# Atrial fibrillation patients who sustained warfarin-associated intracerebral haemorrhage have poor neurological outcomes: results from a matched case series

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## ABSTRACT

**Introduction:** Coagulopathy-associated intracerebral haemorrhage has become increasingly common because of the rising demand in the ageing population for anticoagulation for atrial fibrillation. This study compared the clinical features and neurological outcomes of intracerebral haemorrhage in patients with atrial fibrillation who were prescribed warfarin with those who were not.

**Methods:** This was a retrospective matched case series of patients with intracerebral haemorrhage from three tertiary hospitals in Hong Kong from 1 January 2006 to 31 December 2011. Patients who developed intracerebral haemorrhage and who were prescribed warfarin for atrial fibrillation (ICH-W group) were compared with those with intracerebral haemorrhage and not prescribed warfarin (ICH-C group); they were matched for age and gender in 1:1 ratio. Clinical features and neurological outcomes were compared, and the impact of coagulopathy on haematoma size was also studied.

**Results:** We identified 114 patients in the ICH-W group with a mean age of 75 years. Both ICH-W and ICH-C groups had a median intracerebral haemorrhage score of 2. There was a non–statistically significant trend of higher intracerebral haemorrhage volume in the ICH-W group (12.9 mL vs 10.5 mL). The median modified Rankin Scale and the proportion with good recovery (modified Rankin Scale score ≤3) at 6 months were comparable. Nonetheless, ICH-W patients had higher hospital mortality (51.8% vs 36.0%; P=0.02) and 6-month mortality (60.5% vs 43.0%; P=0.01) than ICH-C patients. Overall, 60% of ICH-W patients had their admission international normalised ratio within the therapeutic range during intracerebral haemorrhage, and 14% had a subtherapeutic admission international normalised ratio. International normalised ratio at admission was not associated with intracerebral haemorrhage volume or neurological outcome.

**Conclusion:** Warfarin-associated intracerebral haemorrhage in patients with atrial fibrillation carried a higher stroke mortality than the non-warfarinised patients.


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**New knowledge added by this study**

- Warfarin-associated intracerebral haemorrhage (ICH) carries a high mortality.

**Implications for clinical practice or policy**

- The reversal of coagulopathy after warfarin-associated ICH was often incomplete.
- Given the high mortality after warfarin-associated ICH, newer oral anticoagulants may be a safer alternative in patients with a high risk of cerebral bleeding. As a class of drugs, they are associated with fewer ICHs.

## Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke or systemic thromboembolism. Approximately 5% of AF patients develop stroke or other embolic events each year.[1] Anticoagulation with warfarin, a vitamin K antagonist, reduces stroke risk in AF patients by 64%.[2] It has been the drug of choice for many years in both primary and secondary stroke prevention in AF. Unfortunately, anticoagulation increases the risk of bleeding, and intracerebral haemorrhage (ICH) has been the most life-threatening bleeding complication of concern. This study aimed to compare the clinical features and neurological outcomes of ICH in warfarinised

## 心房顫動患者在服用華法林期間出現腦出血引致嚴重神經功能缺損：匹配病例研究的結論

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**引言：**隨着人口老化，心房顫動患者對抗凝血治療的需求不斷增加，使抗凝血治療相關的腦出血也變得越來越普遍。本研究針對因心房顫動而服用華法林的腦出血患者與無服用華法林的腦出血患者作比較，探討他們臨床特徵和神經功能結果。

**方法：**研究對象為2006年1月1日至2011年12月31日期間到香港三間醫院的腦出血患者。採用回顧性匹配病例系列方法，把腦出血患者分為兩組：因心房顫動服用華法林的患者（ICH-W組）和沒有服用華法林的患者（ICH-C組），並以1：1的比例匹配患者年齡和性別。比較兩組的臨床特徵和神經結果，並研究抗凝血治療對血腫塊大小的影響。

**結果：**ICH-W組有114名患者，平均年齡75歲。兩組的腦出血評分中位數均為2。ICH-W組比ICH-C組的腦出血量較高（12.9 mL比10.5 mL），但未達統計學意義；6個月的改良Rankin量表評分（mRS）中位數和有良好恢復的患者比例（即mRS≤3）相若。ICH-W組的住院死亡率（51.8%比36.0%；P=0.02）以及6個月死亡率（60.5%比43.0%；P=0.01）均比ICH-C組高。ICH-W組中有60%患者的入院國際標準化比率（INR）在腦出血的治療範圍內，另14%患者的入院INR未達治療水平。入院INR與腦出血量或神經功能的結果無關。

**結論：**與沒有服用華法林的腦出血患者比較，服用華法林的房顫患者發生腦出血時有較高的中風死亡率。


AF patients with those in non-warfarinised patients.

