

Acute Stroke Through the Perspective of a County Hospital: Problems and Opportunities

Bir İlçe Hastanesi Perspektifinden Akut İnme: Sorunlar ve Fırsatlar

Atay Vural

Besni State Hospital, Clinic of Neurology, Adıyaman, Turkey

Summary

Objective: Stroke is one of the most important public health issues worldwide, and ranks as the second highest cause of mortality in our country. Regular follow-up of stroke statistics and taking necessary precautions upon determining deficits by countries themselves constitute the most important way of improving prognosis and survival after stroke incidents. To achieve this goal, statistical studies should be performed at various levels of healthcare services. Tertiary care hospitals are the most suitable centers to perform these studies. However, the majority of the population receives service at secondary care centers where the actual statistics remain unknown. The objective of this study was to examine all patients with acute stroke who presented to a county hospital over a one-year period and obtain related data, discuss deficits, and provide solution-based recommendations.

Materials and Methods: All patients diagnosed as having acute stroke between July 2013-July 2014 were included in the study. Demographic, clinical, and radiologic data, in addition to the timing of presentation and baseline National Institutes of Health Stroke Scale (NIHSS) scores were recorded retrospectively, and patients were classified by the type of stroke. All patients were followed up for at least one year after the stroke incident and cumulative survival scores were calculated using Kaplan-Meier analysis. **Results:** Hemorrhagic stroke was determined in four out of 49 patients with acute stroke; the 45 patients diagnosed as having ischemic stroke were included in the study. Among these, 44.4% (n=20) of the patients presented within the first three hours of onset of clinical symptoms, 4.4% (n=2) presented at 3.-4.5 hours. Baseline NIHSS was 1-4 (mild stroke) in 50% (n=10) of patients who presented in the first three hours, and >5 (moderate or severe stroke) in 50% (n=10) of the remaining patients. The etiologic cause was embolic in 37.1% (n=13), large artery atherosclerosis in 20% (n=7), small vessel disease in 8.6% (n=3), arterial dissection 2.9% (n=1), and undetermined in 31.4% (n=11) of the patients. Twenty-one patients died during follow-up. The survival rates at one, three, and twelve months were 82.2%, 57.8%, and 53.3%, respectively. **Conclusion:** Treatment of patients with acute stroke is more difficult at secondary care centers compared with tertiary care centers. Precautions taken in developed countries should be adapted to our country to improve stroke prognosis nationwide.

Keywords: Stroke, public health, survival

Öz

Amaç: İnme dünya çapında en önemli halk sağlığı problemlerinden biri olup, ülkemizdeki mortalite sebepleri arasında ikinci sırada yer alır. İnme sonrası prognozun ve sağkalımın iyileştirilmesi amacıyla kullanılan en önemli yöntemlerden biri, ülkelerin kendi inme istatistiklerini düzenli olarak takip etmeleri ve eksik noktalarını tespit ederek gerekli önlemleri almalarıdır. Bunun için, sağlık hizmetlerinin çeşitli basamaklarında gerçekleştirilmiş istatistiksel çalışmalara ihtiyaç vardır. Bu tarz çalışmalar genellikle üçüncü basamak araştırma hastanelerinde gerçekleştirilebilmektedir. Nüfusun önemli bir kısmının tedavi edildiği ikinci basamaktaki durum ise bilinmemektedir. Bu çalışmanın amacı, bir ilçe hastanesine bir yıl boyunca başvuran tüm akut inmeli hastaları inceleyerek, konuyla ilgili veri sağlamak, eksiklikleri tartışmak ve çözüm önerileri sunmaktır.

Gereç ve Yöntem: Temmuz 2013-Temmuz 2014 tarihleri arasında akut iskemik inme tanısı konulan tüm hastalar çalışmaya dahil edilmiştir. Hastaların demografik, klinik, radyolojik verileri ile başvuru süre ve Ulusal İnme Sağlık Ölçeği Skalası 'National Institutes of Health Stroke Scale' (NIHSS) skorları retrospektif olarak toplanmış, inme sınıflandırmaları yapılmıştır. Tüm hastalar inme sonrası en az bir yıl süreyle takip edilmiştir ve kümülatif sağkalım oranları Kaplan-Meier analiziyle hesaplanmıştır. Bulgular: Akut inme tanısı konulan 49 hastadan dördünde hemorajik inme saptanmış, iskemik inme tanısı alan 45 hasta çalışmaya dahil edilmiştir. Bu hastaların %44,4'ü (n=20) belirtilerin başlangıcını takiben ilk üç saatte, %4,4'ü (n=2) 3.-4,5. saatler arasında hastaneye başvurmuştur. İlk üç saatte başvuran hastaların %50'sinde (n=10) NIHSS 1-4 arası (hafif inme), diğer %50'sinde (n=10) NIHSS >=5 (orta veya ağır inme) tespit edilmiştir. Hastaların %37,1'inde (n=13) embolik, %20'sinde (n=7) büyük damar aterosklerozu, %8,6'sında (n=3) küçük damar hastalığı, %2,9'unda (n=1) arterial diseksiyon saptanırken, geri kalan %31,4'ünde (n=11) sebep bulunamamıştır. Hastaların 21'inde takipte ölüm (exitus) gelişmiştir. Bir, üç ve on iki aylık sağkalım oranları sırası ile %82,2, %57,8 ve %53,3 olarak hesaplanmıştır.

Sonuç: Akut iskemik inmeli hastaların ikinci basamakta tedavisi üçüncü basamağa göre daha zor şartlarda gerçekleştirilmektedir. İnme sonrası prognozun ülke genelinde iyileştirilebilmesi için gelişmiş ülkelerdekine benzer önlemlerin ülkemiz şartlarına uyarlanarak uygulanması gerekmektedir.

