**Mortality predictors and effects of antithrombotic therapies in atrial fibrillation: insights from ACTIVE-W**

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**Aims**
To assess the risk of death after the occurrence of different types of non-fatal events in patients with atrial fibrillation (AF). Antithrombotic therapies in AF have primarily focused on stroke prevention and bleeding. However, strokes and bleeds differ in severity, and the level of severity may differently impact mortality.

**Methods and results**
We analysed the risk of subsequent mortality after the occurrence of non-fatal vascular and bleeding events in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE)-W trial. In the 3371 patients randomized to vitamin K antagonists and the 3335 patients randomized to clopidogrel plus aspirin in ACTIVE-W, the hazard ratio (HR) and 95% confidence intervals (95% CIs) for subsequent death associated with the occurrence of non-fatal stroke was 5.58 (95% CI 3.84–8.10, P < 0.0001). Both ischaemic (HR 5.29, 95% CI 3.53–7.93, P < 0.0001) and haemorrhagic strokes (HR 7.38, 95% CI 2.74–19.9, P < 0.0001) increased mortality, but transient ischaemic attacks did not. Disabling strokes (Rankin’s score ≥3) increased mortality (HR 9.54; 95% CI 6.42–14.2, P < 0.0001), but non-disabling strokes did not. Severe bleeding increased mortality (HR 3.35, 95% CI 2.12–5.27, P < 0.0001), but major bleeding that was not severe according to the study definitions did not.

**Conclusion**
Non-fatal strokes increased mortality in ACTIVE-W, but non-disabling strokes did not. Among major bleeding events, only those also classified as severe increased mortality. Future research should emphasize the prevention of disabling strokes and severe bleeds and place less emphasis on non-disabling stroke or major bleeds that are not severe.

**Keywords**
Atrial fibrillation • Stroke • Bleeding • Mortality

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**Introduction**
Atrial fibrillation (AF) is a common condition affecting 0.4% of the general population1 and >6% in people over 80 years.2–4 The prevalence of AF is increasing,5 even after adjustment for age.6,7 Atrial fibrillation is associated with reduced life expectancy.8,9 Atrial fibrillation increases the risk of thrombo-embolic stroke,8 which in turn increases the risk of death.10,11 This is reflected by the inclusion of stroke as a main outcome in many clinical trials testing antithrombotic therapies in AF.12–27 On the other hand, major haemorrhage has generally been of lesser concern and usually not included in the primary study outcomes.

This approach to clinical trial design has recently been challenged. Patients with AF may die of non-stroke-related vascular events, such as myocardial infarction (MI), because of associated co-morbidities.28 Risk factors for non-embolic stroke are common in AF, and as many as 25% of strokes in patients with AF are estimated to be non-cardioembolic, due to intrinsic cerebrovascular disease (present in about 12% of such patients29), other cardioembolic sources, or atheroembolism from the...
proximal aorta. The impact of different vascular events on mortality in AF patients is unknown. Stroke severity also may vary from non-disabling to very severe, and the extent to which severity of stroke in AF influences mortality is unknown.

Therefore, we examined the risk of death after the occurrence of different types of non-fatal vascular events occurring in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE)-W Trial, a large trial examining the effect of clopidogrel plus aspirin (C + A) vs. vitamin K antagonists (VKAs), with the purpose of understanding the clinical importance of different types of vascular events and of haemorrhage.

Methods
Details of the overall programme, study design, and the main results of the ACTIVE-W trial have been published. Patients eligible and willing to take a VKA were enrolled into ACTIVE-W, which compared C + A vs. VKAs. Patients were eligible for ACTIVE-W if they had electrocardiographic evidence of AF and also had at least one of the known risk factors for stroke. Patients were excluded if they had any of the following: requirement for VKAs (such as for prosthetic mechanical heart valves), documented peptic ulcer disease within the previous 6 months, prior intracerebral haemorrhage, significant thrombocytopenia (platelet count <50 × 10^9/L), or mitral stenosis. Patients randomized to VKAs could receive the VKA in use in their country and were monitored to keep the international normalized ratio (INR) between 2.0 and 3.0. Patients randomized to C + A received clopidogrel 75 mg once daily in addition to aspirin (recommended dose: 75–100 mg/day). The median follow-up for the whole of ACTIVE-W study was 1.28 years.

