The effect of preinjury warfarin use on mortality rates in trauma patients: a European multicentre study

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ABSTRACT

Objective To define the relationship between preinjury warfarin use and mortality in a large European sample of trauma patients.

Methods A multicentred study was conducted using data collated from European (predominately English and Welsh) trauma receiving hospitals. Patient data from the Trauma Audit and Research Network database from 2009 to 2013 were analysed. Univariate and multivariate logistic regression was used to estimate OR for mortality associated with preinjury warfarin use in the whole adult trauma cohort and a matched sample of patients comparable in terms of age, gender, GCS, pre-existing medical conditions and injury severity.

Results A total of 136 617 adult trauma patients (2009–2013) were included, with 499 patients reported to be using warfarin therapy at the time of trauma. Preinjury warfarin use was associated with a significantly higher mortality rate at 30 days postinjury compared with the non-users. Following adjustment of age, injury severity and GCS, preinjury warfarin use was associated with increased mortality in trauma patients (adjusted OR 2.14; 95% CI 1.66 to 2.76; p<0.001). In the matched subset, 22% of warfarinised trauma patients died compared with 16.3% of non-warfarinised trauma patients with comparable age, injury severity and GCS (adjusted OR 1.94; 95% CI 1.25 to 3.01; p=0.003).

Conclusions Preinjury warfarin use has been demonstrated to be an independent predictor of mortality in trauma patients. Clinicians managing major trauma patients on warfarin need to be aware of the vulnerability of this group.

Key messages

What is already known on this subject?
Previous studies have given conflicting results as to whether or not warfarin treatment increases the risk of mortality after trauma. None of the previous studies has adjusted sufficiently for all confounders related to patient demographics, injuries and site of hospital care.

What might this study add?
In this retrospective analysis of a large, multicentre trauma database in the UK and Continental Europe, preinjury warfarin use was independently associated with a significantly higher mortality rate at 30 days postinjury compared with the non-users, after matching for age, injury severity, GCS and pre-existing medical conditions.

How might this impact on clinical practice?
Clinicians managing major trauma patients on warfarin need to be aware of the vulnerability of this group.

INTRODUCTION

It has been reported that trauma accounts for approximately 16 000 deaths per year in the UK.[1] It is estimated that major trauma costs the NHS between £0.3 and 0.4 billion a year in immediate treatment.[2] The incidence of trauma continues to increase with at least 20 000 cases of major trauma each year in England resulting in 5400 deaths and many others resulting in permanent disabilities requiring long-term care.[2] Approximately 1% of the UK population are currently using anticoagulant therapy, and it is predicted that this figure will continue to rise as the size of the elderly population increases.[3] It is estimated that >10% of all Americans aged ≥80 years are using warfarin.[4] There is a high reported incidence of trauma in this age group in developed countries with the primary causes being falls from standing and road traffic collisions.[5]

A number of studies have investigated the impact of preinjury warfarin use on mortality rates in trauma patients, but the results of these studies have proved inconsistent.[6–10] Preinjury warfarin was reported to be an independent predictor of mortality in trauma patients in a large retrospective study completed by Dossett et al,[6] and similar results were demonstrated in a number of other studies.[7][8] Conflicting findings, however, were reported in other studies that showed preinjury warfarin use was not associated with increased mortality rates in trauma patients.[9][10] In a study by Pieracci et al,[10] it was highlighted that therapeutic anticoagulation with warfarin, rather than warfarin itself, influenced adverse outcome following traumatic brain injury in elderly patients. Comparison between these studies is limited as a result of differences in study design, the heterogeneity of study populations and small sample sizes.

No large studies have been completed to date combining European and UK data in order to investigate the impact of preinjury warfarin use on mortality rates in trauma patients. As a result of the conflicting evidence regarding the effect of preinjury warfarin use on trauma patients, controversy still exists regarding the optimal management strategies for this patient group. The aim of this study therefore was to define the relationship between preinjury warfarin use and mortality in a large sample of trauma patients using a large European Trauma Registry.

