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Immediate Anticoagulation for Acute Cardioembolic Stroke is Still Popular in Selective Cases in Korea

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Background: Although current guidelines do not recommend immediate anticoagulation therapy (IAC) for acute ischemic stroke, judicious debates are still lingering on whether it might be done for acute cardioembolic stroke (ACES). We surveyed current practice patterns of anticoagulation therapy for ACES in Korea, and analyzed their related factors. **Methods:** Using a web-based system, all neurology staffs of training hospitals in Korea surveyed about when and how they commenced anticoagulation therapy in the hypothetical cases with ACES. **Results:** Of the 359 subjects invited, 281 responded to the e-mail, of whom 76 abstained from participating. The number of participants was therefore 205 (57.1%). Although a few physicians (4.4%) always performed IAC and some (10.7%) never did, most physicians made different decisions according to infarct size and presence of hemorrhagic transformation (HTr): IAC was performed more often in cases with medium-sized or small infarct than large one (68.2% vs. 35.9%, $P<0.001$), and in cases without HTr (68.6% vs. 34.9%, $P<0.001$). The most common method of administration was 'heparin followed by warfarin' (68.2%), and then 'warfarin alone' or 'warfarin with aspirin'. If IAC was not commenced, it resumed most commonly between 1 and 2 weeks after the onset (44.0%). **Conclusion:** Quite many neurologists in Korea did IAC in selective ACES, e.g. small sized infarction without HTr. Further studies are needed to prove the efficacy of IAC therapy in this selective population. (Korean J Stroke 2011;13:120-128)

KEY WORDS: Acute cardioembolic stroke, Atrial fibrillation, Anticoagulation, Heparin

Introduction

The annual risk of stroke is approximately 4.5% in patients with atrial fibrillation (AF).[1] This climbs to 12% in patients with AF and a previous history of stroke.[2] Many randomized controlled studies have clearly established that long-term oral anticoagulation can reduce the risk of stroke by about 65%.[3]

However, anticoagulation therapy (AC) is generally not recommended in acute cardioembolic stroke (ACES), despite the apparent benefits of long-term AC.[4] This is due to concern about the risk of hemorrhagic transformation (HTr). In previous studies with patients with ACES, early AC was shown to give no advantage in terms of long-term functional outcome, due to the benefits from stroke prevention being cancelled out by the increased risk of HTr.[5,6] HTr can result in unfavourable functional outcome, and is more common in patients with ACES than in patients with other stroke types.[7]

Despite these previous discouraging results, however, in clinical practice many physicians seem to favour immediate anticoagulation therapy (IAC) in ACES patients with small infarct. More research in this area is needed due to the lack of practice guidelines in the appropriate time and method for the

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commencement of AC. In this study, we conducted a survey of current AC practice in ACES. We also elicited factors related to the AC practice in the acute phase.

Methods

Study design and subjects

We surveyed 359 teaching hospital staff faculties (including instructors and professors) registered with the Korean Neurological Association as of May 2010, using a web-based online survey system.

E-mails were sent to all subjects, explaining the aims of the survey and requesting participation. When the recipients of the e-mail clicked on the button to participate in the survey, it was linked to the survey website so that they could respond to the survey. The survey results from the website were sent online to the investigators. If a recipient clicked on the button to decline survey participation, they could select a reason for declining before ending the survey: 1) not in charge of any acute stroke cases, 2) not interested in the topic, 3) others. The options chosen as the reasons for declining were also sent online to the investigators. We encouraged recipients who did not respond to the e-mail by sending two additional e-mails at 4 day intervals.

Survey Structure and Content

Preliminary questions

The list of survey participants was generated from the Korean Neurological Association database. Prior to the AC questions, the respondents were asked the following preliminary questions: 1) whether the participant was a stroke specialist (or whether stroke is a major field of interest); 2) the average number of monthly admitted acute stroke patients, 3) whether their hospital had a stroke unit.

