■ HIP

Fatal pulmonary embolism following elective total hip arthroplasty

A 12-YEAR STUDY

E. Bayley,
S. Brown,
N. S. Bhamber,
P. W. Howard

From The Royal Derby Hospital, Derby, United Kingdom

Aims

The place of thromboprophylaxis in arthroplasty surgery remains controversial, with a challenging requirement to balance prevention of potentially fatal venous thromboembolism with minimising wound-related complications leading to deep infection. We compared the incidence of fatal pulmonary embolism in patients undergoing elective primary total hip arthroplasty (THA) between those receiving aspirin, warfarin and low molecular weight heparin (LMWH) for the chemical component of a multi-modal thromboprophylaxis regime.

Patients and Methods

A prospective audit database was used to identify patients who had died within 42 and 90 days of surgery respectively between April 2000 and December 2012. A case note review was performed to ascertain the causes of death.

Results

During this period 7983 THAs were performed. The rate of mortality was 0.43% and 0.58% at 42 and 90 days respectively. The groups comprised 1571 patients (19.7%) on warfarin, 1838 (23.0%) on LMWH and 4574 (57.3%) on aspirin. The 90-day mortality for these three groups was 0.38%, 1.09% and 0.43% respectively. The higher mortality rate for LMWH was significant ($p < 0.05$).

There were six fatal pulmonary emboli (PEs) (0.08%). A total of three occurred within 42 days, all in the LMWH group. A total of three occurred between 42 and 90 days; one on warfarin, two on LMWH. The leading causes of death in all three groups were lower respiratory tract infections and myocardial infarction.

Conclusion

We confirmed that fatal PE following elective THA with a multi-modal prophylaxis regime is rare. We further found that LMWH conferred no benefit over aspirin in this context, and is associated with a higher all-cause rate of mortality.

Take home message: This study proposes that aspirin may be an appropriate thromboprophylaxis agent when used as part of a multi-modal regimen, suggesting current guidelines should be reviewed.

Cite this article: ***Bone Joint J*** **2016;98-B:585–8.**

■ E. Bayley, BM BS, MRCSEd, FRCS (Tr&Orth), ST7 Trauma and Orthopaedics, Department of Trauma and Orthopaedics The Royal Derby Hospital, Uttoxeter Road, Derby, DE22 3NE, UK.

■ S. Brown, MBChB, Speciality Trainee in Histopathology Royal Hallamshire Hospital, Sheffield S10 2JF, UK.

■ N. S. Bhamber, MBBS, Bsc, MRCS, ST5 Trauma and Orthopaedics St George's University Hospital NHS FoundationTrust, Blackshaw Road, Tooting London SW17 0QT, UK.

■ P. W. Howard, FRCS, Consultant Trauma and Orthopaedics, Department of Trauma and Orthopaedics Royal Derby Hospital, Derby DE22 3NE, UK.

Correspondence should be sent to Mr E. J. Bayley; e-mail: edbayley12@gmail.com

doi:10.1302/0301-620X.98B5.34996 $2.00

Bone Joint J 2016;98-B:585–8.
Received 22 August 2014; Accepted after revision 11 November 2015

Post-operative thromboprophylaxis following lower limb arthroplasty remains controversial and despite recent National Institute for Health and Clinial Excellence (NICE)[1] guidelines, practice varies widely. Parker-Williams and Vickers reported in 1991,[2] a rate of pulmonary embolus (PE) following total hip arthroplasty (THA) of 5%, half of which were fatal. They advocated routine chemical thromboprophylaxis in patients undergoing this procedure.