Study outcomes and definitions
The primary outcome of ACTIVE-W was the first occurrence of any of the following vascular events: stroke, non-central nervous system (CNS) systemic embolism, MI, or vascular death. Strokes were classified into those that were ischaemic or primarily haemorrhagic, and the severity of stroke was measured with the modified Rankin score at the time of discharge from hospital or at 7 days after the event. Subdural haematomas were included as intracranial haemorrhages, but not classified as haemorrhagic strokes. Strokes were defined as disabling when the modified Rankin score was ≥3. Myocardial infarction was diagnosed according to American Heart Association/American College of Cardiology guidelines. Vascular death was any death clearly not due to non-vascular cause such as trauma. Major bleeding was defined as any bleeding requiring transfusion of at least 2 U of red blood cells or equivalent of whole blood, or any bleeding defined as severe. Severe bleeding was major bleeding that was also associated with any of the following: death, drop in haemoglobin of at least 5 g/dL, significant hypotension with the need for inotropic agents, intraocular bleeding leading to significant loss of vision, bleeding requiring surgical intervention (other than vascular site repair), symptomatic intracranial haemorrhage, or requirement for a transfusion of at least 4 U of blood. We here, therefore, indicate as major non-severe those bleeding events that were major, but not severe, according to the previous definitions. In practice, these were bleeds with a need for transfusions of at least 2 U but <4 U of blood. Non-fatal events were defined for this analysis as those not causing death within 7 days. There were 14 and 15 fatal strokes on C + A and VKAs, respectively, and 7 and 11 fatal haemorrhages, respectively, in the ACTIVE-W cohort, as reported previously.

For the current analysis, we eliminated the immediately fatal (<7 days) strokes and bleeds, since—in ACTIVE-W case report forms—investigators would sometimes check an event as fatal also when the time to death was >7 days. The number of fatal events omitted from analysis by the treatment group were: fatal strokes = 20 (9 on VKAs and 11 on C + A); fatal haemorrhages = 14 (8 on VKAs and 6 on C + A).

Transient ischaemic attacks (TIAs) were not among the outcomes of the study. They were diagnosed by local neurologists as acute episodes of temporary neurological dysfunction ascribed to a vascular occlusion to a particular area of the brain that persisted for <24 h, and captured in the database for further analyses. Patients were excluded from the analysis if they had a fatal stroke or a fatal bleed (see definitions above).

Statistical analysis
The primary analysis was based on a time-to-event model using the non-fatal event as a time-dependent covariate. Cox’s regression analysis was used to quantify the risk of non-fatal outcomes on subsequent within-trial death. These regressions were adjusted for age, history of coronary artery disease, history of stroke, diabetes, history of heart failure, and study medication. Hazard ratios (HRs) and their 95% confidence interval (CI) were calculated using Cox’s regression.

Extended Kaplan–Meier estimator curves were constructed to display the effect of the non-fatal event as the time-dependent risk on time to mortality. All analyses were done related to all-cause mortality.

The P-value threshold for significance used was a two-sided value of 0.05. Analyses were carried out with the SAS version 9.1 statistical software.

Results
The effect of non-fatal stroke on mortality
The overall median follow-up time for patients in ACTIVE-W was 1.28 years. For the present analysis, however, follow-up after first non-fatal events was shorter, namely 0.51 years after a stroke, 0.53 years after an MI, 0.37 years after a non-CNS embolism, 0.59 years after a major bleed, and 0.82 years after a minor bleed. Overall, the occurrence of non-fatal stroke increased the risk of death: HR (95% CI): 9.3 (6.3–13.7), P < 0.0001 (Figure 1). The increase in relative risk (RR) was significant for both haemorrhagic stroke and ischaemic stroke (Figure 1 and Table 1). Transient ischaemic attacks had no effect on mortality (Figure 1 and Table 1), despite being predictors of a subsequent stroke (HR 4.37, 95% CI 1.78–10.73, P = 0.001).

