Incidence of Oral Anticoagulant–Associated Intracerebral Hemorrhage in the Netherlands

Angel M.R. Schols, MD; Floris H.B.M. Schreuder, MD; Elisabeth P.M. van Raak, MD, PhD; Tobien H.C.M.L. Schreuder, MD; Fergus A. Rooyer, MD; Robert J. van Oostenbrugge, MD, PhD; Julie Staals, MD, PhD

Background and Purpose—The aim of this study was to estimate the annual adult incidence and risk of intracerebral hemorrhage (ICH) and oral anticoagulant–associated ICH (OAC-ICH) in the Netherlands.

Methods—We retrospectively selected all consecutive adult patients with a nontraumatic ICH seen in 1 of 3 hospitals in the region South-Limburg, the Netherlands, from 2007 to 2009. Crude incidences were age-adjusted to Dutch and European population.

Results—We identified 652 ICH cases, of which 168 (25.8%) were OAC associated. The adult Dutch age-adjusted annual incidence of ICH and OAC-ICH was 34.8 (95% confidence interval, 32.0–37.8) and 8.7 (95% confidence interval, 7.3–10.3) per 100,000 person-years, respectively. The absolute risk of OAC-ICH was estimated at 0.46% per patient-year of OAC treatment.

Conclusions—The annual incidences of ICH and OAC-ICH are relatively high in the Netherlands when compared with international literature. (Stroke. 2014;45:268-270.)

Key Words: anticoagulants ■ cerebral hemorrhage ■ epidemiology ■ incidence

A serious complication of oral anticoagulants (OAC) is the occurrence of an OAC-associated intracerebral hemorrhage (OAC-ICH). In the Netherlands, acenocoumarol and phenprocoumon are mainly used, and strict dose-regulation of OAC is performed by a nation-wide network of specialized anticoagulation clinics. Although it is thought that OAC-ICH is low because of strict dose-regulation, recent Dutch data on the adult incidence of OAC-ICH are scarce. The aim of this study is to estimate the annual adult incidence of ICH and OAC-ICH, as well as the risk of OAC-ICH in the Netherlands.

Methods

We retrospectively analyzed all consecutive adult (≥18 years) patients with a brain scan-confirmed nontraumatic ICH, seen in the emergency department, inpatient or outpatient clinic, in 3 hospitals of South-Limburg, the Netherlands, from 2007 to 2009 (Figure). Patients were selected using diagnosis-treatment codes retrieved from hospital Medical Registration Archives complemented with hospital stroke registries. OAC-ICH was defined as an ICH while on treatment with oral vitamin-K antagonists at admission. Recurrent ICH cases were included. The study was approved by the medical ethical committees of all the 3 hospitals.

The crude annual adult incidence rates of ICH and OAC-ICH were calculated by dividing the number of ICH or OAC-ICH cases by the total adult person-years at risk for ICH. Person-years at risk were calculated by dividing the number of ICH or OAC-ICH cases by the total person-years at risk for ICH. Person-years at risk for OAC-ICH were calculated by dividing the number of OAC-ICH cases by the total patient-years of OAC treatment, which was estimated with data provided in the annual reports of the anticoagulation clinics. See Methods in the online-only Data Supplement for details.

Results

We included 652 ICH cases in 617 patients; 588 (90.2%) patients had a first-ever ICH. Of all ICH cases, 168 (25.8%) were OAC associated and 153 of these (91.1%) were first-ever OAC-ICH. Aacenocoumarol was used by 134 (79.8%) patients, phenprocoumon was used by 20 (11.9%), and a combination of OAC with another antithrombotic drug was used by 14 (8.3%). Indications for OAC were atrial fibrillation (77.4%), cardiac valve prosthesis (71.1%), venous thrombosis (60.0%), peripheral artery disease (42.4%), and other indications (54.4%). Table 1 shows clinical characteristics of (OAC-)ICH cases.

