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Effect of Increased Warfarin Use on Warfarin-Related Cerebral Hemorrhage

A Longitudinal Population-Based Study

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Background and Purpose—Warfarin use has rapidly increased with the aging of the population. We investigated the temporal trends in the incidence and outcome of warfarin-related intracerebral hemorrhages (ICHs) in a defined population.

Methods—We identified all subjects with first-ever primary ICH during 1993 to 2008 among the population of Northern Ostrobothnia, Finland. The number of warfarin users was obtained from the national register of prescribed medicines kept by the Social Insurance Institution of Finland. We calculated the annual incidence of warfarin-related ICHs, 28-day case fatality, and deaths from the primary bleed.

Results—The proportion of warfarin users among the population increased 3.6-fold from 0.68% in 1993 to 2.28% in 2008. Of a total of 982 patients with ICH, 182 (18.5%) had warfarin-related ICH. One-year survival rate after onset of stroke was 35.2% among warfarin users and 67.9% among nonusers. The annual incidence ($P=0.062$) and 28-day case fatality of warfarin-related ICHs ($P=0.002$) decreased during the observation period. Warfarin users were older (mean difference 6.6; 95% CI, 5.0 to 8.1; $P<0.001$) than nonusers. Admission international normalized ratio values above the therapeutic range (2.0 to 3.0) decreased through the observation period, suggesting improved control of anticoagulant therapy over time.

Conclusions—The annual incidence and case fatality of warfarin-related ICHs decreased, although the proportion of warfarin users almost quadrupled in our population. **(*Stroke*. 2011;42:2431-2435.)**

Key Words: epidemiology ■ intracerebral hemorrhage ■ outcome ■ warfarin

Warfarin is used to prevent cardioembolism resulting from atrial fibrillation and mechanical heart valves as well as for primary prevention and treatment of deep venous thrombosis and pulmonary embolism. The use of warfarin has rapidly increased with the aging of the population,[1,2] and the increase in use seems to enhance the risk for severe hemorrhagic complications, including intracerebral hemorrhage (ICH).[3–6] A recent study from the United States showed a marked increase in the incidence of ICH concomitant with an increase of oral anticoagulant use.[6] Although this study screened both hospitalized people and decedents identified by coroners, we still lack reliable population-based data to show the effect of increased warfarin use on morbidity and mortality from ICH.

In Finland, >1400 new cases of spontaneous ICH are recorded every year.[7] The number of warfarin-related bleedings has not been reported, but the use of warfarin has steeply increased, as pointed out by a recent report.[2] Therefore, we conducted a population-based study to explore the association between warfarin use and the occurrence of warfarin-related primary ICH (WA-ICH) in the population of Northern Ostrobothnia. We wanted to describe the effects of the increasing use of warfarin on both mortality and morbidity from primary ICH. We tested whether increased use of warfarin had resulted in an increased incidence of WA-ICHs.

Methods

The study protocol was approved by the ethics committee of the Northern Ostrobothnia Hospital District. We identified all subjects with primary ICH associated with oral anticoagulant use from January 1, 1993, through December 31, 2008, among the population of Northern Ostrobothnia, Finland. The study included all patients admitted to Oulu University Hospital, which is the only hospital serving patients with acute stroke in the area (population 1993 to 2008, 356 026 to 389 671). ICH was verified by a brain CT scan on admission in all cases. We excluded patients not living in the hospital's catchment area; those who had a brain tumor, aneurysm, vascular malformation, hematologic malignancy, hemophilia, or head trauma; and those who had been using an anticoagulant other than warfarin. We also identified the subjects who had died from ICH without being admitted to our hospital by collecting data from death records obtained from the Causes of Death Register (Statistics Finland). The register collects the death certificates of all decedents

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in Finland by using personal social security numbers. These data included the use of anticoagulants by the subjects at the time of death. Seven patients died outside of the hospital, and all of them were on warfarin. All except 1 of these cases was verified by autopsy. The cause of death was primary bleed if ICH was registered as the immediate cause of death in the death certificate or autopsy report.