Of the 139 strokes occurring during the trial, 56% (n = 78) were disabling (Rankin’s score ≥3) and 42% (n = 58) were not (Rankin’s score 1–2); 3 strokes were not classified in severity. There was an increase in the RR of death after a disabling stroke (HR 14.3, 95% CI 9.5–21.7, P < 0.0001), but not after a non-disabling stroke (HR 2.5, 95% CI 0.93–6.78, P = 0.07; Figure 1 and Table 1).

The impact of haemorrhage on mortality
The occurrence of any non-fatal bleeding increased the risk of death [HR (95% CI): 2.5 (1.8–3.5), P < 0.001]. Non-fatal major bleeding especially had an important impact on subsequent mortality [HR (95% CI): 4.2 (2.8–6.4), P < 0.001], whereas minor bleeding had a weaker, albeit still significant, effect [HR (95% CI): 1.6 (1.0–2.5, P = 0.04); Table 2]. A pre-specified classification of major bleeding events in ACTIVE designated these bleeds as severe or not. Only severe bleeding events
had a significant impact on mortality (HR 5.7, 95% CI 3.6–9.1, \( P < 0.0001 \); Table 2 and Figure 2). Major, but non-severe, bleeds did not affect mortality significantly.

Figure 3 shows the subsequent mortality rate of patients experiencing non-fatal events compared with patients who had not had an event. This is shown for disabling and non-disabling strokes, as well as for severe haemorrhages and for major, but non-severe haemorrhages. The lack of effect of a major non-severe haemorrhage (as opposed to that of severe haemorrhage) on subsequent mortality was also evident at all time points throughout the duration of the follow-up (Figure 3).

The impact of other non-fatal outcomes on mortality

The occurrence of MI was associated with a subsequent increase in mortality, the HR being 7.3 (95% CI 4.1–13.2, \( P < 0.0001 \); Table 1).

A non-CNS embolism (HR 6.5, 95% CI 2.1–20.6, \( P = 0.0014 \)) also was associated with increased mortality.

The impact of treatment on death and on non-fatal events having a subsequent impact on mortality

Having determined that disabling strokes, MI, and severe bleeding events were significantly and strongly (HR > 3.0) associated with subsequent increased mortality, we estimated the cumulative number of such events (which we now term ‘severe events’, having an important impact on mortality), with or without vascular death or total death (Figure 4), as a function of treatments tested in ACTIVE-W. Clopidogrel plus aspirin was associated with a significantly higher number of severe events (not including death) than VKAs [RR = 1.39 (1.09–1.77), \( P = 0.0084 \)]. When vascular death was included in this analysis, the cumulative outcome of
disabling stroke, MI, severe bleeding, and vascular death was significantly higher with C + A than with VKAs [RR = 1.28 (1.06–1.55), P = 0.0121; Figure 4]. There was a trend towards fewer outcomes of disabling stroke, MI, severe bleeding, and total death with VKAs compared with C + A [RR = 1.17 (0.98–1.40), P = 0.078].

Discussion

This report indicates that in the AF population recruited in the large ACTIVE-W study, the risk of death is increased by disabling strokes, MI, severe bleeding events. However, non-disabling strokes and major non-severe bleeding events appear not to increase mortality. These findings emphasize the importance for clinicians to appropriately assess the risk–benefit ratio for treatments commonly used in AF and suggest that evaluation of the net benefits of antithrombotic agents in patients with AF should be based on the composite of outcomes that are more prognostically important rather than simply on the general category of ‘strokes’ and ‘bleeding events’. Such results may also have relevance in the planning of future clinical studies, both within and outside the AF setting, by refining the mortality predictions based on the characteristics of the entry populations.