Contents of Survey

The survey was structured for participants to select the treatment methods they would use in hypothetical cases.We first

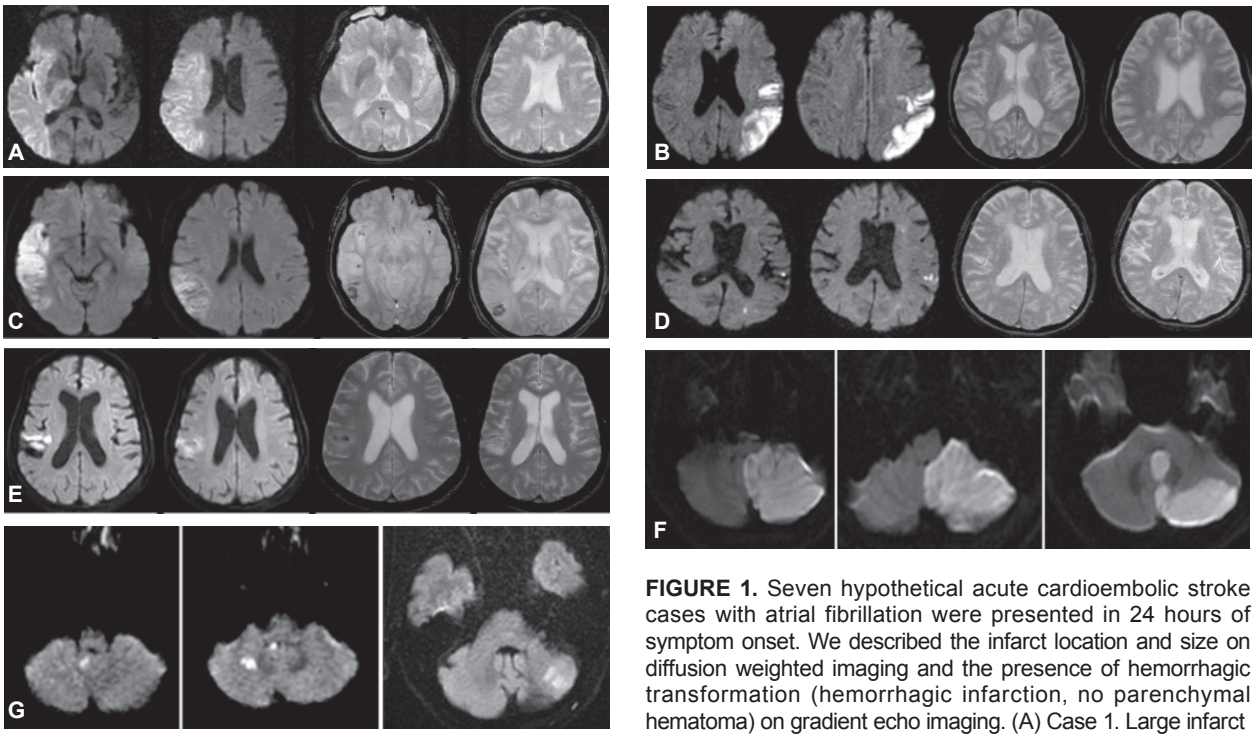

FIGURE 1. Seven hypothetical acute cardioembolic stroke cases with atrial fibrillation were presented in 24 hours of symptom onset. We described the infarct location and size on diffusion weighted imaging and the presence of hemorrhagic transformation (hemorrhagic infarction, no parenchymal hematoma) on gradient echo imaging. (A) Case 1. Large infarct involving a half or more of middle cerebral artery territory with no hemorrhagic transformation. (B) Case 2. Medium-sized infarct involving 1/2 to 1/3 of middle cerebral artery territory with no hemorrhagic transformation. (C) Case 3. Medium-sized infarct involving 1/2 to 1/3 of middle cerebral artery territory with no hemorrhagic transformation. (D) Case 4. Small infarct involving less than one third of middle cerebral artery territory with no hemorrhagic transformation. (E) Case 5. Small infarct involving less than one third of middle cerebral artery territory ith mild hemorrhagic transformation. (F) Case 6. Lare cerebellar infarct involving whole or near whole territory of posterior infererior cerebellar artery with no hemorrhagic transformation. (G) Case 7. Small cerebellar infarct involving less than whole or near whole territory of posterior infererior cerebellar artery with no hemorrhagic transformation.