Incidence of (OAC-)ICH

The adult Dutch age-adjusted annual incidence of ICH and OAC-ICH was 34.8 (95% CI, 32.0–37.8) and 8.7 (95% CI, 2007 to 2009, resulting in 1 595,800 person-years. We age-adjusted the incidence rates to the Dutch and European population of 2008. For all rates, we calculated the 95% or 1-sided 97.5% Poisson confidence interval (95% CI or 97.5% CI), if applicable.

The absolute risk of OAC-ICH per year of OAC treatment was calculated by dividing the number of OAC-ICH cases by the total patient-years of OAC treatment, which was estimated with data provided in the annual reports of the anticoagulation clinics. See Methods in the online-only Data Supplement for details.

Conclusions—The annual incidences of ICH and OAC-ICH are relatively high in the Netherlands when compared with international literature. (Stroke. 2014;45:268-270.)

Key Words: anticoagulants ■ cerebral hemorrhage ■ epidemiology ■ incidence

A serious complication of oral anticoagulants (OAC) is the occurrence of an OAC-associated intracerebral hemorrhage (OAC-ICH). In the Netherlands, acenocoumarol and phenprocoumon are mainly used, and strict dose-regulation of OAC is performed by a nation-wide network of specialized anticoagulation clinics. Although it is thought that OAC-ICH is low because of strict dose-regulation, recent Dutch data on the adult incidence of OAC-ICH are scarce. The aim of this study is to estimate the annual adult incidence of ICH and OAC-ICH, as well as the risk of OAC-ICH in the Netherlands.

Methods

We retrospectively analyzed all consecutive adult (≥18 years) patients with a brain scan-confirmed nontraumatic ICH, seen in the emergency department, inpatient or outpatient clinic, in 3 hospitals of South-Limburg, the Netherlands, from 2007 to 2009 (Figure). Patients were selected using diagnosis-treatment codes retrieved from hospital Medical Registration Archives complemented with hospital stroke registries. OAC-ICH was defined as an ICH while on treatment with oral vitamin-K antagonists at admission. Recurrent ICH cases were included. The study was approved by the medical ethical committees of all the 3 hospitals.

The crude annual adult incidence rates of ICH and OAC-ICH were calculated by dividing the number of ICH or OAC-ICH cases by the total adult person-years at risk for ICH. Person-years at risk were calculated by dividing the number of ICH or OAC-ICH cases by the total person-years at risk for ICH. Person-years at risk for OAC-ICH were calculated by dividing the number of OAC-ICH cases by the total patient-years of OAC treatment, which was estimated with data provided in the annual reports of the anticoagulation clinics. See Methods in the online-only Data Supplement for details.

Results

We included 652 ICH cases in 617 patients; 588 (90.2%) patients had a first-ever ICH. Of all ICH cases, 168 (25.8%) were OAC associated and 153 of these (91.1%) were first-ever OAC-ICH. Aacenocoumarol was used by 134 (79.8%) patients, phenprocoumon was used by 20 (11.9%), and a combination of OAC with another antithrombotic drug was used by 14 (8.3%). Indications for OAC were atrial fibrillation (77.4%), cardiac valve prosthesis (71.1%), venous thrombosis (60.0%), peripheral artery disease (42.4%), and other indications (54.4%). Table 1 shows clinical characteristics of (OAC-)ICH cases.

Incidence of (OAC-)ICH

The adult Dutch age-adjusted annual incidence of ICH and OAC-ICH was 34.8 (95% CI, 32.0–37.8) and 8.7 (95% CI, 2007 to 2009, resulting in 1 595,800 person-years. We age-adjusted the incidence rates to the Dutch and European population of 2008. For all rates, we calculated the 95% or 1-sided 97.5% Poisson confidence interval (95% CI or 97.5% CI), if applicable.