Proper assessment of the risk–benefit ratio for commonly used therapies in atrial fibrillation

We found here that only some types of commonly considered ‘major’ outcomes have an effect on mortality. Severe haemorrhages, as defined in ACTIVE-W, impacted mortality, whereas some strokes did not. Our analysis was adjusted for a history of hypertension—which might have influenced the severity of both strokes and bleeding—in the model, although we recognize a limitation in this analysis, in that >80% of the ACTIVE-W population had such a history. Our analysis also was adjusted for other covariates likely affecting mortality, such as age, history of coronary artery disease, history of stroke, diabetes, history of heart failure, and study medications. In any case, our findings contrast previous belief that strokes are often disabling. Since clinicians prescribing antithrombotic treatments in their patients are constantly confronted with the problem of the choice between the risk of bleeding and the risk of thrombosis, knowing what events are really relevant and what are less relevant can help in decision-making. Doctors should also know that such evaluation may affect patients’ events not remotely in time, but relatively soon, since our analysis is based on the relatively short follow-up of little more than 1 year (1.28 years as median) allowed by our study. Such predictions may, therefore, have direct practical implications.

Outcomes and mortality in atrial fibrillation

Most previous studies in AF have focused on stroke or the combination of stroke and systemic embolism, and not on mortality, as the primary outcome. This choice is due in part to understandable pathophysiological considerations, directly relating blood stasis in the left atrium with the occurrence of CNS and non-CNS systemic embolism and (ischaemic) stroke, and in part to the more frequent rate of strokes (most of which are non-fatal) and TIAs when compared with death, making comparisons of different therapies feasible even with a relatively small number of recruited patients. However, the severity of strokes may vary

Table 2  Effect of non-fatal bleeding events on subsequent mortality (over the 1.28 years of the median follow-up duration of the study)

<table>
<thead>
<tr>
<th>Event</th>
<th>With the event</th>
<th>Without the event</th>
<th>Effect of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Deaths</td>
<td>Mortality (%)</td>
<td>Total Deaths</td>
</tr>
<tr>
<td>Bleeding events (any)</td>
<td>593 46</td>
<td>7.8</td>
<td>6113 272</td>
</tr>
<tr>
<td>Major</td>
<td>181 24</td>
<td>13.3</td>
<td>6526 294</td>
</tr>
<tr>
<td>Major, severe</td>
<td>123 20</td>
<td>16.3</td>
<td>6583 298</td>
</tr>
<tr>
<td>Major non-severe</td>
<td>58 4</td>
<td>6.9</td>
<td>6648 314</td>
</tr>
<tr>
<td>Minor</td>
<td>412 22</td>
<td>5.3</td>
<td>6294 296</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.
enormously in terms of functional consequences and prognostic importance, from strokes with no or little permanent impairment to disabling, or fatal. We found that TIAs have no impact on subsequent mortality, despite being themselves predictors of a subsequent stroke. One reason for this may lie in the somewhat uncertain diagnosis of TIAs, likely also including non-cerebrovascular events. However, also non-disabling strokes, which were 42% of all strokes in this study and which are of much less uncertain diagnosis, did not impact significantly on mortality. These findings suggest that non-disabling strokes (and TIAs) should not be grouped together with disabling strokes in outcome AF studies, because such two types have quite different

Figure 3 Late mortality following immediate survival from stroke or haemorrhage according to stroke or bleeding severity. Note the impact on later mortality of a disabling stroke and of severe haemorrhages, but not of a non-disabling stroke and of a major-non-severe bleeding event.