described the seven hypothetical cases of ACES with AF according to the infarct location and size as seen on diffusion weighted imaging (DWI) in 24 hours of onset, and the presence of HTr (hemorrhagic infarction, no parenchymal hematoma) seen on gradient echo imaging (GRE) (Figure 1): Case 1) Large supratentorial infarct (>1/2 middle cerebral artery (MCA) territory) without HTr, Case 2) Medium sized supratentorial infarct (1/2-1/3 MCA territory) without HTr, Case 3) Medium sized supratentorial infarct with HTr, Case 4) Small supratentorial infarct (<1/3 MCA territory) without HTr, Case 5) Small supratentorial infarct with HTr, Case 6) Large cerebellar infarct (entire/nearly entire posterior inferior cerebellar artery (PICA) territory) without HTr, Case 7) Small cerebellar infarct (<PICA territory) without HTr. In each case, we asked whether they would commence IAC. If they did commence IAC, they chose the method of AC from the following: 1) heparin bridging (warfarin after administration of dose adjusted intravenous unfractionated heparin or low-molecular-weight heparin (LMWH)), 2) aspirin bridging (warfarin with aspirin), 3) warfarin alone. If they did not commence IAC (delayed anticoagulation, DAC), they chose the time of AC commencement from the following: 1) within 1 week of symptom onset, 2) between 1 and 2 weeks after onset, 3) >2 weeks after onset. Next, regarding one case with a past history of spontaneous intracerebral hemorrhage (ICH, Case 8), and one with multiple cerebral microbleeds (CMBs) detected on GRE (Case 9), we asked participants to select the following options on AC: 1) usually no AC, 2) usually AC regardless, 3) not applicable because no AC for any acute patients. The original questionnaire is presented in Appendix 1.

Analysis of survey results

For each case, we performed a descriptive analysis of the responses. We then analysed factors related to decisions to commence IAC, method of IAC administration, and commencement time in cases of DAC, by combining participants' responses for all cases. Parameters analysed were participant age, whether the participant was a stroke specialist, number of acute stroke patients, presence of a dedicated stroke unit, large infarct, HTr, and the infarct site. Age and the number of acute stroke patients were stratified as above and below the median value, and above and below 30 monthly patients, respectively. The infarct site was classified as supratentorial and cerebellar infarcts. Univariate analysis was performed using the chi-square test. We performed logistic regression analysis including all variables above for determination of independent factors related to the decision whether to start IAC. A P value of <0.05 was interpreted as statistically significant.

Results

Survey response rate and participant characteristics

Of the 359 subjects invited to participate, 281 (78.3%) responded to the e-mail, of whom 76 stated that they did not wish to participate. The number of participants was therefore 205 out of 359 (57.1%). For the reason for non-participation, 54 respondents (71.1%) selected 1) not in charge of any acute stroke cases, 11 (14.5%) selected 2) not interested in the study, 5 (5.0%) selected 3) others, and 6 (6.0%) did not specify.

The mean age of the 205 survey participants was 43.3±5.7 years, with 103 participants above the age of 43. Stroke was the specialty for 139 participants (67.8%). The number of monthly admissions for acute stroke exceeded 30 for 131 (63.9%) participants, and 103 (50.2%) stated that their hospital had a dedicated stroke unit.

Treatment methods for each case

The reported treatment method for each case is shown in detail in Table 1. For a large supratentorial or large cerebellar infarct without HTr (Cases 1 & 6), most participants chose DAC (64.4% and 63.9%, respectively), and many of them chose to commence AC between 1-2 weeks after onset (53.0%, 46.6%). On the other hand, for small or medium size infarcts without HTr (Cases 2, 4, & 7), most participants chose IAC (86.6-93.2%). However, DAC was preferred over IAC if even small or medium size infarcts were complicated by HTr. For IAC, the preferred method of administration was heparin bridging (68.2%), followed by warfarin alone (16.9%), and aspirin bridging (15.0%). Of those who practice acute AC, approximately 60% responded that they would commence treatment regardless of past history of spontaneous ICH or CMBs.

Factors related to IAC practice

Twenty two participants (10.7%) stated that they would initiate IAC in all 7 cases, and 9 (4.4%) replied that they would not commence IAC in any cases. The remainder, the majority of participants, decided whether to initiate IAC on a case by case