The annual proportions of warfarin users among all subjects living in Northern Ostrobothnia and the whole Finnish population were obtained from the national register of prescribed medicines kept by the Social Insurance Institution of Finland. We calculated the annual prevalences of warfarin use in Northern Ostrobothnia, the annual numbers of warfarin-associated new ICH cases per 1000 warfarin users, and the annual 28-day case fatality rates and death rates due to primary bleeds among these subjects. We observed similar case-fatality rates of primary ICH as has been observed in other studies from Finland. The incidence of primary ICH (17/100 000) was comparable to observations for the whole population of Finland.[7]

Information about previous diseases, blood pressure histories, and use of anticoagulants was extracted from the hospital records. Data were extracted from the forensic autopsy charts of those who had died on the scene. The subjects were considered to be hypertensive if their blood pressure readings preceding the index stroke had repeatedly exceeded 160/90 mm Hg in accordance with the World Health Organization/International Society of Hypertension statement[8] or if they were taking antihypertensive medication. The patients were recorded as having diabetes mellitus if they used oral hypoglycemic agents or insulin. Cardiac disease included myocardial infarction, coronary artery disease, heart failure, and atrial fibrillation.

The patient's clinical condition on admission was assessed using the Glasgow Coma Scale score.[9] All CT scans (and other imaging studies) were analyzed and the locations and volumes of hematomas measured by experienced neuroradiologists blinded to the case history of each patient, except for the time of surgery. Because this project was an ongoing process, 2 different methods were used to measure ICH volume over the years. The majority were measured using an accurate planimetric method[10–12] but a minority (a small part of those from year 2004 on) by the ABC/2 method, which offers reasonable approximation of hematoma volume in WA-ICH and non-WA-ICH.[13] Secondary structural abnormalities were searched for by follow-up brain imaging (CT or MRI) 2 to 3 months after the bleed. Angiography was performed immediately if aneurysmal bleeding was suspected. To rule out structural abnormalities causing the hemorrhage, a control CT was done on 58%, CT angiography on 18%, digital subtraction angiography on 18%, MR angiography on 8%, and MRI on 3% of survivors.

Categorical variables were compared by the Pearson χ^2 test. Univariate association of continuous variables was tested by Spearman rank correlation coefficients. Each patient was followed to death or until 1 year after ICH. Cumulative survival rates were estimated by the Kaplan-Meier product-limit method, and the curves of the different groups were compared by the log-rank test. Analyses of variance and covariance were used to explore the interactions among age, use of warfarin, and year of stroke onset. Logistic regression analysis was used to determine ORs and 95% CIs of significance of variables in predicting case-fatality. The following variables were tested by the forward stepwise method: age; sex; history of hypertension, cardiac disease, and diabetes; and use of warfarin. The test for significance was based on changes in log (partial) likelihood. A 2-tailed probability value of <0.05 was considered to be statistically significant.

Results

We identified altogether 982 subjects with first-ever primary ICH among the population of Northern Ostrobothnia from 1993 through 2008. Of them, 182 (18.5%) were on warfarin therapy (175 were admitted to the hospital and 7 died on the scene), whereas 800 (none died on the scene) were not. Their characteristics are shown in Table 1. Warfarin users were significantly older (mean age difference, 6.6 years; 95% CI, 5.0 to 8.1; $P<0.001$), had more frequently cardiac disease and diabetes, and showed larger hematomas on admission than nonusers. No significant differences were observed in Glasgow Coma Scale scores and history of hypertension. Indications for warfarin use among the patients with ICH were atrial fibrillation (60%), cerebral infarction (14%), former thromboembolism (11%), cardiac disease (6%), prosthetic valve (5%), and other or unknown (4%). Nine of the subjects were on both aspirin and warfarin. Those being on both aspirin and warfarin did not have either larger hematomas on admission nor more significant hematoma growth after admission compared with other patients.