## Methods

This was a retrospective matched case series of consecutive patients with first acute ICH admitted to the medical unit of three tertiary hospitals in Hong Kong—Princess Margaret Hospital (PMH) and Caritas Medical Centre (CMC) in Kowloon West, and Queen Elizabeth Hospital (QEH) in Kowloon Central—from 1 January 2006 to 31 December 2011. The three hospitals cover about one quarter of the 7 million population in Hong Kong. It is a general practice in Hong Kong that patients with acute stroke symptoms are admitted to the medical unit (to acute stroke unit first, and to general medical ward if acute stroke unit is full) for further management, with computed tomography (CT) brain scans done within 24 hours of admission. If ICH is identified, a neurosurgeon will be consulted for assessment. Therefore ICH patients in the medical unit are a good indication of the general ICH population.

We searched our electronic database for all patients aged 18 years or above who developed first ICH in the presence of anticoagulation with warfarin for non-valvular AF (ICH-W group) from the three hospitals, and matched them with a comparison group (ICH-C group) without taking warfarin at a 1:1 ratio for age (±1 year), gender, and admission year. The comparison group comprised patients from the medical unit of PMH (principal study centre) who had a first episode of ICH without anticoagulation, regardless of any AF. Patients with isolated subdural, subarachnoid, or intraventricular haemorrhage were excluded. We retrieved and compared the data regarding neurological impairment and investigation findings, estimated the ICH volume on CT through the ABC/2 method, and calculated the ICH score.[3,4] Hospital mortality and 6-month modified Rankin Scale score (mRS, 0-6) were selected as primary and secondary outcomes, respectively. We used independent sample *t* test and Mann-Whitney *U* test for univariate comparisons of continuous variables (Glasgow Coma Scale score, ICH score, ICH volume, mRS), and Chi squared test for categorical variables. Descriptive summary statistics, where appropriate, are presented as mean (range) or median (interquartile range [IQR]). All calculations were two-end conducted at a 0.05 level of significance. The study was approved by the local ethics committee (KW/EX-12-057[52-06]), with the requirement of patient informed consent waived because of its retrospective nature.

## Results

Overall, 114 patients were identified and recruited in the ICH-W group (37 from PMH, 8 from CMC, and 69 from QEH; Table 1) with a mean age of 75 years (range, 47-92 years) and a slight male predominance (56.1%). The same number of patients matched for age (±1 year) and gender were grouped for comparison (ICH-C). Both ICH-W and ICH-C groups had a median ICH score of 2, but there was a trend for higher ICH volume in ICH-W patients than in ICH-C patients (12.9 mL vs 10.5 mL) although it did not reach statistical significance. A total of 59 patients in ICH-W died during the same admission, and a further 10 patients had died by 6 months. The ICH-W patients had significantly higher hospital mortality (51.8% vs 36.0%; Chi squared test, P=0.02) and 6-month mortality (60.5% vs 43.0%; Chi squared test, P=0.01) than the ICH-C patients. The median mRS and the proportion with good recovery (mRS ≤3) at 6 months were comparable for the two groups (Table 1).

Two patients in the ICH-W group died before determination of international normalised ratio (INR). For the remaining 112, the admission INR was <2.0 in 16 (14.3%) patients, 2.0-3.0 in 66 (58.9%) patients, and >3.0 in 30 (26.8%) patients. The INR was re-checked in 85 patients after 12 hours and in 72 patients after 24 hours. The median INR was corrected from 2.6 (IQR, 2.1-3.1) to 1.4 (IQR, 1.2-1.7) at 12 hours post-event, and 1.3 (IQR, 1.1-1.5) at 24 hours post-event. The corresponding percentage of INR >1.5 was 96.4% (108/112) on admission, 35.3% (30/85) at 12 hours, and 22.2% (16/72) at 24 hours. No association was found between admission

INR and ICH volume, hospital mortality, or 6-month mRS (Spearman's rank correlation coefficient).

Regarding the warfarin reversal strategies, QEH had an in-patient protocol whereas PMH and CMC did not. Nevertheless, there was no significant difference in mortality rate among the three hospitals—hospital mortality/6-month mortality in PMH 18 (48.6%)/20 (54.1%), in CMC five (62.5%)/six (75.0%), and in QEH 36 (52.2%)/43 (62.3%). Prothrombin complex concentrate (PCC), fresh frozen plasma (FFP), vitamin K1 (VitK1), factor VII, and transamin were used alone or in combination in our ICH-W patients. Their frequency was as follows: FFP alone (69, 60.5%), FFP + VitK1 (17, 14.9%), FFP + PCC (9, 7.9%), PCC alone (3, 2.6%), transamin alone (3, 2.6%), VitK1 alone (2, 1.8%), FFP + transamin (1, 0.9%), and FFP + factor VII (1, 0.9%). Nine (7.9%) patients received no treatment—two patients died before admission INR was available, three patients died soon after admission INR was available, three patients had admission INR of <1.5, and one patient was on warfarin and aspirin for ischaemic heart disease. The high variation in anticoagulation reversal strategy made it impossible for any valid comparison.