TABLE 1. Summary of participants' anticoagulation treatment method for each case

Case no.	Case description		Q1*	Q2†	Q1*	Q3‡
	Location and size of infarct	HTr	IAC?	How?	IAC?	When?
Case 1	Large supratentorial infarct (>1/2 of MCA)	No	Yes (35.6%)	H (71.2%) A (11.0%) W (17.8%)	No (64.4%)	~1wk (27.3%) 1~2wk (53.0%) 2wk~ (19.7%)
Case 2	Medium supratentorial infarct (1/2-1/3 of MCA)	No	Yes (86.3%)	H (71.8%) A (14.1%) W (14.1%)	No (13.7%)	~1wk (57.1%) 1~2wk (39.3%) 2wk~ (3.6%)
Case 3	Medium supratentorial infarct (1/2-1/3 of MCA)	Yes	Yes (24.4%)	H (66.0%) A (12.0%) W (22.0%)	No (75.6%)	~1wk (12.9%) 1~2wk (45.2%) 2wk~ (41.9%)
Case 4	Small supratentorial infarct (<1/3 of MCA)	No	Yes (93.2%)	H (66.5%) A (16.2%) W (17.3%)	No (6.8%)	~1wk (85.7%) 1~2wk (0.0%) 2wk~ (14.3%)
Case 5	Small supratentorial infarct (<1/3 of MCA)	Yes	Yes (45.4%)	H (57.0%) A (22.6%) W (20.4%)	No (54.6%)	~1wk (27.7%) 1~2wk (38.4%) 2wk~ (33.9%)
Case 6	Large cerebellar infarct (whole or near whole PICA)	No	Yes (36.1%)	H (71.6%) A (12.2%) W (16.2%)	No (63.9%)	~1wk (24.4%) 1~2wk (46.6%) 2wk~ (29.0%)
Case 7	Small cerebellar infarct	No	Yes (91.7%)	H (69.7%) A (14.4%) W (16.0%)	No (8.3%)	~1wk (76.5%) 1~2wk (23.5%) 2wk~ (0.0%)
				Q: Do you commence AC in acute phase?		
Case 8	Previous histroy of spontaneous ICH			Usually, do not (35.8%) Usually, do (60.3%) Not applicable (3.9%)		
Case 9	Multiple CMBs on GRE			Usually, do not (36.8%) Usually, do (60.8%) Not applicable (2.4%)		

* "Do you commence IAC?", † "Which method of administration do you favor?", ‡ "When do you start anticoagulation therapy?".
HTr: hemorrhagic transformation of hemorrhagic infarct type, IAC: immediate anticoagulation therapy, MCA: middle cerebral artery, PICA: posterior infererior cerebellar artery, H: heparin bridging, A: aspirin bridging, W: warfarin alone, AC: anticoagulation therapy, Q: question, ICH: intracerebral hemorrhage, CMBs: cerebral microbleeds, GRE: gradient echo image.

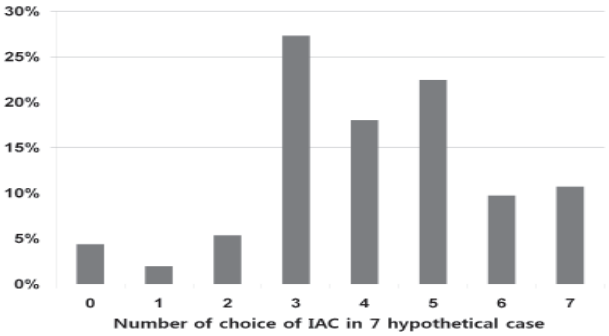

FIGURE 2. The minority of participants stated that they would initiate immediate anticoagulation therapy (IAC) in all 7 cases (25 participants, 10.7%) or not in any cases (9 participants, 4.4%). However, most participants decided whether to initiate IAC on a case by case basis.

basis (Figure 2).

We analysed factors related to the IAC decision (Table 2). Those who reported stroke to be their specialty were less likely to initiate IAC than those who did not (56.4% vs. 64.3%, P=0.005). IAC was less likely performed in cases with large infarcts and HTr (35.9% vs. 68.2%, P=0.001; 34.9% vs. 68.6%, P=0.001). Multivariable analysis revealed a statistically significant relationship between stroke specialty, large infarct, and presence of HTr with the decision to initiate IAC (P=0.001, P<0.001, P<0.001). Although IAC was more often chosen in cases with cerebellar than supratentorial infarction (63.9% vs. 57.0%), multivariable analysis did not show a statistically sig-

TABLE 2. Factors related to the decision to commence immediate anticoagulation therapy