The absolute risk of OAC-ICH per year of OAC treatment was calculated by dividing the number of OAC-ICH cases by the total patient-years of OAC treatment, which was estimated with data provided in the annual reports of the anticoagulation clinics. See Methods in the online-only Data Supplement for details.
7.3–10.3) per 100,000 person-years, respectively. The crude incidence rates and the age-adjusted rates of the European population of 2008 are presented in Table 2. For results on first-ever (OAC-)ICH incidence rates, see Table I in the online-only Data Supplement.

**Absolute Risk of OAC-ICH**

Total patient-years of OAC treatment in the study period was estimated at 36,494. Hence, the absolute risk of OAC-ICH was estimated at 0.46% per patient-year of OAC treatment.

**Discussion**

We found an adult Dutch age-adjusted annual ICH incidence of 34.8 (95% CI, 32.0–37.8) per 100,000 person-years. Recent data on ICH incidence in the Netherlands are scarce. The Dutch Rotterdam population cohort study showed a crude annual incidence of 80 ICH cases per 100,000 person-years in subjects aged >55 years. This is comparable with our study when selecting subjects aged >55 years (data not shown). The ICH incidence is relatively high in our study when compared with international studies. A meta-analysis summarizing all population-based data up to November 2008 showed a crude annual incidence of 24.6 ranging from 1.8 to 129.6 per 100,000 person-years. The heterogeneity between studies is high (eg, regarding hospital versus population-based studies, inclusion criteria, and organization of healthcare). We determined the adult incidence rate, whereas many studies reported life-time incidence. Besides methodological issues, lifestyle and genetic factors could also explain differences in the incidence rates.

In our study, a quarter of ICH were OAC related, which is relatively high when compared with previous studies in which the proportion of OAC-ICH ranges from 5% to 27%. Highest proportions are seen in more recent studies, which may reflect the rise in OAC use. Other factors could also be involved in explaining a high proportion of OAC-ICH in our study, such as poor INR monitoring or vulnerability to bleeding.

We estimated the absolute risk of OAC-ICH at 0.46% per patient-year OAC treatment. Although this is an estimation and a prospective study would be needed to determine an

### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>All ICH Cases</th>
<th>Non–OAC-ICH</th>
<th>OAC-ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>652</td>
<td>484 (74.2)</td>
<td>250 (51.7)</td>
<td>92 (54.8)</td>
</tr>
<tr>
<td>Sex, men</td>
<td>652</td>
<td>338 (51.8)</td>
<td>283 (60.6)</td>
<td>83 (50.9)</td>
</tr>
<tr>
<td>Age, median in y (IQR)</td>
<td>652</td>
<td>76.3 (66.6–83.0)</td>
<td>75.3 (63.2–82.0)</td>
<td>79.1 (72.6–84.2)*</td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
<td>633</td>
<td>154 (24.3)</td>
<td>92 (19.7)</td>
<td>62 (37.6)*</td>
</tr>
<tr>
<td>Prior ICH</td>
<td>652</td>
<td>64 (9.8)</td>
<td>49 (10.1)</td>
<td>15 (8.9)</td>
</tr>
<tr>
<td>Prior ischemic stroke or TIA</td>
<td>647</td>
<td>179 (27.7)</td>
<td>119 (24.8)</td>
<td>60 (35.9)*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>631</td>
<td>431 (68.3)</td>
<td>283 (60.6)</td>
<td>148 (90.2)*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>636</td>
<td>110 (17.3)</td>
<td>73 (15.4)</td>
<td>37 (22.8)*</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>626</td>
<td>260 (41.5)</td>
<td>177 (38.2)</td>
<td>83 (50.9)*</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>652</td>
<td>254 (39.0)</td>
<td>162 (33.5)</td>
<td>92 (54.8)*</td>
</tr>
</tbody>
</table>

Data are presented as number (percentages). ICH indicates intracerebral hemorrhage; IQR, interquartile range; n, number; OAC, oral anticoagulant associated; and TIA, transient ischemic attack.