Table 1. Characteristics of 982 Subjects With Primary ICH

Characteristics	Warfarin Users (n=182)	Nonusers of Warfarin (n=800)	Total (n=982)
Men, no. (%)	102 (56.0)	426 (53.3)	528 (53.8)
Mean age, y (SD)	74.4 (8.8)*	67.9 (12.6)	69.1 (12.3)
Median GCS score on admission‡	13 (7, 15)	14 (10, 15)	14 (10, 15)
Mean hematoma volume (SD)	47.8 (58.0)*	29.6 (37.0)	32.9 (42.1)
Mean INR (SD)	3.1 (1.2)*	1.1 (0.2)	1.5 (1.0)
Risk factors, no. (%)			
Diabetes	45/179 (25.1)†	125/799 (15.6)	170/978 (17.4)
Cardiac disease§	133/180 (73.9)*	251/798 (31.5)	384/978 (39.3)
Hypertension	115/178 (64.6)	500/800 (62.5)	615/978 (62.9)

GCS indicates Glasgow Coma Scale; INR, international normalized ratio; SD, standard deviation; ICH, intracerebral hemorrhage.

*$P<0.001$ for difference between warfarin users and control subjects.

†$P=0.002$ for difference between warfarin users and control subjects.

‡Twenty-fifth and 75th percentiles in parentheses.

§Including previous myocardial infarction, coronary artery disease, heart failure, and atrial fibrillation.

Those not on warfarin had a significantly ($P<0.001$) better 1-year survival rate (67.9% versus 35.2%) than those who had been on warfarin (Figure 1). The case-fatality rates of WA-ICHs were 54.4%, 61.1%, and 64.8% for the first 28, 90, and 365 days, respectively. The corresponding figure for ICHs unrelated to warfarin use were 23.4%, 27.6%, and 32.1%. The 28-day case-fatality rate of warfarin users (54.4%) was significantly higher ($P<0.001$) than that of nonusers (23.4%). A marked difference between the death rates developed already during the first week after stroke onset. Thereafter, the curves were parallel, showing no further increase in the death rate of warfarin users compared with nonusers. A logistic regression analysis showed that use of warfarin, older age, and presence of cardiac disease or diabetes were independent predictors for 28-day case-fatality (Table 2). Age and use of warfarin were also significant predictors for immediate (2-day) mortality.

Crude data of warfarin use and ICHs among the general population are shown in Table 3. The number of subjects using warfarin increased year by year. As a result, the prevalence of users was almost 4-fold in 2008 compared with

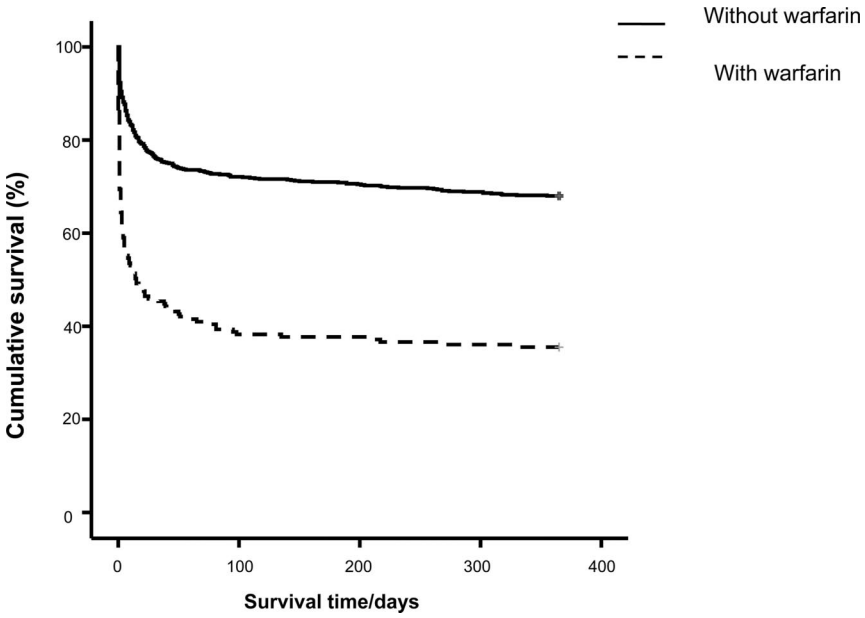

Figure 1. Survival of subjects with ICH at the time of being on warfarin therapy (n=182) compared with those not on warfarin (n=800). There is a significant difference between the survival curves ($P<0.001$, log-rank test). ICH indicates intracerebral hemorrhage.