Variables		IAC (-) n (%)	IAC (+) n (%)	Univariate	Multivariate
				P value	*P* value
Age (of the participant)	~42	293 (41.0)	421 (59.0)	0.995	0.789
	43~	296 (41.1)	425 (58.9)		
Stroke specialty	No	165 (35.7)	297 (64.3)	0.005	0.001
	Yes	424 (43.6)	549 (56.4)		
Number of acute stroke patients per month	~30	216 (41.7)	302 (58.3)	0.705	0.271
	31~	373 (40.7)	544 (59.3)		
Stroke unit	Absent	284 (39.4)	437 (60.6)	0.2	0.11
	Present	305 (42.7)	409 (57.3)		
Large infarct	No	326 (31.8)	699 (68.2)	<0.001	<0.001
	Yes	263 (64.1)	147 (35.9)		
HTr	No	322 (31.4)	703 (68.6)	<0.001	<0.001
	Yes	267 (65.1)	143 (34.9)		
Location of infarct	Supratentorium	441 (43.0)	584 (57.0)	0.016	0.593
	Cerebellum	148 (36.1)	262 (63.9)		
Total	1435	589 (41.0)	846 (59.0)		

IAC: immediate anticoagulation therapy, HTr: hemorrhagic transformation of hemorrhagic infarct type.

TABLE 3. Factors related to the method of anticoagulation administration

Variables		H. bridging n (%)	A. bridging n (%)	Warfarin alone n (%)	*P* value
Age (of the participant)	~42	297 (70.7)	53 (12.6)	71 (16.9)	0.144
	43~	281 (65.8)	74 (17.3)	72 (16.9)	
Stroke specialty	No	208 (69.6)	33 (11.0)	58 (19.4)	0.035
	Yes	370 (67.4)	94 (17.1)	85 (15.5)	
Number of acute stroke patients per month	~30	228 (75.0)	29 (9.5)	47 (15.5)	0.001
	31~	350 (64.3)	98 (18.0)	96 (17.6)	
Stroke unit	Absent	311 (71.2)	61 (14.0)	65 (14.9)	0.140
	Present	267 (65.0)	66 (16.1)	78 (19.0)	
Large infarct	No	473 (67.5)	110 (15.7)	118 (16.8)	0.435
	Yes	105 (71.4)	17 (11.6)	25 (17.0)	
HTr	No	490 (69.7)	100 (14.2)	113 (16.1)	0.105
	Yes	88 (60.7)	27 (18.6)	30 (20.7)	
Location of infarct	Supratentorium	394 (67.2)	91 (15.5)	101 (17.2)	0.677
	Cerebellum	184 (70.2)	36 (13.7)	42 (16.0)	
Total	848	578 (68.2)	127 (15.0)	143 (16.9)	

H: heparin, A: aspirin, HTr: hemorrhagic transformation of hemorrhagic infarct type.

nificant difference (*P*=0.593). No statistically significant correlations were seen between other variables and IAC.

We analysed factors related to the method of administration if IAC was initiated (Table 3). Participants who reported stroke to be their specialty tended to prefer aspirin bridging more than those who did not (*P*=0.035). Participants working in hospitals with ≥31 monthly acute stroke admissions also preferred aspirin bridging (*P*=0.001). No statistically significant correlations were seen between other variables and method of administration.

When DAC was initiated, those who reported stroke to be their specialty mostly preferred to start AC within one week than those who did not (Table 4). A significant correlation was also seen between large infarct and HTr with the decision when to commence AC.

TABLE 4. Factors related to commencement time of anticoagulation therapy in cases of delayed anticoagulation

Variables		~1 wk n (%)	1~2 wk n (%)	2 wk~ n (%)	*P* value
Age (of the participant)	~42	66 (22.5)	149 (50.9)	78 (26.6)	0.003
	43~	94 (31.8)	110 (37.2)	92 (31.1)	
Stroke specialty	No	22 (13.3)	71 (43.0)	72 (43.6)	<0.001
	Yes	138 (32.5)	188 (44.3)	98 (23.1)	
Number of acute stroke patients per month	~30	57 (26.4)	102 (47.2)	57 (26.4)	0.445
	31~	103 (27.6)	157 (42.1)	113 (30.3)	
Stroke unit	Absent	81 (28.5)	119 (41.9)	84 (29.6)	0.605
	Present	79 (25.9)	140 (45.9)	86 (28.2)	
Large infarct	No	92 (28.2)	128 (39.3)	106 (32.5)	0.025
	Yes	68 (25.9)	131 (49.8)	64 (24.3)	
HTr	No	109 (33.9)	146 (45.3)	67 (20.8)	<0.001
	Yes	51 (19.1)	113 (42.3)	103 (38.6)	
Location of infarct	Supratentorium	115 (26.1)	194 (44.0)	132 (29.9)	0.482
	Cerebellum	45 (30.4)	65 (43.9)	38 (25.7)	
Total	589	160 (27.2)	259 (44.0)	170 (28.9)	

HTr: hemorrhagic transformation of hemorrhagic infarct type.