The debate is centred less around the absolute requirement for prophylaxis and more around what form offers the best balance of risk and benefit.[3,4] Current NICE guidance is that chemical thromboprophylaxis should involve a low molecular weight heparin (LMWH) in the absence of contra-indications, and does not support antiplatelets or warfarin as many surgeons have used in the past.[1] Guidance in the United States however, has recently been updated to re-introduce aspirin as part of guidelines supporting routine thromboprophylaxis.[5-7]

Aspirin has been shown to lower the risk of venous thromboembolism (VTE) in in-patients,[8-10] and has been used for chemoprophylaxis

Table I. Table of all causes of death

Cause of death	Number at ≤ 42 days	Number at > 42 days
Pulmonary embolus	3	3
LRTI	9	6
IHD	5	1
Myocardial infarction	6	
Valvular heart disease	2	
Ischaemic bowel	2	1
Cerebrovascular disease	3	
Fat embolism	1	
Biliary sepsis	1	
Obstruction pneumonitis*		1
GI bleed	1	
Septicaemia†	1	

* 1b stated disseminated lung cancer
† 1b stated lower respiratory tract infection (LRTI)
IHD, ischaemic heart disease; GI, gastrointestinal bleed

following THA[11] but is not recommended for this indication in the United Kingdom. It has yet to be evaluated in the context of new agents such as factor Xa inhibitors which have thus far been compared only with LMWH or warfarin[12-15] and meta-analysis has not shown a benefit of these agents over antiplatelet medication.[16] The absence of like for like comparison presents a strong case for further research in this area, especially in the context of evidence-based practice, commissioning and payment tariffs.

We have therefore undertaken an observational, retrospective study of prospectively gathered data from our practice in a district general hospital. The hypothesis was that the use of aspirin as the chemoprophylactic component of a multi-modal regimen does not confer a significantly increased risk of fatal PE following elective primary THA.

Patients and Methods

Our local database was used to identify patients undergoing elective THA between April 2000 and December 2012. Outcome measures were death at 42 and 90 days post-operatively. A total of 7983 THAs were performed during that time.

The thromboprophylaxis regimen employed during this period was one of regional anaesthesia where possible, calf compression per-operatively, foot pumps until mobile, anti-embolism stockings for six weeks, mobilisation within 24 hours. Chemical thromboprophylaxis involved either aspirin 75 mg once daily, warfarin with a dose to maintain an international normalised ratio (INR) of 1.5 or LMWH 40 mg once daily as preferred by the surgeon. All were continued for six weeks. The surgeons all adhered to one of these protocols for their patients not assessed to be at high risk of VTE, dependent on which was their preference. Those patients assessed as high risk received warfarin.

Non-steroidal anti-inflammatory drugs were not stopped routinely pre-operatively. Tranexamic acid was not in use in our centre for arthroplasty during this time. Aspirin would only be given in conjunction with LMWH if cardiac risk factors were deemed high enough to necessitate both (and the risk of bleeding was low), but was not given to patients taking warfarin.

Dates of death were taken from our database and clinical notes were reviewed to ascertain both the cause of death and the thromboprophylaxis regimen which was used. Where autopsy was performed, this information was recorded, otherwise the cause of death was taken from the death certificate.

Statistical analysis. Wilson's method was used to calculate 95% confidence intervals (CI) to avoid a lower limit of less than zero.[17] Statistical significance was set at $p < 0.05$.[18]

Results

Chemoprophylaxis was provided by warfarin in 1571 (19.7%) patients, LMWH in 1838 (23.0%) and aspirin in 4574 (57.3%). The mean age was 66.1 years in the warfarin group (95% CI 65.3 to 66.9), 69.3 years (68.7 to 70.0) in the LMWH group and 68.7 years (68.2 to 69.2) in the aspirin group. There was no significant difference in mean ages between the aspirin or LMWH groups ($p > 0.05$).