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METHODS

Study design and data source

A retrospective cohort study of hospitals submitting data to the Trauma Audit and Research Network (TARN) registry of patients between 2009 and 2013 was completed. During this study period, TARN received patient data from between 60% and 100% of all NHS England hospitals and about 70% of all trauma receiving hospitals in Wales; however, the subset was representative.[11] Hospitals from Ireland and continental Europe also submitted data to TARN over the period of study (3.4% of final data).

TARN data include patients of all ages, who arrive at hospital alive after sustaining trauma resulting in at least one of the following four consequences: hospitalisation for >72 h, intensive care admission, transfer for specialised care or death prior to discharge. Patients with isolated femoral shaft/supracondylar fractures are included, but all other patients with isolated closed limb injuries/simple spinal strains/undisplaced facial fractures are excluded. Patients aged ≥64 years with an isolated fracture neck of femur or public ramus fracture are also excluded. All TARN trauma patients in England and Wales are assessed using a standardised protocol, and data are collated systematically from the clinical presentation.

The standard TARN core dataset is collected prospectively and includes age, gender, Injury Severity Score (ISS), probability of survival, outcome, outcome date (discharge or death date), arrival date, injury mechanism, length of stay, Abbreviated Injury Score codes, whether the centre is a specialised neurology centre, GCS, preinjury warfarinisation, intubation/ventilation and pre-existing medical conditions (PMCs). The use of warfarin and other anticoagulants is not part of the core dataset, but participating centres are encouraged to input these data if they exist. In some cases, international normalised ratio (INR) and blood products given to the patient were recorded. The data extracted for use in this study included gender, age, GCS, ISS, PMCs, number of days in hospital and clinical outcomes.

Patient selection and definitions

From the TARN registry, we studied all patients aged ≥16 years at time of injury. Exclusion criteria included patients whose outcomes were unknown. In order not to confound the relationship between warfarin, PMCs and outcome, specific PMCs requiring warfarin therapy (cardiomyopathy, deep vein thrombosis, pulmonary embolism, atrial fibrillation, peripheral vascular disease, stroke, transient ischaemic attack, thrombocytosis, valvular heart disease, vasculitis) were not included as an additional PMC.

Statistical analysis

The outcome of interest in this study was 30-day mortality. Patients were separated into two groups for analysis: preinjury warfarin users and non-users. As a result of the skewed distribution, continuous variables were summarised using median and IQRs and compared using the Mann–Whitney test. Categorical variables were summarised using the χ^2 test for comparison between warfarinised and non-warfarinised patients. Due to significant differences between a number of covariables in the two groups, a sample of non-warfarin users was matched for age, gender, PMC, GCS and ISS and the same analysis repeated with this case-matched design. The cases were matched as follows: gender (exact match); PMC status (in same group: no PMC, warfarin-related PMC or non-warfarin-related PMC); ISS (within 2 years above or below); age (within 2 years above or below); and GCS (within 1 year above or below). A subset of the non-warfarin cohort (those matching at least one case in the warfarin cohort on the criteria above) was selected. Cases that did not fall within the parameters of one or more of the criteria were excluded. A scoring system was used to select the best match for each case in the warfarin cohort. This created a matched dataset where warfarinised patients are paired with non-warfarinised patients with the same or very similar characteristics. This analysis was completed in an attempt to control residual confounding. The only other missing values in the dataset were for PMC, and these were categorised as 'not known' so they could still be included in the analysis.

Using the original samples (non-matched), univariate and multivariate logistic regression were used to estimate the unadjusted and adjusted OR and 95% CIs of mortality associated with prewarfarin use. Multivariate analysis included all clinically relevant variables including age, ISS, GCS, warfarin use, PMCs and care in a specialist neurological centre as independent variables with mortality as the dependent variable. In the logistic regression model, missing values for GCS were imputed by chained equations procedure from the statistical software Stata V.12 with the assumption that missingness is at random.[12] For case-matched analysis, where no cases had a missing GCS, conditional logistic regression was used with no imputation being necessary. The conditional logistic regression model used only unmatched confounders and warfarin status as predictors with mortality being the outcome variable.