TABLE 5. Factors related to the decision to commence anticoagulation therapy in acute cardioembolic infarct patients with previous spontaneous intracerebral hemorrhage (Case 8) or multiple cerebral microbleeds on gradient echo MR (Case 9)

Variables		Case 8: Do you commence AC in acute phase?				Case 9: Do you commence AC in acute phase?			
		Usually, do n (%)	Usually, do not n (%)	NA n (%)	*P* value	Usually, do n (%)	Usually, do not n (%)	NA n (%)	*P* value
Age (of the participant)	~42	61 (60.4)	38 (37.6)	2 (2.0)	0.224	65 (64.4)	36 (35.6)	0 (0.0)	0.042
	43~	62 (60.2)	34 (33.0)	7 (6.8)		59 (57.3)	38 (36.9)	6 (5.8)	
Stroke specialty	No	91 (65.5)	40 (28.8)	8 (5.8)	0.011	92 (66.2)	42 (30.2)	5 (3.6)	0.028
	Yes	32 (49.2)	32 (49.2)	1 (1.5)		32 (49.2)	32 (49.2)	1 (1.5)	
Number of acute stroke patients per month	~30	80 (61.1)	44 (33.6)	7 (5.3)	0.589	82 (62.6)	45 (34.4)	4 (3.1)	0.746
	31~	43 (58.9)	28 (38.4)	2 (2.7)		42 (57.5)	29 (39.7)	2 (2.7)	
Stroke unit	Absent	59 (58.4)	35 (34.7)	7 (6.9)	0.221	62 (61.4)	35 (34.7)	4 (4.0)	0.649
	Present	64 (62.1)	37 (35.9)	2 (1.9)		62 (60.2)	39 (37.9)	2 (1.9)	
Total	204	123 (60.3)	72 (35.3)	9 (4.4)		124 (60.8)	74 (36.3)	6 (2.9)	

AC: anticoagulation therapy, NA: not applicable.

We analysed factors related to acute AC practice in cases with a past history of spontaneous ICH, or with CMBs on GRE (Table 5). In these cases, participants who reported stroke to be their specialty perform AC therapy less often (*P*=0.011, *P*=0.028). No statistically significant correlations were seen between other variables and acute AC in these cases.

Discussion

In this study, we found that staff faculties (including instructors and professors) of Korean training hospitals selectively initiate IAC according to infarct size and the presence of HTr on initial imaging. Notably, if the cerebral infarction was not large in size and not complicated by HTr, nearly 90% of respondents stated they would initiate IAC. When performing IAC, the preferred method of administration was heparin bridging. When IAC was not commenced, the preferred option was to start AC between 1-2 weeks after onset, although this varied with the size of infarct and the presence of HTr. In acute phase AC, most responded they would give AC regardless of a history of spontaneous ICH, or CMBs on GRE.

There have been few studies on AC in ACES. The Interna-

tional Stroke Trial, comparing the effects of aspirin and subcutaneous unfractionated heparin initiated within 48 hours, revealed that the group treated with heparin had a lower recurrence rate of ischemic stroke within 2 weeks, although this effect was offset by an increased incidence of cerebral hemorrhage.[6] However, it has been pointed out that this study has a number of limitations in that it was an open trial, with no clear definition for recurrent stroke, 50% of the heparin treated group were also taking 300 mg aspirin, some patients received heparin before CT scanning, and patients with severe stroke were not excluded. The Heparin in Acute Embolic Stroke Trial, where LMWH and aspirin were compared in acute cerebral infarct patients with AF, did not demonstrate superior efficacy for LMWH over aspirin.[5] This study excluded patients with a Scandinavian Stroke Scale score below 8. However, a treatment strategy based on infarct volume rather than neurologic severity score may be more reasonable.[8] Accordingly, even though these earlier studies claim no benefits for AC in ACES, this cannot be generalised due to the limitations of these studies. Also, questions continue to be raised about the benefits of selective AC in ACES patients with a low risk of HTr, e.g. small infarcts. In this study, the finding that most of our participants prefer IAC for small to medium sized cerebral infarcts with no HTr can be interpreted as high expectations for the benefits of selective AC.