The overall mortality rates at 42 and 90 days were 0.43% and 0.58%, respectively. The mortality rates fell during the study period from 0.48% and 0.86% (42 and 90 days, respectively) in 2000/2001, to 0.21% and 0.27% in 2011/2012. The 90-day mortality for the three groups was six patients 0.38% (95% CI 0.18 to 0.83), 20 patients 1.09% (95% CI 0.71 to 1.67) and 20 patients 0.43% (95% CI 0.28 to 0.67), respectively. The difference between LMWH and aspirin reaches statistical significance ($p < 0.05$, 95% CIs do not overlap).[18]

A total of six (0.08%) deaths were attributable to PE, three occurring within 42 days of surgery and three within 90 days. All three of the early PEs were in the LMWH group. Of those occurring later, two were in the LMWH group and one the warfarin group. None of the six patients had a history of VTE. No such events occurred in the aspirin group.

The leading causes of death were myocardial infarction and lower respiratory tract infection. One patient in the LMWH group died from haemorrhage from a gastric ulcer (Table I).

Discussion

We have confirmed fatal PE is rare after elective primary THA. No such events occurred in those treated with aspirin, supporting our current practice. While it may be argued that patients stratified as high risk for VTE would have received warfarin, we nonetheless saw a number of deaths in those with no prior history of VTE. The overall mortality rate of 0.43% at 42 days compares favourably with the literature,[12,16,19-23] and reflects trends seen in the National Joint Registry for England, Wales and Northern Ireland (NJR).[24,25]

This is the largest single-centre study of aspirin as the chemical component of a multi-modal thromboprophylaxis regimen following elective THA. Although aspirin featured in previous studies, low numbers and a mixture of general

and regional anaesthetic techniques have not provided clear evidence on which to base practice.[19,23,26-29]

As early as 1996 concerns were being raised over thromboprophylaxis in general for THA. Murray, Britton and Bulstrode[30] stated that there was 'not enough evidence to conclude that any form of pharmacological thromboprophylaxis decreases the death rate after THA'. This was based on a rate of fatal PE of 0.2% to 0.3%, almost five times higher than that in this study. Recent meta-analysis of NJR data has shown no significant decrease in the rate of mortality when LMWH is used[29,31] and a concomitant increase in the incidence of VTE. This trend is mirrored with the newer generation of anticoagulants.[16,32]

Many studies have raised concern with regards to increased complication rates when using LMWH, or more potent anticoagulants, for thromboprophylaxis.[12-15,28,29,31,33-36] These include haemorrhagic wound complications of up to 5% in the Record and Advance trials. This is one of the greatest concerns for most surgeons because of its association with delayed healing, and superficial and deep infections.[37,38] It is also often the main reason why surgeons prefer to use aspirin over other anticoagulants.

Although these trials reported improved rates of VTE,[12-15] this has not been borne out by independent analysis.[39,40] Both reported increased wound complications, with no improvement in VTE rates. Anecdotally, this is also a common reason for surgeons preferring aspirin over other anticoagulants and in addition to the benefit to patients, there are concerns about the increasing costs to the NHS of treating an increasing number of iatrogenic complications.[31,39]

There are some limitations to our study. We have not taken other significant risk factors for VTE into account, although the patients who died were known to be low risk pre-operatively based on no previous episodes in their past medical history. We have not analysed the rates of wound complications, returns to theatre or the incidence of all symptomatic VTE. These are future directions for our ongoing analysis.

Our study echoes the meta-analyses of Sharrock et al[32] and Poultsides et al[16] in finding a lower rate of mortality with aspirin than with LMWH. With nearly 8000 THAs over a 12-year period, we conclude that rates of mortality are low, and fatal PE is rare following elective THA when aspirin has been used as the chemical component of a multimodal thromboprophylaxis regimen. LMWH confers no benefit in this context, and is associated with a higher all-cause rate of mortality.

Author contributions:
E. Bayley: Data Collection, Data analysis, Writing the paper.
S. Brown: Study design, Data collection, Data analysis.
N. S. Bhamber: Data collection, Data analysis, Writing the paper.
P. W. Howard: Study design, Data analysis, Writing the paper, Performed some of the surgeries.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

This article was primary edited by P. Page and first proof edited by J. Scott.