A p value of 0.05 was considered statistically significant. The Statistical Package for Social Sciences V.19 was used to complete the analysis.

RESULTS

After excluding patients with an unknown outcome, data from 136 617 adult trauma patients from 2009 to 2013 from 180 trauma receiving hospitals from all regions of England, Wales and European hospitals were retrospectively analysed (figure 1). A total of 499 (0.36%) of these patients were using warfarin preinjury. Baseline characteristics of all patients included in the analysis are outlined in table 1. Patients on warfarin regimens had a median age of 80 years compared with a mean age of 58 years in the non-warfarin users. Patients on warfarin had more severe
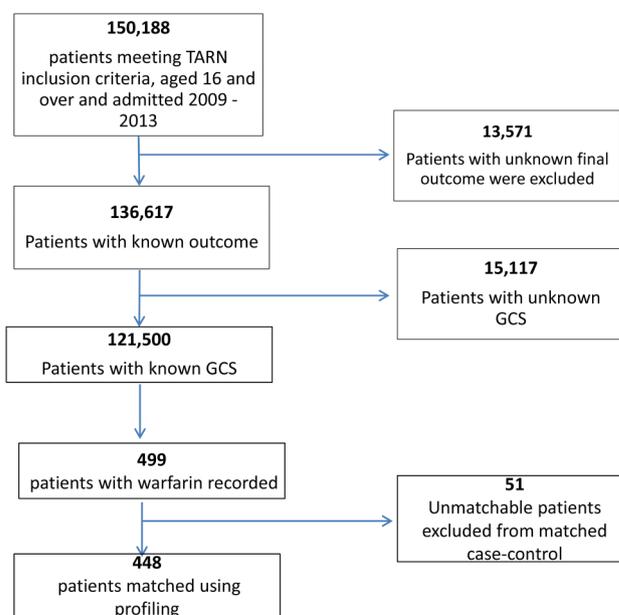

Figure 1 Patient selection from the Trauma Audit and Research Network database.

Table 1 Demographics and characteristics of study patients 2009–2013

	Non-warfarinised patients (n=136 118)	Warfarinised patients (n=499)	p Value	Unadjusted OR (95% CI)
Age median (IQR)	58.1 (38.9–77.1)	80.2 (70.3–85.4)	<0.001	1.05 (1.04 to 1.06)
ISS median (IQR)	9 (9–17)	13 (9–25)	<0.001	1.02 (1.01 to 1.03)
GCS 3–8, n (%)	7925 (6.5%)	39 (7.8%)	0.110	1.31 (0.94 to 1.83)
GCS 9–14, n (%)	19 349 (16%)	108 (21.6%)	<0.001	1.49 (1.20 to 1.84)
Women, n (%)	55 695 (40.9%)	220 (44.1%)	0.151	1.40 (0.95 to 1.36)
Head injury, n (%)	34 169 (25.1%)	212 (42.5%)	<0.001	2.20 (1.84 to 2.63)
Specialist neuro centre, n (%)	52 012 (38.2%)	290 (58.1%)	<0.001	2.24 (1.88 to 2.68)
PMC yes, n (%)	75 452 (55.4%)	494 (99%)	<0.001	46.5 (19.3 to 112.6)
PMC not known, n (%)	25 176 (18.5%)	0 (0%)	N/A*	N/A*
30-day mortality, n (%)	9622 (7.1%)	112 (22.4%)	<0.001	3.80 (3.08 to 4.70)

*No case recorded for warfarinised group to make comparison. ISS, Injury Severity Score; PMC, pre-existing medical condition.

injuries and were more likely to have a PMC. The most common PMC in the warfarinised patients were ulcerative colitis, heart disease, thyroid disorders and asthma. We also observed that warfarinised patients had a higher incidence of head injuries (traumatic brain injury or complex skull fracture on CT scan) than non-warfarinised patients (42.5% vs 25%). Overall analysis of data without adjustment for age, ISS and GCS demonstrated a significantly higher mortality rate for warfarinised trauma patients (112/499=22% vs 9, 622/136 118=7%; p<0.001; unadjusted OR: 3.80, 95% CI 3.08 to 4.70). In this unadjusted analysis, increasing age, injury severity, presence of head injury, presence or uncertainty of PMC, reduced GCS and treatment in a specialist centre were all significantly associated with warfarin use.