TABLE 1. Clinical characteristics and neurological outcomes

| Variable | Median, median (IQR), or No. (%) | | P value |
|---|---|---|---|
| | ICH-W group (n=114) | ICH-C group (n=114) | |
| GCS | 14 (8-15) | 11 (7-15) | 0.53 |
| ICH score | 2 | 2 | 0.45 |
| ICH volume (mL) | 12.9 | 10.5 | 0.34 |
| Hospital mortality | 59 (51.8) | 41 (36.0) | 0.02 |
| mRS (at 6 months) | 6 | 5 | 0.63 |
| mRS ≤3 (at 6 months) | 22 (19.3) | 28 (24.6) | 0.38 |
| Mortality (at 6 months) | 69 (60.5) | 49 (43.0) | 0.01 |

Abbreviations: GCS = Glasgow Coma Scale score; ICH = intracerebral haemorrhage; ICH-C = patients not taking warfarin for atrial fibrillation showing intracerebral haemorrhage; ICH-W = patients taking warfarin for atrial fibrillation showing intracerebral haemorrhage; IQR = interquartile range; mRS = modified Rankin Scale score

## Discussion

Cardioembolic stroke related to AF carries significant morbidity, yet anticoagulation is not without risk. How to prevent stroke and at the same time minimise bleeding complications has always been a dilemma for physicians and patients. Risk assessment tools (eg $CHA_2DS_2$-VASc and HAS-BLED score, for assessment of thromboembolic and bleeding risk, respectively) have been developed to assist the decision making.[5,6] It is important for clinicians to exercise individualised medical practice, however. In a recently published observation study on a large hospital cohort of Chinese AF patients from Hong Kong, the investigators found that the stroke risk in Chinese AF patients was higher than that in Caucasians at a given $CHA_2DS_2$-VASc score, and that excessive risk was more prominent in the low-risk group from $CHA_2DS_2$-VASc.[7] At the same time, the ICH incidence in Chinese AF patients taking warfarin was also higher than that in Caucasians.[8] These observations really drive clinicians towards a better anticoagulation strategy for Chinese AF patients.

Unfortunately ICH remains a significant threat even with very careful patient selection and treatment monitoring. Up to 25% of ICH can be associated with anticoagulant usage, and the rate is still increasing given the higher utilisation of anticoagulation in ageing populations with rising AF prevalence.[9,10] Several features of warfarin-associated ICH in our patients deserve further elaboration, as listed below.

First, we found a large proportion (73.2%) of warfarin-associated ICH occurred when the INR was within or even below the therapeutic range (INR ≤3.0). Our findings were supported by a similar observation from another prospective study in which 68% of warfarin-associated ICH occurred at INR of ≤3.0.[11] This shows that bleeding is increased even with an INR within the therapeutic range. Moreover, those ICH-W patients with a subtherapeutic INR reaffirm the high intrinsic ICH risk in AF patients who are old with multiple co-morbidities.

Second, we did not find any correlation between initial ICH volume and admission INR. The initial ICH volume in warfarinised and non-warfarinised patients was not significantly different. This is consistent with the results from some other studies.[9,12,13] In contrast, Cucchiara et al[14] reported larger haematoma volume in anticoagulant-associated ICH than spontaneous ICH, whereas Flaherty et al[15] reported larger initial haematoma volume if admission INR was >3.0. It is reasonable to suppose that coagulopathy would have an impact on haematoma volume, but is difficult to confirm in clinical studies because it is hard to control other covariates that affect haematoma size. The relatively small number of subjects in the warfarin-associated ICH group is often underpowered to reach any solid conclusion. Nonetheless, other studies did show that warfarin use was a known predictor of haematoma expansion, and haematoma expansion an independent determinant of neurological outcomes in spontaneous ICH.[12,14,16] All the consensus guidelines agree that coagulopathy should be reversed as soon as possible in warfarin-associated ICH.