1993. A similar increase occurred among the whole Finnish population during these years (data not shown), and the prevalence of warfarin users in Northern Ostrobothnia followed that development. However, the number of WA-ICHs did not increase; rather, a modest decrease was observed, whereas the incidence of ICHs not related to warfarin use remained constant. The annual 28-day case-fatality rates also seemed to decrease among warfarin users, whereas it remained constant among nonusers.

Figure 2 illustrates the annual increase of warfarin use in relation to the incidence of WA-ICHs and the annual 28-day mortality rates due to WA-ICHs. The incidence of WA-ICHs did not follow the annual prevalence of warfarin use in Northern Ostrobothnia. There was a negative correlation (Spearman rank −0.477; $P=0.062$) between the annual prevalence of warfarin use and the incidence of WA-ICHs during the observation period and a significant ($P=0.041$) linear-by-linear association between the increase in the prevalence of warfarin use and the decrease of WA-ICH incidence. There was also a significant negative correlation between the annual 28-day mortality rates of WA-ICHs and the annual prevalence of warfarin use (Spearman rank −0.779; $P=0.002$) and a significant ($P=0.012$) linear-by-linear association between the increase in the prevalence of warfarin use and the decrease of WA-ICH mortality. Similar findings were obtained from a comparison of deaths due to primary bleed instead of case-fatality (Spearman rank −0.799; $P<0.001$).

To explain the lower occurrence and improved outcome of WA-ICHs, we explored the subjects' age as well as the admission hematoma volumes and international normalized ratios (INRs) as potential confounding factors. The subjects were older year by year (Spearman rank 0.079; $P=0.013$), but there was no significant difference between subjects with and without WA-ICH. Those with ICH unrelated to warfarin also were older over time. However, the increase in age by year

Table 2. Adjusted Multivariate Logistic Regression Analysis for 28-Day Case-Fatality*

Multivariate Analysis	OR (95% CI)	*P*
Use of warfarin	2.502 (1.728–3.624)	0.000
Age per y	1.028 (1.013–1.044)	0.000
Cardiac disease	1.714 (1.224–2.400)	0.002
Diabetes	1.555 (1.062–2.275)	0.023
Hypertension	0.770 (0.558–1.061)	0.110

OR indicates odds ratio; CI, confidence interval.
*Adjusted for sex.

Table 3. Use of Warfarin, WA-ICH Mortality Rate per 1000 Users and Non-WA-ICH Mortality Rate per 1000 Population

Year	Population, No.	No. of Users	Percentage of Users, %	WA-ICH Mortality Rate*	Non-WA-ICH Mortality Rate†
1993	356 026	2235	0.63	2.24	0.04
1994	356 026	2876	0.81	1.04	0.03
1995	361 067	3345	0.93	3.29	0.03
1996	362 850	3741	1.03	2.14	0.03
1997	364 046	4164	1.14	0.72	0.06
1998	364 981	4450	1.22	1.80	0.02
1999	366 526	4855	1.32	2.27	0.02
2000	369 399	5295	1.43	1.51	0.03
2001	372 005	5895	1.58	0.68	0.04
2002	373 868	6195	1.66	0.81	0.02
2003	375 760	5900	1.57	0.85	0.03
2004	378 679	6291	1.66	0.48	0.03
2005	381 724	6792	1.78	1.03	0.04
2006	384 280	8021	2.09	1.00	0.03
2007	386 972	8384	2.17	0.48	0.02
2008	389 671	8886	2.28	0.68	0.04

WA-ICHs indicates warfarin-related intracerebral hemorrhages.
*WA-ICH mortality rate per 1000 users.
†Non-WA-ICH mortality rate per 1000 people.