Figure 4 The impact of therapy (clopidogrel + aspirin, C + A) vs. vitamin K antagonists (VKAs) (Kaplan–Meier curves) on the cumulative incidence of non-fatal events having a significant impact on mortality (disabling stroke, myocardial infarction, and severe bleeding) (left panel) and on the cumulative incidence of non-fatal events having a significant impact on mortality (disabling stroke, myocardial infarction, and severe bleeding) plus vascular death. RR indicates the relative risk along with its 95% confidence interval and significance (P-value).
consequences. Similar considerations pertain to major bleeding events, which here increased mortality only if ‘severe’, whereas even bleeding events termed as major, but not-severe did not affect prognosis. These, in the definitions adopted in ACTIVE, involve the need for transfusions of \( \geq 2 \) U but \(< 4 \) U of blood. The effect of non-fatal disabling strokes and of non-fatal severe bleeding events (as opposed to that of non-fatal non-disabling strokes and non-fatal minor or even major, but not severe, bleeding events) on subsequent death was constant over time, with a progressive separation of the Kaplan–Meier curves, indicating that both these types of prognostically relevant events started immediately to detrimentally affect prognosis and continued to affect subsequent death at a relatively constant rate thereafter.

**Impact of non-stroke events on mortality**

Since the risk factors for AF largely overlap with those for coronary artery disease and vascular disease in general (age, male gender, hypertension, and diabetes among others), it is important to consider that AF patients are likely to die from causes unrelated to thrombo-embolic stroke, including MI. Myocardial infarction did indeed occur in 0.9% of patients throughout the study follow-up and had a significant impact on mortality (HR 7.3, 4.1–13.2, \( P < 0.0001 \)).

**The impact of bleeding on mortality**

We attempted at defining the relevance of bleeding severity for subsequent mortality and the differential effects of the two tested treatment strategies on such events, in the light of the recent increasing emphasis on bleeding as a determinant of prognosis in trials of antithrombotic agents.\(^{33,36} \) As for stroke, the overall category of bleeding encompasses widely different severities, with some bleeding events—even within the category defined as ‘major’—having little—if any—prognostic significance. Major bleeding events defined as severe (68% of all major bleeds) significantly increased mortality. Since the difference between what were here defined as severe bleeding (happening to have an impact on mortality) and major non-severe bleeding (having no impact on mortality) essentially lies in the need of transfusions (\( \geq 2 \) U but \(< 4 \) U of blood in the case of major non-severe bleeding), our findings underscore the inappropriateness of including minor transfusion needs as a relevant outcome in AF trials. Here, the two treatment strategies tested had a differential impact on minor bleeding, which was significantly (and surprisingly) more frequent with C + A, but not on major or severe bleeding.\(^{33} \)

**Treatment impact on strokes in ACTIVE-W**

The inappropriateness of grouping all strokes into one single category is further illustrated by the differential impact of the two treatment strategies tested in ACTIVE-W on stroke subtypes. Here, VKAs, with INR values in the therapeutic range (2.0–3.0) \(63.8\% \) of the time,\(^{31} \) were overall superior to C + A on total strokes, but their impact was larger on the less severe type of strokes. Vitamin K antagonists were actually associated with an increased incidence in primarily haemorrhagic strokes, likely not related to AF per se, and thereby likely caused by the adverse consequences of VKAs on haemostasis. This is in line with previous reports on the relative safety of antiplatelet therapies (even combining two antiplatelet agents such as C and A) from the standpoint of intracranial haemorrhage,\(^{37} \) whereas treatment with VKAs have long been known to be affected by a substantially increased number of this event.\(^{38} \)

Vitamin K antagonists were superior to C + A in preventing all strokes (ACTIVE-W main findings). However, the benefit of VKAs over C + A decreases with increasing stroke severity (\( P = 0.036 \)). The RR for non-disabling stroke (modified Rankin’s score 0–2) was 2.49, but for disabling strokes (modified Rankin’s score 3–6) or fatal strokes was only 1.47. Thus, compared with C + A, VKAs were significantly more likely to prevent a minor stroke than a more serious one.