After adjusting for age, ISS, GCS, gender, PMCs and hospital type (neuro/non-neuro centre), the risk factors for mortality were age, increasing ISS and GCS, PMC and preinjury warfarin use. Care in a specialist neurology centre was found to be protective even in patients without head injury, hence there is no interaction specified in this final model. Eleven per cent of cases had a missing GCS, which was imputed for this analysis. Results of the analysis still showed a significant increase in the odds of death associated with warfarin therapy (adjusted OR: 2.14; 95% CI 1.66 to 2.76; p<0.001) (table 2).

In the subgroup analysis, it was not possible to match 51 warfarinised patients sufficiently to a non-warfarinised patient (figure 1). Results of this subgroup analysis of 448 paired cases and matches are outlined in table 3 for the remaining covariables. The analysis revealed that when matched for age, gender, PMC, GCS and ISS, the warfarinised trauma patients had a statistically significant higher mortality rate than the matched group (adjusted OR 1.94; 95% CI 1.25 to 3.01; p=0.003). Although

the sample was well matched for most confounders, rates of specialist neuroscience care were significantly higher in the warfarinised group (table 3). The supplementary files give further details of matched characteristics (see online supplementary file 1) and cross-tabulate unmatched characteristics (see online supplementary file 2).

DISCUSSION

This is the first trauma study in England, Wales and Europe to investigate the association between warfarinised trauma patients and mortality rate in comparison with a similar matched group. The results of this study support the findings of Dossett et al[6] in their large American study, who demonstrated that preinjury warfarin use was associated with increased mortality in trauma patients, even after adjusting for PMCs. The adjusted OR for mortality reported by Dosset et al[6] was 1.72 (95% CI 1.63 to 1.81; p<0.001) compared with the adjusted OR of 2.14 (95% CI 1.66 to 2.76) demonstrated in this study in our entire cohort, adjusting for confounders. In a similar American study by Williams et al,[13] increased mortality was also reported in warfarinised patients after adjusting for age, gender and ISS. Bonville et al[14] also reported in another American study that trauma patients on warfarin were three times more likely to die after adjusting for potential confounders. Further comparison with other studies is limited as these studies did not use matched pairs in their analysis, potentially resulting in residual confounding. The effect of this residual confounding was addressed in our study through the use of matched pairs, and our analysis revealed a smaller, but clinically significant OR of mortality in warfarinised trauma patients of 1.94 (95% CI 1.25 to 3.01).

The development of specialist trauma centres in England and Wales has continued to improve the care of trauma patients; however, the results of this study demonstrate that the mortality

Table 2 Adjusted ORs (95% CI) of mortality in overall study sample

	p Value	Adjusted OR (95% CI)
Age	<0.001	1.05 (1.05 to 1.05)
ISS	<0.001	1.08 (1.08 to 1.08)
GCS 3–4	<0.001	25.82 (23.84 to 27.98)
GCS 9–14	<0.001	2.32 (2.18 to 2.74)
Warfarin	<0.001	2.14 (1.66 to 2.76)
PMC	<0.001	1.99 (1.82 to 2.18)
PMC not known	<0.001	2.03 (1.84 to 2.24)
Specialist neurology centre	0.01	0.93 (0.88 to 0.98)

ISS, Injury Severity Score; PMC, pre-existing medical condition.

Table 3 Adjusted ORs (95% CI) of matched patients 2009–2013

	Warfarin group (n=448)	Non-warfarin group (n=448)	p Value	Adjusted OR (95% CI)
30-day mortality	99 (22%)	73 (16%)	0.003	1.94 (1.25 to 3.01)
Head injury	170 (38%)	156 (35%)	0.134	1.41 (0.90 to 2.21)
Specialist neuro centre	270 (60%)	157 (35%)	<0.001	3.09 (2.28 to 4.20)

rate in the UK and Europe is still substantially higher than that of the USA. The reported mortality rate for non-warfarinised trauma patients in a similar study from the USA was 4.8% compared with our rate of 7%.[6] In warfarinised patients, the difference was more pronounced with a mortality rate in the USA of 9.3% compared with our rate of 22%.[6] It could be suggested that the higher mortality rate in Europe compared with the USA simply reflects the differences in severity and types of trauma between the two areas.

