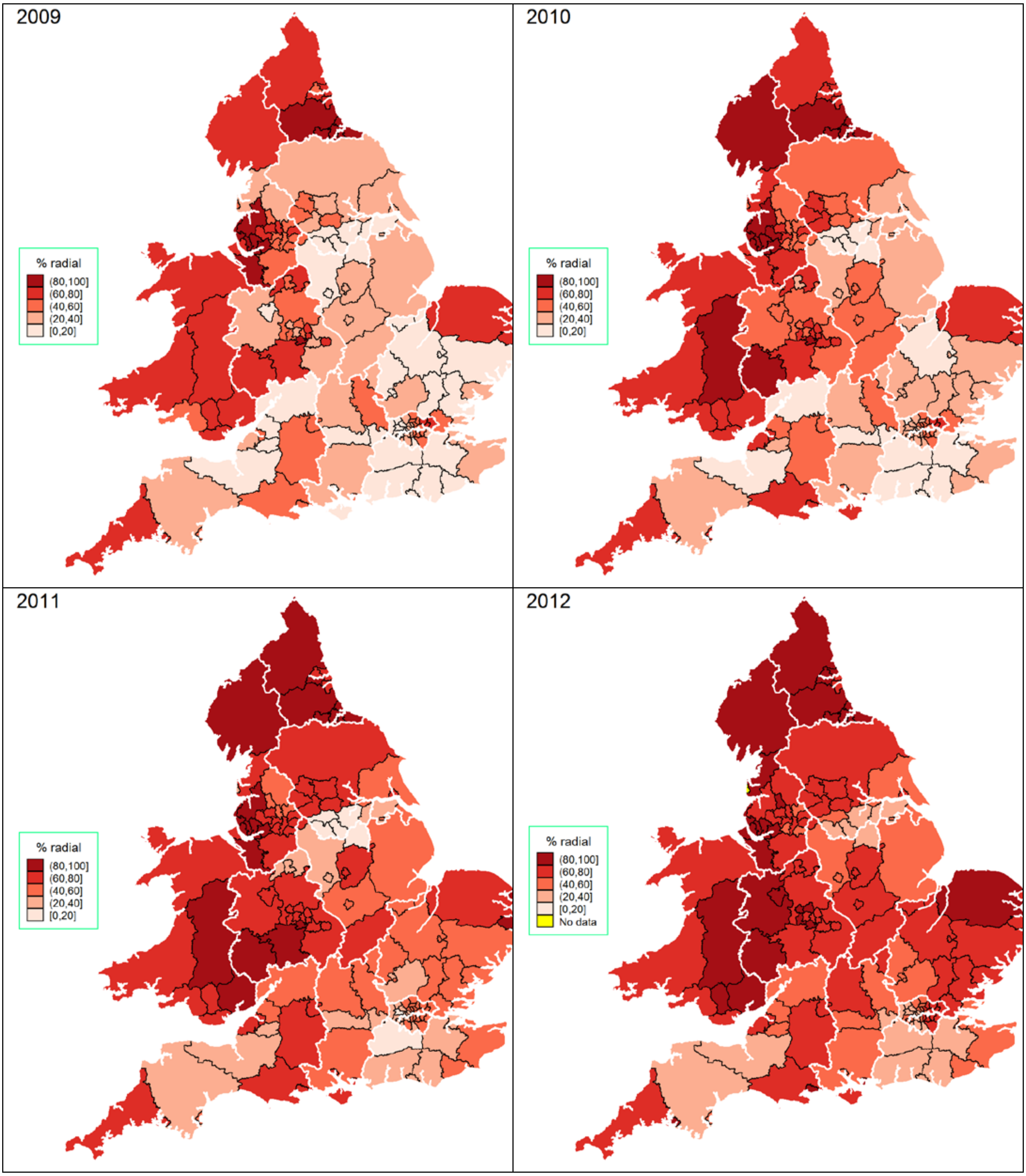
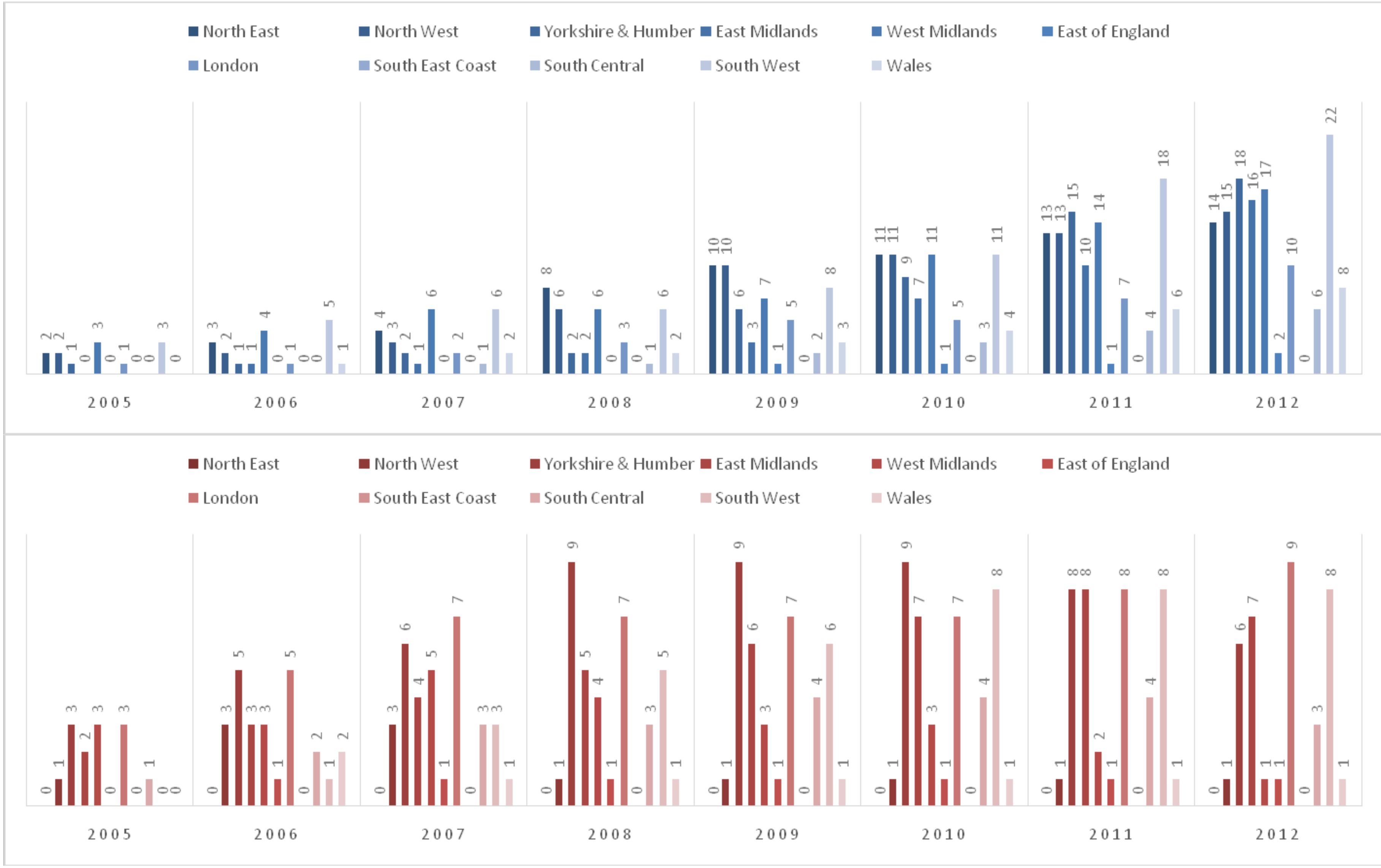


Figure 3: Mean estimates of 30-day lives 'saved' (top) and 'lost' (bottom), by Strategic Health Authority over time*†



* 'Saved', when compared to a hypothetical scenario where no radial access operations are performed in any areas

† 'Lost', when compared to a hypothetical scenario where radial access rates across all strata are set to the highest percentage observed within each year