*P<0.05 for the difference between non–OAC-ICH and OAC-ICH.
exact risk, it is within the range found in clinical trials using warfarin, in which the risk of OAC-ICH ranged from 0.3% to 0.6% per patient-year. However, it must be noted that ICH rates in trials may be lower than in common practice because of patient selection and controlled care.

We have conducted a hospital-based study in a well-demarcated study region with easily accessible hospital care and where patients with stroke are always referred on short notice. Hence, only few patients hospitalized outside the region and patients not seen in a hospital may have been missed. Study limitations include patient selection using diagnosis-treatment codes, which may result in missing incorrectly coded patients. We used stroke registries to limit this possibility. Second, patient-years of OAC treatment were estimated, which may have led to a slight over- or underestimation. Third, acenocoumarol or phenprocoumon were used, whereas warfarin is more common in international literature. However, bleeding risks between OAC types are similar.

Finally, South-Limburg has slightly poorer socioeconomic and lifestyle factors, which may negatively affect the representation of our data for the overall Dutch population. Notwithstanding the earlier raised methodological issues, we conclude that the adult annual incidence of ICH and the proportion of OAC-ICH in the Netherlands are relatively high when compared with previous studies, despite a nation-wide network of specialized anticoagulation clinics.

Disclosures
None.

Table 2. Annual Incidence Rates (Per 100,000 Person-Years) of (OAC-)ICH

<table>
<thead>
<tr>
<th>Age Groups, y*</th>
<th>Population at Risk (Person-Years)</th>
<th>ICH n</th>
<th>Rates (95% CI)</th>
<th>OAC-ICH n</th>
<th>Rates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–44</td>
<td>628,438</td>
<td>20</td>
<td>3.2 (1.9–4.9)</td>
<td>0</td>
<td>0 (0–0.6)†</td>
</tr>
<tr>
<td>45–54</td>
<td>315,607</td>
<td>31</td>
<td>9.8 (6.7–13.9)</td>
<td>0</td>
<td>0 (0–1.2)†</td>
</tr>
<tr>
<td>55–64</td>
<td>285,791</td>
<td>96</td>
<td>33.6 (27.2–41.0)</td>
<td>12</td>
<td>4.2 (2.2–7.3)</td>
</tr>
<tr>
<td>65–74</td>
<td>199,670</td>
<td>139</td>
<td>69.6 (58.5–82.2)</td>
<td>40</td>
<td>20.0 (14.3–27.3)</td>
</tr>
<tr>
<td>75–84</td>
<td>126,912</td>
<td>260</td>
<td>204.9 (180.7–231.3)</td>
<td>81</td>
<td>63.8 (50.7–79.3)</td>
</tr>
<tr>
<td>≥85</td>
<td>39,384</td>
<td>106</td>
<td>269.1 (220.4–325.5)</td>
<td>35</td>
<td>88.9 (61.9–123.6)</td>
</tr>
</tbody>
</table>

†Incidence adjusted to the age distribution of the NL in 2008. §Incidence adjusted to the age distribution of the EU in 2008.

CI indicates confidence interval; EU, European Union; ICH, intracerebral hemorrhage; n, number of (OAC-)ICH; NL, Netherlands; and OAC, oral anticoagulant associated.

References
Incidence of Oral Anticoagulant–Associated Intracerebral Hemorrhage in the Netherlands
Angel M.R. Schols, Floris H.B.M. Schreuder, Elisabeth P.M. van Raak, Tobien H.C.M.L. Schreuder, Fergus A. Rooyer, Robert J. van Oostenbrugge and Julie Staals

Stroke. 2014;45:268-270; originally published online November 7, 2013;
doi: 10.1161/STROKEAHA.113.003003

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/1/268

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/11/07/STROKEAHA.113.003003.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
ONLINE SUPPLEMENT