References

1. **No authors listed.** National Institute for Health and Clinical Excellence. Venous thromboembolism: reducing the risk (clinical guideline 92). http://www.nice.org.uk/nicemedia/live/12695/47195/47195.pdf (date last accessed 02 February 2016).
2. **Parker-Williams J, Vickers R.** Major orthopaedic surgery on the leg and thromboembolism. *BMJ* 1991;303:531–532.
3. **Barrack RL.** Thromboprophylaxis for patients undergoing joint replacement. *Bone Joint J* 2014;96-B:3–4.
4. **Jameson SS, Baker PN, Deehan DJ, Port A, Reed MR.** Evidence-base for aspirin as venous thromboembolic prophylaxis following joint replacement. *Bone Joint Res* 2014;3:146–149.
5. **Falck-Ytter Y, Francis C, Johanson N, et al.** Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th edition: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141:e278S – e325S.
6. **Jacobs JJ, Mont MA, Bozic KJ, et al.** American Academy of Orthopaedic Surgeons clinical practice guideline on: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Bone Joint Surg Am* 2012;94:746–747.
7. **McKee J.** SCIP VTE Measures Changing in 2014: New measures go into effect on Jan. 1, 2014. AAOS Now (online) 2013;7: http://www.aaos.org/Default.aspx?ssopc=1 (date last accessed 02 February 2016).
8. **Karthikeyan G, Eikelboom JW, Turpie AGG, Hirsh J.** Does acetyl salicylic acid (ASA) have a role in the prevention of venous thromboembolism? *Br J Haematol* 2009;146:142–149.
9. **No authors listed.** Collaborative overview of randomised trials of antiplatelet therapy - III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994;308:235–246.
10. **No authors listed.** Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;355:1295–1302.
11. **Sarmiento A, Goswami AD, Goswami ADK.** Thromboembolic prophylaxis with use of aspirin, exercise, and graded elastic stockings or intermittent compression devices in patients managed with total hip arthroplasty. *J Bone Joint Surg Am* 1999;81:339–346.
12. **Eriksson BI, Kakkar AK, Turpie AGG, et al.** Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *J Bone Joint Surg Br* 2009;91:636–644.
13. **Eriksson BI, Borris LC, Friedman RJ, et al.** Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765–2775.
14. **Raskob GE, Gallus AS, Pineo GF, et al.** Apixaban versus enoxaparin for thromboprophylaxis after hip or knee replacement: pooled analysis of major venous thromboembolism and bleeding in 8464 patients from the ADVANCE-2 and ADVANCE-3 trials. *J Bone Joint Surg Br* 2012;94:257–264.
15. **Lassen MR, Gallus A, Raskob GE, et al.** Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010;363:2487–2498.
16. **Poultsides LA, Gonzalez Della Valle A, Memtsoudis SG, et al.** Meta-analysis of cause of death following total joint replacement using different thromboprophylaxis regimens. *J Bone Joint Surg Br* 2012;94:113–121.
17. **No authors listed.** EpiTools epidemiological calculators. http://epitools.ausvet.com.au/content.php?page=CIProportion (date last accessed 21 January 2016).
18. **Cusick LA, Beverland DE.** The incidence of fatal pulmonary embolism after primary hip and knee replacement in a consecutive series of 4253 patients. *J Bone Joint Surg [Br]* 2009;91-B:645–648.
19. **Neyman J.** Outline of a theory of statistical estimation based on the classical theory of probability. *Philosophical Transactions of the Royal Society A* 1937;236:333–380.
20. **Gillespie W, Murray D, Gregg PJ, Warwick D.** Risks and benefits of prophylaxis against venous thromboembolism in orthopaedic surgery. *J Bone Joint Surg Br* 2000;82:475–479.
21. **Coventry MB, Beckenbaugh RD, Nolan DR, Ilstrup DM.** 2,012 total hip arthroplasties. A study of postoperative course and early complications. *J Bone Joint Surg Am* 1974;56:273–284.
22. **Johnson R, Green JR, Charnley J.** Pulmonary embolism and its prophylaxis following the Charnley total hip replacement. *Clin Orthop Relat Res* 1977;123–132.
23. **Khatod M, Inacio MCS, Bini SA, Paxton EW.** Prophylaxis against pulmonary embolism in patients undergoing total hip arthroplasty. *J Bone Joint Surg Am.* 2011;93:1767–1772.
24. **Hunt LP, Ben-Shlomo Y, Clark EM, et al.** 90-day mortality after 409,096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. *Lancet* 2013;382:1097–1104.
25. **No authors listed** National Joint Registry. http://www.njrcentre.org.uk/njrcentre/default.aspx (date last accessed 07 March 2016).