Oral administration of warfarin takes several days until an adequate anticoagulation effect is achieved. Early in the course of warfarin therapy, there may be net procoagulant effect due to a transient reduction in vitamin K-dependent coagulation inhibitors.[9] Heparin bridging is therefore recommended when starting oral warfarin, to achieve a rapid and effective anticoagulation effect.[10] In this survey, most participants preferred heparin bridging when initiating IAC. However, a number of participants (30%) responded that they would not use heparin bridging, preferring aspirin bridging or warfarin alone. This can be interpreted as intent to slowly achieve an anticoagulation effect, reducing the possibility of HTr following ACES.

When IAC is not initiated, many responded that they would commence AC between 1-2 weeks after onset. There is no clear evidence to support this practice. In the European Atrial Fibrillation Trial, where secondary preventative effects of anticoagulants were shown in cerebral infarct patients with AF, 46% of patients in the anticoagulant therapy group commenced treatment within 2 weeks of onset.[2] Even though this study does not give a clear rationale for commencing AC in ACES within 2 weeks, it does show that many clinicians consider it desirable to do so.

There have been no studies of the efficacy and safety of AC in acute stroke patients with a history of spontaneous ICH. Perhaps reflecting the lack of evidence, many participants to this survey initiated AC in acute stroke despite a history of spontaneous ICH. However, we believe caution is required in administering acute AC in these patients. This is because, as demonstrated in our earlier study, a past history of spontaneous ICH increases the risk of HTr.[8] CMBs on GRE, along with spontaneous ICH, also suggest a haemorrhagic tendency, and have been identified as risk factors for subsequent ICH after an ischemic stroke.[11] However, there have been reports that CMBs, unlike spontaneous ICH, may not be related to HTr in acute cerebral infarction.[8,12] There is therefore no solid evidence as yet that CMBs are a contraindication for acute phase AC.

Analysis of factors related to AC practice revealed that stroke specialists were less likely to initiate IAC (56.4% versus 64.3%), and tended to prefer aspirin bridging (17.1% versus 11.3%), more than non-specialists. Also, when initiating DAC, stroke specialists were more likely to commence AC 2 or more weeks after onset (43.6% versus 31.1%), and tended to refrain from AC if there was a history of spontaneous ICH or CMBs were present (49.2% versus 28.8%, 49.2% versus 30.2%, respectively). This may be attributed to the tendency of stroke specialists to adhere to the current guidelines, which state that heparin is not effective in acute ischemic stroke, and aspirin is the gold standard. Despite these differences, stroke specialists nevertheless did initiate aggressive AC in the acute phase using heparin.

There are several points in this survey that require attention. Firstly, one might think our results do not adequately reflect the opinion of all our subjects considering the response rate was 57.1%. However, as the majority of the reasons for non-participants were either “not in charge of any stroke patients” or “not interested in the topic”, we can say that most staff members directly involved in acute stroke treatment have participated in this survey. Secondly, the survey results are not necessarily identical to actual AC practice. Clinicians may choose more conservative treatments for the safety of their actual patients, as opposed to survey results based on hypothetical cases. Thirdly, we simplified hypothetical cases according to the infarct location, size, and HTr. We did not consider other factors related to AC practice, such as AC therapy for prevention of deep vein

thrombosis. We also simplified antithrombotic therapy as heparin bridging, aspirin bridging, and warfarin alone. We did not consider the various regimens and titration schedules.

Despite the negative recommendations in the current guidelines, the high proportion of IAC therapy in acute cardioembolic stroke patients seen in this survey indicates that there are many questions to be answered in this area. In particular, many practitioners selectively initiate IAC according to the presence of HTr and the size of the cerebral infarction, studies are further required into the effectiveness of selective IAC treatment in patients with a low risk of HTr.

Conflicts of Interest

The authors have no financial conflicts of interest.