The Incidence of Oral Anticoagulant-Associated Intracerebral Hemorrhage in the Netherlands

AMR Schols; FHBM Schreuder; EPM van Raak; AHCML Schreuder; FA Rooyer; RJ van Oostenbrugge; J Staals

Methods

Patient selection
We retrospectively analyzed all consecutive adult (≥18 years) patients with a brain scan-confirmed non-traumatic ICH, seen in the emergency department, inpatient or outpatient clinic, in the three hospitals in the region South-Limburg, the Netherlands, from January 2007 until December 2009. Patients were selected using diagnosis-treatment codes retrieved from hospital Medical Registration Archives complemented with hospital stroke registries.

Study region
South-Limburg is a geographically well-demarcated area surrounded by international borders (Figure 1). We selected inhabitants from this region using the postal area code of their home address. Our study region comprises 141 postal area codes.

Statistics Netherlands provides annual averaged population numbers for designated regions. These numbers account for migration, births and deaths. The region of South-Limburg had 531,557, 531,547 and 532,696 inhabitants in 2007, 2008 and 2009 respectively, thus providing a total of 1,595,800 person-years at risk.

Exclusion criteria
Patients living outside of South-Limburg were excluded. Other exclusion criteria were traumatic intracerebral hemorrhage (ICH) or non-parenchymatous hemorrhage (e.g. subdural, epidural, subarachnoid hemorrhage, intraventricular hemorrhage without visible parenchymatous involvement), ischemic stroke with hemorrhagic transformation of the infarct zone (including hemorrhage after thrombolytic treatment) or hemorrhage associated with a brain tumor or encephalitis. We did not exclude other secondary causes for ICH (e.g. hemorrhage from arteriovenous malformations, cavernomas or thrombocytopenia) since this was not systematically studied in all subjects. Patients with non-accessible charts and/or scans were also excluded from analyses. Patients living in the region, who were hospitalized elsewhere and subsequently transferred to one of the participating hospitals, were included.

Data extraction of (first-ever) oral anticoagulant-associated ICH (OAC-ICH)
We recorded antithrombotic treatment (aspirin, acenocoumarol, phenprocoumon, dipyridamole, clopidogrel, heparins, or combinations) at the time of admission. OAC-ICH was defined as an ICH while on treatment with oral vitamin-K-antagonists. Recurrent ICH cases were included. First-ever (OAC-)ICH was defined as no ICH in the medical history and the first ICH during the study period.

Data analysis
The crude annual adult incidence rates of ICH and OAC-ICH were calculated by dividing the number of ICH or OAC-ICH cases by the total adult person-years at risk for ICH. Person-years at risk were defined as the number of adult inhabitants in South-Limburg during 2007-2009, resulting in 1,595,800 person-years. We age-adjusted the incidence rates to the Dutch
and European population of 2008.\textsuperscript{2,3} For all rates we calculated the 95% or one-sided 97.5% Poisson confidence interval (95%-CI), if applicable. The absolute risk of OAC-ICH per year of OAC treatment was calculated by dividing the number of OAC-ICH cases by the total patient-years of OAC treatment. Data on the use of OAC were derived from the medical annual reports of the three anticoagulation clinics in the study region South-Limburg.\textsuperscript{4} These three anticoagulation clinics are situated at the three study hospitals and as such cover the study region completely. The annual reports provided the total number of patients using OAC during each year as well as the total number of newly enrolled patients in each year, but contained no exact information on treatment duration. Therefore, we had to estimate the patient-years of OAC treatment. First, we subtracted the number of newly enrolled patients from the total number of treated patients, resulting in the amount of “current users”. The “current users” were multiplied by a factor 0.8 to account for the fact that a proportion of the subjects would stop using OAC during the year (e.g. a six-month indication for deep venous thrombosis, side-effects making it necessary to cease OAC therapy or mortality while using OAC). The factor 0.8 was based upon more detailed information from the annual reports of 2010 and 2011, which for the first time report patient-years of OAC treatment. Secondly, we multiplied the number of newly enrolled patients by a factor 0.5, accounting for the fact that newly enrolled patients were treated only part of the year. Thus, the equation could be summarized as:

\[0.8 \times (\text{total number OAC users} - \text{newly enrolled users}) + 0.5 \times (\text{newly enrolled users})\]