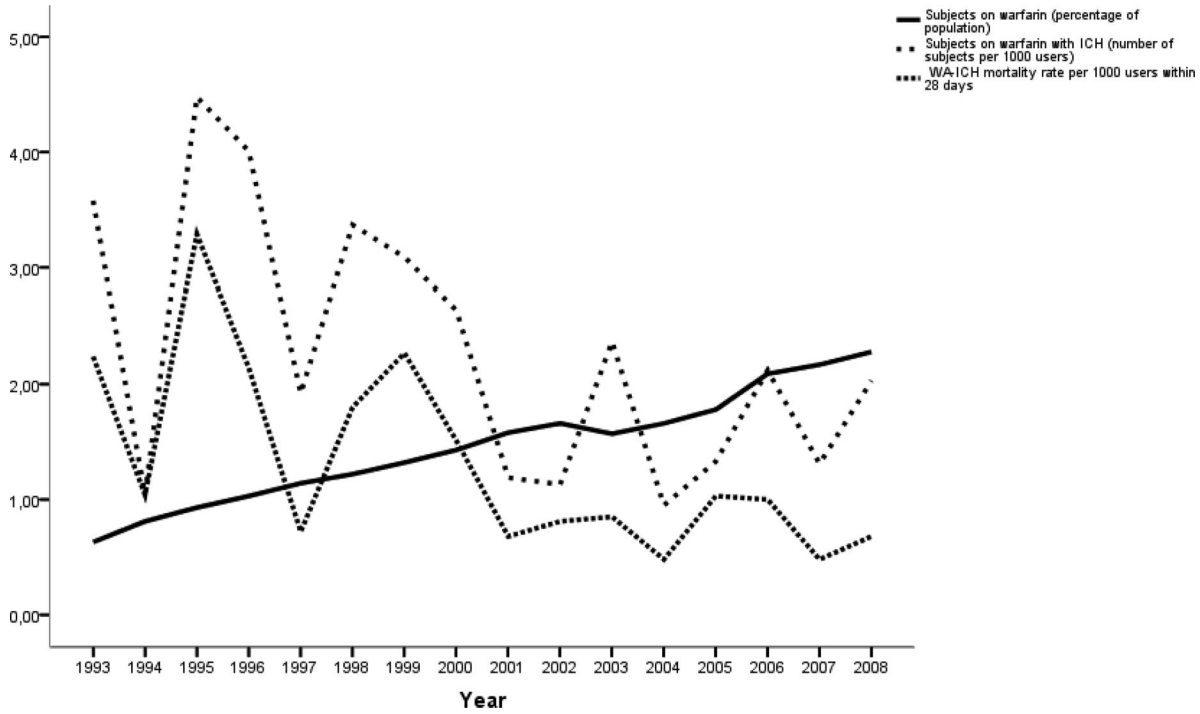

Figure 2. Annual increase of warfarin use in relation to the incidence of WA-ICHs and the annual 28-day mortality rates due to WA-ICHs. WA-ICHs indicates warfarin-related intracerebral hemorrhages.

was slightly steeper among those with WA-ICH ($P=0.059$). Hematomas were slightly smaller toward the end of the observation period, but there was no difference between the groups. INR values were dichotomized into those within the therapeutic range (2.0 to 3.0) and those above this range. We observed fewer INR values above the therapeutic range at the end of the observation period compared with the early years ($P=0.043$), suggesting improved control of anticoagulant therapy over time (improved coagulation monitoring). The 28-day case-fatality rate was 61.3% among those who had INR >3.0 and 45.6% among those with INR <3.0 ($P=0.051$). Patients with INR >3 did not differ from other warfarin patients by age, sex, and presence of diabetes, hypertension, or cardiac disease. There was no significant correlation between age and INR on admission among those being on warfarin.