Third, both the hospital and 6-month mortalities in our ICH-W patients were significantly higher than those in ICH-C patients (Table 1). This observation is highly consistent with other reports in which warfarin-associated ICH had higher mortality than patients without taking warfarin (Table 2).[9,11-15,17-20] Our study adopted a matched case series design in order to eliminate the effect of age,

TABLE 2. Effect of warfarin on mortality and initial ICH volume in different studies

| | Present study | Rosand et al, 2004[11] | Flibotte et al, 2004[12] | Flaherty et al, 2006[17] | Zubkov et al, 2008[18] |
|---|---|---|---|---|---|
| Study design | Retrospective, matched case series | Prospective, cohort | Prospective, cohort | Retrospective, case-control | Retrospective, case series |
| No. of subjects | Warfarin, 114<br>Control, 114 | Warfarin, 102<br>Control, 333 | Warfarin, 42<br>Control, 141 | Anticoagulant, 190<br>Control, 851 | Warfarin, 88 |
| Mean age in years (warfarin / non-warfarin) | 74.9 / 74.9 | 75.7 / 74.0 | 75.7 | 74.8 / 68.9 | 76 |
| INR in warfarin group | Median 2.6 | Not reported | Median 3.1 | Not reported | Median 3.2 |
| Initial ICH volume in warfarin vs non-warfarin | No significant difference | Not reported | No significant difference; warfarin associated with haematoma expansion | Not reported | Not reported |
| INR and ICH volume | No correlation | Not reported | Not reported | Not reported | Not reported |
| Mortality (warfarin vs non-warfarin) | Hospital: 51.8% vs 36%; 6-month: 60.5% vs 43% | 3-Month: 52.0% vs 25.8% | Not reported | 1-Day: 33.2% vs 16.3%; 1-year: 66.3% vs 50.3% | 7-Day: 39.8% |

Abbreviations: ICH = intracerebral haemorrhage; INR = international normalised ratio

and to minimise the age-related co-morbidities that are known predictors of poor neurological outcome from ICH. As a result, our selected ICH-C patients were older and probably had more co-morbidities than the general ICH patients. This explained the higher-than-usual mortality and poor neurological outcomes in our ICH-C group compared with other studies. Nonetheless, AF-related co-morbidity could not be controlled in this design, and we believe our observed difference in mortality and neurological outcomes is a compound effect from AF and warfarin use in the ICH-W patients.

Currently, the optimal therapy for coagulopathy reversal in warfarin-associated major bleeding is unclear and recommendations of international guidelines are mainly derived from consensus opinions. Treatment options include FFP, VitK1, PCC, and recombinant factor VIIa, in different combinations.[21] One of the three study hospitals (QEH) had an in-house protocol for warfarin reversal. The other two hospitals provide guidelines only. Because of the incomplete data collection from this retrospective study design, we were unable to analyse the haematoma growth and warfarin reversals. The mortality, however, did not differ among the three hospitals.

Since 2010, newer oral anticoagulants have become available and provide an alternative to warfarin in AF stroke prevention. The three new oral anticoagulants—dabigatran, rivaroxaban, and apixaban[22-24]—might differ in efficacy, but the lower ICH rate compared with warfarin was a universal finding from their clinical trials, and is a class effect of these new agents. They should be considered in Chinese AF patients at a high risk of warfarin-associated ICH.

### Limitations of study

As a retrospective study, this study has several limitations. First, the methods and timing of warfarin reversal were not standardised and could have affected the neurological outcome. Second, there was no protocol for serial CT brain and serial INR monitoring to investigate the effect of coagulopathy reversal on haematoma expansion, and the effect of haematoma expansion on neurological outcome. Third, we were uncertain about compliance with the coagulopathy reversal protocol in QEH, and were unable to comment on whether the standardised protocol could improve ICH outcome. Moreover, ICH-W patients were AF patients who had additional vascular risk factors (to justify the use of warfarin) that may not have been present in ICH-C patients. This difference could potentially affect the ICH outcome. Finally, other possible confounders such as smoking or alcohol use were not adjusted for in this retrospective study.

## Conclusion

Warfarin-associated ICH in AF patients may be associated with higher stroke mortality. It could be a serious problem in Chinese AF patients who are known to have more warfarin-associated ICH.

## Declaration

The authors declared no conflicts of interest in this study.

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|---|---|---|---|---|---|
| Retrospective, nested case-control | Retrospective, case-control | Retrospective, nested matched case-control | Retrospective, case-control | Prospective cohort | Retrospective case series |
| Anticoagulant, 21<br>Control, 282 | Warfarin, 51<br>Control, 207 | Warfarin, 50<br>Control, 50 | Warfarin, 182<br>Control, 800 | Anticoagulant, 51<br>Control, 155 | Warfarin, 3<br>Control, 389 |
| 75 / 65 | 68.5 | Not reported | 74.4 / 67.9 | 75 / 72 | 64.4 / 61.0 |
| Median 2.0 | Median 2.7 | Median 3.2 | Mean 3.1 | Median 2.7 | Mean 4.78 |
| Large in oral anticoagulant group; oral anticoagulant associated with haematoma expansion | Not reported | No significant difference | Not reported | No significant difference | Not reported |
| Not reported | INR >3 had greater haematoma volume | Not reported | Not reported | Not reported | Not reported |
| Not reported | Not reported | Not reported | 1-Year: 64.8% vs 32.1% | 3-Month: 45.1% vs 32.4% | 65.6% vs 30.1% |


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