26. Dorr LD, Gendelman V, Maheshwari AV, et al. Multimodal thromboprophylaxis for total hip and knee arthroplasty based on risk assessment. *J Bone Joint Surg [Am]* 2007;89-A:2648–2657.

27. Parry M, Wylde V, Blom AW. Ninety-day mortality after elective total hip replacement: 1549 patients using aspirin as a thromboprophylactic agent. *J Bone Joint Surg [Br]* 2008;90-B:306–307.

28. Imperiale TF, Speroff T. A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. *JAMA* 1994;271:1780–1785.

29. Jameson SS, Charman SC, Gregg PJ, Reed MR, van der Meulen JH. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after hip replacement: a non-randomised comparison from information in the National Joint Registry. *J Bone Joint Surg [Br]* 2011;93-B:1465–1470.

30. Murray DW, Britton AR, Bulstrode CJK. Thromboprophylaxis and death after total hip replacement. *J Bone Joint Surg [Br]* 1996;78-B:863–870.

31. Jameson SS, Bottle A, Malviya A, Muller SD, Reed MR. The impact of national guidelines for the prophylaxis of venous thromboembolism on the complications of arthroplasty of the lower limb. *J Bone Joint Surg [Br]* 2010;92-B:123–129.

32. Sharrock NE, Gonzalez Della Valle A, Go G, Lyman S, Salvati EA. Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. *Clin Orthop Relat Res* 2008;466:714–721.

33. Samama C- M, Ravaud P, Parent F, et al. Epidemiology of venous thromboembolism after lower limb arthroplasty: the FOTO study. *J Thromb Haemost* 2007;5:2360–2367.

34. Shaieb MD, Watson BN, Atkinson RE. Bleeding complications with enoxaparin for deep venous thrombosis prophylaxis. *J Arthroplasty* 1999;14:432–438.

35. Bloch BV, Patel V, Best AJ. Thromboprophylaxis with dabigatran leads to an increased incidence of wound leakage and an increased length of stay after total joint replacement. *Bone Joint J* 2014;96-B:122–126.

36. Novicoff WM, Brown TE, Cui Q, et al. Mandated venous thromboembolism prophylaxis: possible adverse outcomes. *J Arthroplasty* 2008;23:15–19.

37. Saleh K, Olson M, Resig S, et al. Predictors of wound infection in hip and knee joint replacement: results from a 20 year surveillance program. *J Orthop Res* 2002;20:506–515.

38. Patel VP, Walsh M, Sehgal B, et al. Factors associated with prolonged wound drainage after primary total hip and knee arthroplasty. *J Bone Joint Surg [Am]* 2007;89-A:33–38.

39. Sindali K, Rose B, Soueid H, et al. Elective hip and knee arthroplasty and the effect of rivaroxaban and enoxaparin thromboprophylaxis on wound healing. *Eur J Orthop Surg Traumato.* 2013;23:481–486.

40. Jameson SS, Rymaszewska M, Hui AC, et al. Wound complications following rivaroxaban administration: a multicenter comparison with low-molecular-weight heparins for thromboprophylaxis in lower limb arthroplasty. *J Bone Joint Surg [Am]* 2012;94-A:1554–1558.