In the study period 2007-2009, a total of 49,418 patients were treated with OAC, of which 10,136 subjects were newly enrolled.\textsuperscript{4} Using the equation above, this results in an estimated 36,494 patient-years of OAC treatment.

Statistical analyses were performed using Stata/SE version 11.2 and IBM SPSS statistics version 20.

\textit{Ethical considerations}

The study was approved by the medical ethical committees of all three hospitals.

\textbf{Supplementary references}

Supplementary table I: Annual incidence rates (per 100,000 person-years) of first-ever (OAC-)ICH.

<table>
<thead>
<tr>
<th>Age groups*</th>
<th>Population at Risk (person-years)</th>
<th>N</th>
<th>Rates (95%-CI)</th>
<th>N</th>
<th>Rates (95%-CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-44 years</td>
<td>628,438</td>
<td>17</td>
<td>2.7 (1.6-4.3)</td>
<td>0</td>
<td>0 (0-0.6)†</td>
</tr>
<tr>
<td>45-54 years</td>
<td>315,607</td>
<td>30</td>
<td>9.5 (6.4-13.6)</td>
<td>0</td>
<td>0 (0-1.2)†</td>
</tr>
<tr>
<td>55-64 years</td>
<td>285,791</td>
<td>91</td>
<td>31.8 (25.6-39.1)</td>
<td>12</td>
<td>4.2 (2.2-7.3)</td>
</tr>
<tr>
<td>65-74 years</td>
<td>199,670</td>
<td>122</td>
<td>61.1 (50.7-73.0)</td>
<td>36</td>
<td>18.0 (12.6-25.0)</td>
</tr>
<tr>
<td>75-84 years</td>
<td>126,912</td>
<td>229</td>
<td>180.4 (157.8-205.4)</td>
<td>72</td>
<td>56.7 (44.4-71.4)</td>
</tr>
<tr>
<td>≥85 years</td>
<td>39,384</td>
<td>99</td>
<td>251.4 (204.3-306.1)</td>
<td>33</td>
<td>83.8 (57.7-117.7)</td>
</tr>
<tr>
<td>All ages*</td>
<td>1,595,800</td>
<td>588</td>
<td>36.9 (33.9-40.0)</td>
<td>153</td>
<td>9.6 (8.1-11.2)</td>
</tr>
<tr>
<td>Age-adjusted rate NL‡</td>
<td></td>
<td></td>
<td>31.4 (28.7-34.3)</td>
<td></td>
<td>8.0 (6.6-9.5)</td>
</tr>
<tr>
<td>Age-adjusted rate EU.§</td>
<td></td>
<td></td>
<td>33.9 (31.1-36.9)</td>
<td></td>
<td>8.8 (7.4-10.4)</td>
</tr>
</tbody>
</table>

We included 652 ICH cases in 617 patients. The medical history stated an ICH in 29 patients (4.7%) and 35 patients (5.7%) had a recurrent ICH during the study period, resulting in 588 first-ever ICH cases. Five patients with an uncertain history of prior ICH were included as first-ever ICH. Of all first-ever ICH cases, OAC-ICH occurred in 153 cases (26.0%).

Abbreviations: CI, confidence interval; N, number of ICH; ICH, intracerebral hemorrhage; OAC, oral anticoagulant-associated

* = crude incidence rates per 100,000 person-years
† = one-sided 97.5%-CI
‡ = rate adjusted to the age distribution of the Netherlands (NL) in 2008
§ = rate adjusted to the age distribution of the European Union (EU) in 2008