The National Audit Office report in 2010 highlighted that major trauma care delivery in the UK lacked coordination, resulting in delayed diagnosis and initiation of appropriate management, leading to worse clinical outcomes.[15] The results of this study supported this statement, reporting that only 39% of trauma patients were transferred to a specialist trauma centre and there was also a considerable delay in this process of transferring. The remaining 61% of patients were managed in non-specialist trauma centres, which has well-recognised implications in survival of trauma patients. In order to improve these deficiencies in care, emphasis should be placed on early diagnosis of trauma patients in addition to more efficient coordination of transferring patients to specialist centres.

Research has demonstrated that the coagulation defects that occur in trauma patients are complex and these abnormalities are caused by a number of interrelated factors, including dilution of haemostatic factors by fluid resuscitation or blood transfusion, severe hypothermia and acidosis due to tissue damage from trauma.[16–19] The mechanism of coagulopathy related to transfusion and haemodilution is still not fully understood, and further studies are needed.[20] In addition to these factors, the warfarinised trauma patients are often in a state of hypocoagulation and more likely to present to the emergency department and Trauma Units with hypovolemic shock and greater intravascular depletion. These challenges will continue to confront emergency clinicians, trauma surgeons and neurosurgeons. These patients are potentially a distinctive subgroup of trauma patients that is continually growing, and, as Leiblich and Mason[3] conclude, there is uncertainty as to whether the National Institute for Health and Care Excellence guidance provides a suitable protocol for managing anticoagulated patients. Further interventional studies are needed to either support or refute this conclusion.

There were a number of limitations in this study. The main limitation of this study was the lack of available data describing the resuscitation strategies of both warfarinised and non-warfarinised patients. As a result, it is not possible to investigate the causes for the differences reported in mortality rates between the two groups. It is also possible that a number of matched groups may have been using warfarin, but this was not recorded by the participating TARN hospital, which would influence the study's results. Furthermore, pre-existing conditions were categorised as a binary variable in this study and this may have introduced residual confounding as an explanation for this observed association. By excluding pre-existing conditions that are associated with warfarin use, we may also have made this group seem less ill at baseline. It could be suggested therefore that warfarin use simply serves as a marker of higher risk.

Another limitation is potential misclassification of patients taking warfarin as non-warfarinised during data extraction from the clinical record. However, given the significantly different characteristics of the two groups and the high level of training of hospital TARN data coordinators, we think the risk of this having occurred is minimal. A further limitation of this study was the lack of data regarding reversal of anticoagulants. Reversal of elevated INR levels with agents such as vitamin K, prothrombin

complex concentrate and fresh frozen plasma is recommended and outlined in both the European Trauma Guidelines[21] and the British Committee for Standards in Haematology guidelines.[22] The potential influence on the analysis of new oral anticoagulants and the lack of a known reversal agent was also not addressed in this study and is therefore a limitation that should be considered when interpreting the results. Similarly, the use of tranexamic acid was introduced during the study period and was not included in the analysis, so this should be considered as a potential confounder.

CONCLUSIONS

This is the first study that has demonstrated similar findings to previous research that suggests that the risk of mortality increases in warfarinised trauma patients compared with non-warfarinised trauma patients. Understanding the relationships and mechanisms between preinjury anticoagulation and the systemic effects on the trauma patient may be important in patient management and, more specifically, in directing appropriate resuscitation targets in this specialised subgroup.

We propose that a large prospective study on this distinctive subgroup of trauma patients should be completed in order to collect further data that will enable investigation into the relationship between trauma and preinjury warfarin use and also to enable the development of an effective care pathway to improve patient outcomes. Future research should focus on developing a practical guideline and clear care pathways for UK trauma centres to reduce mortality and morbidity in warfarinised trauma patients.

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