**Overall impact of vitamin K antagonists and clopidogrel plus aspirin on prognostically relevant outcomes and clinical implications**

ACTIVE-W was terminated early because of a clear superiority of VKAs over C + A on the primary outcome of the study, which was the first occurrence of stroke, non-CNS systemic embolism, MI, or vascular death. However, there was no difference on mortality.\(^{33} \) The negative impact of VKAs on haemorrhagic strokes, which substantially increases the risk of death, certainly contributed to the neutral effects on mortality. However, the number of deaths in ACTIVE-W was only 318, and the 95% CI do not exclude a modest differential impact of VKAs vs. C + A on mortality. It was, therefore, of some importance to distinguish between a trial truly negative and a trial simply not powered enough to show differences in death rates between the two treatments tested, despite the sample size larger than for any of previous AF trials. When all non-fatal events subsequently substantially affecting mortality were grouped together, or all these were put together with total vascular death, VKAs were superior to C + A (to a statistically significant extent for the latter combined outcome). A similar trend, close to statistical significance, was apparent when total death was also included in the grouping. These analyses are exploratory, since they are the results of a post hoc analysis of the trial and do not ascertain whether VKAs were superior to C + A on mortality. They, however, show that VKAs, especially when adequately controlled\(^{39} \) may be indeed superior to C + A on events prognostically related to mortality. The definite proof of an advantage of VKAs on mortality would have required a substantially larger and longer trial, which would not be interrupted due to a difference in strokes or other non-fatal events. It is unlikely that any such trial will ever be undertaken again, thus supporting the need of gathering the information presented here.

**Limitations**

The observations from this study pertain to a selected AF population and may not necessarily be applied to the general patient population with this condition. This is a limit of the present study as well as of all studies specifying inclusion and exclusion criteria that may render the study population different from the real
world. In addition, however, ACTIVE-W was done in a population eligible for therapy with VKAs and to a large extent warfarin-experienced. Confirmation of the different prognostic value of subtypes of strokes and bleeding events in different populations, e.g. in patients judged unsuitable to VKAs, is certainly worthwhile and is actually being planned in the ACTIVE-A cohort. Despite being one of the largest studies in AF conducted so far, the number of deaths in this study was still relatively small. Such an analysis should be, therefore, repeated in future studies to replicate the findings.

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Conflict of interest

R.D.C. has received honoraries and grant support from Sanofi-Aventis and Bristol Myers-Squibb; S.J.C. has received research grants and speaking fees from both Sanofi Aventis and Bristol Myers-Squibb; A.B. has received research grants and honoraria from Sanofi-Aventis; S.Y. has received research grants and speaking fees from both Sanofi Aventis and Bristol Myers-Squibb.

References

In 2002, Thiene and co-workers reported the possibility that echocardiography might not be able to correctly differentiate a bicuspid valve with a median cleft (simulating a rudimentary commissure) from a true tricuspid valve. This is the only published report on this subject so far.

In this brief report, we describe a similar case where transthoracic echocardiography (TTE) missed the diagnosis which was later established by cardiac magnetic resonance imaging (MRI).

The patient is a 36-year-old male with an ascending aorta diameter of 5 cm, moderate aortic stenosis, and a tricuspid aortic valve by TTE (Panel A). The patient underwent a cardiac MRI at our institution: the presence of a bicuspid aortic valve was documented along with a pseudoraphe (Panel B: systolic short-axis view; Panel C: diastolic short axis view) and a 5 cm aneurysm of the ascending aorta (Panel D). On the basis of the MRI findings, the patient underwent the Bentall procedure with favourable outcome.

Both the aortic valve specimen (Panel E) and the 3D reconstruction of a CT scan of the excised aortic valve (Panel F) demonstrate a bicuspid valve. In both instances, the valve presented a small incision (pseudoraphe) involving the larger cusp and simulating a tricuspid configuration (white arrow).

Cardiac MRI is an important diagnostic tool for the evaluation of patients with abnormalities of the ascending aorta and of the aortic valve. The high-contrast resolution, the absence of acoustic window limitations, and the good temporal resolution provide an accurate definition of aortic valve morphology. This is quite relevant because, as evidenced in this case, the combination of bicuspid valve-dilated ascending aorta will dictate the surgical therapeutic strategy.

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