Discussion

Warfarin use almost quadrupled from 1993 to 2008 among our population. However, the incidence of WA-ICHs as well as case-fatality among warfarin users did not increase but rather decreased. By contrast, the annual incidence of new cases of primary ICH among nonusers and their case-fatality remained constant during the observation period.

Our findings contrast with those of a study from the United States, which showed a marked increase in the incidence of ICH related to oral anticoagulant therapy concomitant to an increase of warfarin use among elderly people.[6] The authors speculated that their alarming observation may be due to a disproportionate increase in warfarin use among elderly people at high risk for bleeding. There were methodological differences between the studies. We compared official national statistics of warfarin use (the number of subjects who used warfarin) with the incidence of strokes among a defined population, whereas Flaherty et al[6] used counting units, which are not equivalent to the number of warfarin users, and the population in their study was not as completely ascertained as ours. However, we believe that these small methodological differences do not explain the difference in observations.

In our population, the proportion of WA-ICHs was initially rather high (18.5%) but tended to decrease year by year (Figure 2). Other studies have reported lower rates (5% to 17%).[6,14–16] We believe that the selection of patients for warfarin therapy and the monitoring of warfarin treatment were not optimal in our country during the early part of the study period but subsequently improved. This assumption is supported by the finding that our patients had less often INR values above the therapeutic range at the end of the observation period compared with the early years. Subjects with INR >3.0 have greater hematoma volumes and higher mortality rates than others.[17–19] Management of warfarin treatment in elderly patients is hampered by drug interactions and the need for scrupulous dose adjustment to maintain the desired INR value.[20] We did not observe more expeditious arrival to the hospital nor were hematoma volumes significantly larger during the earlier years. However, we started to use prothrombin complex concentrate and vitamin K for the reversal of INR for patients with WA-ICH in 2004. This may have diminished the case-fatality but does not explain the decreased incidence of WA-ICH over time. Neither did surgical treatment of ICH because the number of patients operated did not show either a trend to increase nor decrease during the observation period. Operations were performed with similar frequency for those with and without warfarin at onset of stroke. Moreover, the prevention and treatment of complica-

tions such as thromboembolism and cardiac problems have advanced in the 21st century parallel to the increase of warfarin use.

Case-fatality rates among warfarin users were 2-fold compared with nonusers, the difference being mainly due to the larger hematomas of warfarin users already on admission. Warfarin use was a significant and independent predictor for immediate (2-day) and 28-day case-fatality together with advanced age. Cardiac disease and diabetes were also significant and independent predictors for 28-day case-fatality. A history of hypertension did not predict case-fatality but seemed to protect against death within 1 year (data not shown).

Some other studies failed to reveal a significant difference in hematoma volume between warfarin versus WA-ICHs, but these studies were not population-based and thus subject to case selection.[13,21,22] The crucial point in improving the outcome of WA-ICHs is certainly the prevention of hematoma growth.[22,23] Accordingly, all subjects with ICH should be expedited to the nearest hospital and measures to prevent hematoma growth should be immediately used.

There are several limitations in our study. First, the patients who died before follow-up radiological examinations were performed may have had undetected structural abnormalities contributing to their stroke, because autopsies were not done for all of these cases. Moreover, 1 of the cases who died on the scene was not autopsied. Second, the statistics kept by the Social Insurance Institution of Finland were not quite complete for the first 2 years of the study period, which may have caused underestimation of warfarin use. Third, it is not known whether all those subjects reported by the Social Insurance Institution of Finland as warfarin users had really used the medicine for a whole year or only for a shorter period. However, as far as we know, our study is the first from Europe to describe associations between warfarin use and morbidity and mortality from ICH in a defined population over time. The strengths of the study include the reliable radiological analysis ruling out secondary abnormalities, the statutory registration of dead certificates in Finland, and the population-based case ascertainment.

It has long been known that ICH associated with oral anticoagulant use carries a high (52% to 73%) mortality risk due to early hematoma growth.[3,22] Concern about an increase in morbidity is justified because warfarin use among elderly people has markedly increased. Therefore, we conducted a population-based study of this important issue. We conclude that, despite the increasing use of warfarin, the annual risk of users to experience a fatal ICH has not increased among the population of Northern Ostrobothnia; rather, it has decreased.