REFERENCES

1. Stern S, Altkorn D, Levinson W. Anticoagulation for chronic atrial fibrillation. *JAMA* 2000;283:2901-2903.
2. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) study group. *Lancet* 1993;342:1255-1262.
3. Benavente O, Hart R, Koudstaal P, Laupacis A, McBride R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2000:CD001927.
4. Adams HP, Jr., del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF. Guidelines for the early management of adults with ischemic stroke: a guideline from the American heart association/American stroke association stroke council, clinical cardiology council, cardiovascular radiology and intervention council, and the atherosclerotic peripheral vascular disease and quality of care outcomes in research interdisciplinary working groups: The American academy of neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007;38:1655-1711.
5. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. *Lancet* 2000;355:1205-1210.
6. Saxena R, Lewis S, Berge E, Sandercock PA, Koudstaal PJ. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the international stroke trial. *Stroke* 2001;32:2333-2337.
7. Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, Caso V, Micheli S, Bertolani L, Venti M, Palmerini F, Biagini S, Comi G, Previdi P, Silvestrelli G. Early hemorrhagic transformation of brain infarction: Rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. *Stroke* 2008;39:2249-2256.
8. Lee JH, Park KY, Shin JH, Cha JK, Kim HY, Kwon JH, Oh HG, Lee KB, Kim DE, Ha SW, Cho KH, Sohn SI, Oh MS, Yu KH, Lee BC, Kwon SU. Symptomatic hemorrhagic transformation and its predictors in acute ischemic stroke with atrial fibrillation. *Eur Neurol* 2010;64:193-200.
9. Sallah S, Thomas DP, Roberts HR. Warfarin and heparin-induced skin necrosis and the purple toe syndrome: Infrequent complications of anticoagulant treatment. *Thromb Haemost* 1997;78:785-790.
10. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin k antagonists: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;126:204S-233S.
11. Fan YH, Zhang L, Lam WW, Mok VC, Wong KS. Cerebral microbleeds as a risk factor for subsequent intracerebral hemorrhages among patients with acute ischemic stroke. *Stroke* 2003;34:2459-2462.
12. Lee SH, Kang BS, Kim N, Roh JK. Does microbleed predict haemorrhagic transformation after acute atherothrombotic or cardioembolic stroke? *J Neurol Neurosurg Psychiatry* 2008;79:913-916.

APPENDIX 1. The original questionnaire

(Case 1 – 7)
심방세동(atrial fibrillation)이 동반된 환자들의 diffusion-weighted image(DWI)와 gradient-echo sequence(GRE)입니다. 현재 발병 후 24시간이 지난 시점이며, 항혈전제(항응고제 또는 항혈소판제) 치료의 다른 금기사항은 없습니다. 각각의 환자에서 선생님께서 주로 시행하는 항응고제 치료 방법을 선택해 주십시오.

1. 항응고제(anticoagulants: heparin or Warfarin) 투약을 바로 시작합니까?
   ① 네 (→ 2번 질문으로 가십시오)
   ② 아니오 (→3번 질문으로 가십시오)

2. 항응고제(anticoagulants) 투약을 바로 시작한다면 방법은?
   ① Unfractionated heparin 또는 LMWH으로 시작하여 Warfarin으로 바꾼다.
   ② Aspirin을 비롯한 항혈소판제와 함께 Warfarin을 시작한다.
   ③ 항혈소판제 동반 투여 없이 Warfarin을 시작한다.

3. 항응고제(anticoagulants) 투약을 바로 시작하지 않는다면, 언제 시작을 고려합니까?
   ① 발병 후 1주일 이내
   ② 발병 후 1주일 –2주일
   ③ 발병 후 2주일 이후

(Case 8, 9)
심방세동(atrial fibrillation)이 동반된 뇌경색으로 발병 후 24시간이 지난 시점이라고 가정하고, 다음 질문에 답 하십시오.

1. 급성기에 항응고제(anticoagulants) 치료를 하게 되는 상황에서 과거에 뇌출혈의 병력을 고려합니까?
   ① 과거에 뇌출혈이 있는 경우에는 대개 항응고제(anticoagulants) 치료를 하지 않는다.
   ② 과거에 뇌출혈 여부와 상관없이 대개 항응고제(anticoagulants) 치료를 한다.
   ③ 급성기에 전혀 항응고제(anticoagulants) 치료를 하지 않기 때문에 해당 없음.

2. 급성기에 항응고제(anticoagulants) 치료를 하게 되는 상황에서 GRE의 multiple cerebral microbleeds (CMBs) 여부를 고려합니까?
   ① Multiple CMBs가 있는 경우에는 대개 항응고제(anticoagulants) 치료를 하지 않는다.
   ② Multiple CMBs와 상관없이 대개 항응고제(anticoagulants) 치료를 한다.
   ③ 급성기에 전혀 항응고제(anticoagulants) 치료를 하지 않기 때문에 해당 없음.