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None.

References

1. Quintero-González JA. Fifty years of clinical use of warfarin. *Invest Clin*. 2010;51:269–287.
2. Virjo I, Mäkelä K, Aho J, Kalliola P, Kurunmäki H, Uusitalo L, et al. Who receives anticoagulant treatment with warfarin and why? A population-based study in Finland. *Scand J Prim Health Care*. 2010;28:237–241.
3. Hart RG, Boop BS, Anderson DC. Oral anticoagulants and intracranial hemorrhage. Facts and hypotheses. *Stroke*. 1995;26:1471–1477.
4. Lakshminarayan K, Anderson DC, Herzog CA, Qureshi AI. Clinical epidemiology of atrial fibrillation and related cerebrovascular events in the United States. *Neurologist*. 2008;14:143–150.
5. Kucher N, Castellanos LR, Quiroz R, Koo S, Fanikos J, Goldhaber SZ. Time trends in warfarin-associated hemorrhage. *Am J Cardiol*. 2004;94:403–406.
6. Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology*. 2007;68:116–121.
7. Meretoja A, Roine RO, Kaste M, Linna M, Juntunen M, Erilä T, et al. Stroke monitoring on a national level. PERFECT Stroke, a comprehensive, registry-linkage stroke database in Finland. *Stroke*. 2010;41:2239–2246.
8. Whitworth JA, World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens*. 2003;21:1983–1992.
9. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2:81–84.
10. Saloheimo P, Juvela S, Riutta A, Pyhtinen J, Hillbom M. Thromboxane and prostacyclin biosynthesis in patients with acute spontaneous intracerebral hemorrhage. *Thromb Res*. 2005;115:367–373.
11. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24:987–993.
12. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, et al. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke*. 1996;27:1304–1305.
13. Sheth KN, Cushing TA, Wendell L, Lev MH, Romero JM, Schwab K, et al. Comparison of hematoma shape and volume estimates in warfarin versus non-warfarin-related intracerebral hemorrhage. *Neurocrit Care*. 2010;12:30–34.
14. Lawrentschuk N, Kariappa S, Kaye AH. Spontaneous intracerebral haemorrhages—warfarin as a risk factor. *J Clin Neurosci*. 2003;10:550–552.
15. Jeffree RL, Gordon DH, Sivasubramaniam R, Chapman A. Warfarin related intracranial haemorrhage: a case-controlled study of anticoagulation monitoring prior to spontaneous subdural or intracerebral haemorrhage. *J Clin Neurosci*. 2009;16:882–885.
16. Cordonnier C, Rutgers MP, Dumont F, Pasquini M, Lejeune J-P, Garrigue D, et al. Intra-cerebral haemorrhages: are there any differences in baseline characteristics and intra-hospital mortality between hospital-and population-based registries? *J Neurol*. 2009;256:198–202.
17. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. *Ann Neurol*. 1997;42:857–865.
18. Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. *Arch Intern Med*. 2004;164:880–884.
19. Flaherty ML, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, et al. Warfarin use leads to larger intracerebral hematomas. *Neurology*. 2008;71:1084–1089.
20. Gasse C, Hollowell J, Meier CR, Haefeli WE. Drug interactions and risk of acute bleeding leading to hospitalisation or death in patients with chronic atrial fibrillation treated with warfarin. *Thromb Haemost*. 2005;94:537–543.
21. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. *Neurology*. 2004;63:1059–1064.
22. Steiner T, Rosand J, Diringer M. Intracerebral hemorrhage associated with oral anticoagulant therapy. Current practices and unresolved questions. *Stroke*. 2006;37:256–262.
23. Aguilar MI, Hart RG, Kase CS, Freeman WD, Hoeben MBJ, Garcia RC, et al. Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. *Mayo Clin Proc*. 2007;82:82–92.