Anahtar Kelimeler: İnme, halk sağlığı, sağkalım

Address for Correspondence/Yazışma Adresi: Atay Vural MD, Besni State Hospital, Clinic of Neurology, Adıyaman, Turkey Phone: +90 505 534 15 41 E-mail: atayvural@gmail.com Received/Geliş Tarihi: 16.07.2015 Accepted/Kabul Tarihi: 12.11.2015

Introduction

Stroke is defined as an abrupt cessation of blood supply to a brain region due to thromboembolism or hemorrhage. The disease is a significant cause of mortality and morbidity, and ranks as the fourth highest cause of mortality worldwide, whereas it takes second place in Turkey (1,2). Approximately 75% of all strokes are ischemic (3). Recanalization with thrombolytic therapy is currently the only treatment in acute stroke and is critically important in terms of prognosis. This treatment needs to be administered within the first few hours of symptom onset (4.5 hours in intravenous thrombolysis and 8 hours in intra-arterial thrombolysis) in order to prove beneficial and prevent hemorrhagic complications (4,5). However, fewer than the intended number of patients with stroke receive the appropriate treatment both worldwide and nationwide. Developed nations attempt to resolve this problem by assessing their current status, providing solution recommendations, and investigating success rates following the application of these recommendations (6,7,8). In our country, data of university stroke centers have been published; however, our information of smaller healthcare centers, where the majority of stroke patients present for the first and only time, is limited. It is assumed that tissue plasminogen activator is used less frequently at these centers (9). The objective of this study was to assess all patients with stroke who presented to a county hospital over a one-year period, and obtain data regarding the profile of patients with stroke who present to secondary care centers, discuss the deficits in providing healthcare, and provide solution-based recommendations.

Material and Methods

The study was designed as an observational study. All patients were examined by a neurology specialist on compulsory service at Besni County State Hospital (SH). Besni is a county of Adıyaman province, 40 km from the center and at 1050 meters altitude, with a central population of 27 000 and a rural population of 53 000. The hospital embodies a primary intensive care unit (ICU), but lacks a neurosurgeon, full-time ICU staff, and a magnetic resonance imaging (MRI) device.

All patients diagnosed as having acute stroke over a oneyear period between July 15th, 2013, and July 15th, 2014, were included in the study. Patients were either referred to a larger center from the emergency ward, or internalized in the ICU or on a ward. Demographic and clinical data, baseline scores on National Institutes of Health Stroke Scale (NIHSS), and place of referral were recorded for the referred patients. Regarding the patients followed at Besni SH, a standard stroke form was filled out to prospectively record demographic, clinical (age, sex, medical history, timing of presentation, presenting symptom, neurologic examination, and baseline NIHSS score), and laboratory and radiologic data. Information needed to calculate one-year survival was obtained from relatives of patients and local officials.

Computed tomography (CT) and CT-angiography examinations were performed at Besni SH. Brain CT was acquired in all study patients using a Toshiba Advance Alexion 16 detector with 1 mm thin cross-section imaging. MRI (diffusion-weighted (DW), T1, T2 and fluid-attenuated inversion recovery) was performed at the 82nd Year State Hospital of Adiyaman University. The localization and lesion type (single, multiple, dispersed) were recorded for patients with brain MRI (26/35 patients) (Siements Magnetom Symphonu 1.5T) and DW imaging. Biochemistry, complete blood count, activated partial prothrombin time, international normalized ratio (INR), and lipid profile were examined in all patients. Electrocardiography (ECG) and transthoracic echocardiography (ECHO) were obtained in cardiologic examinations within the etiologic investigation. Doppler ultrasonography (USG) of carotid-vertebral artery or brain-cervical CT angiography was obtained to examine large arteries. Etiologic classification was performed using the Causative Classification of Stroke (CCS) (https://ccs.mgh.harvard.edu/ccs_title.php) software (10).

Results

Over the one-year study period, four patients were diagnosed as having hemorrhagic stroke and 45 patients were diagnosed as having ischemic acute stroke. All four patients with hemorrhagic stroke were referred to other centers for their ICU needs. Among the 45 patients with ischemic stroke, 75.6% (n=34) first presented to emergency room, and 24.4% (n=11) first presented to the neurology outpatient clinic. The median patient age (interquartile distance) was 75 years (range, 66-80 years), and the female/male ratio was 1.25. Ten patients (22.2%) were directly referred to an external ICU, 35 patients were internalized (22 on a ward, 13 in the ICU). The analysis of risk factors in the latter 35 patients revealed hypertension in 21 (60%), coronary artery disease (CAD) in 13 (37.1%), diabetes mellitus in 10 (28.6%), hyperlipidemia in nine (25.7%), smoking in seven (20%), and previous history of stroke in four (11.5%) patients (Table 1). Eight patients had been receiving anti-aggregative therapy (due to previous history of stroke in four, and CAD in four), and one patient had been receiving anti-coagulant therapy (due to aortic valve replacement) at the time of stroke.

Regarding the time to arrive at hospital, 44.4% of the patients (n=20) arrived within the first three hours of symptom onset, and 4.4% (n=2) arrived after 3-4.5 hours; the remaining 51.2% (n=23) arrived later (Figure 1). The baseline NIHSS score was calculated as 8.4 ± 9.0 (mean±standard deviation). This figure was 6.3 ± 7.5 for the internalized patients, and 16 ± 10.3 in the referred patients. Also, baseline NIHSS was 1-4 (mild stroke) in 10 patients (50%), and ≥ 5 (moderate or severe stroke) in the 10 patients who referred within the first three hours (Figure 2). Lesion localization of 26 patients with DWI indicated restricted diffusion in the anterior circulation in 16 patients (12 middle cerebral, 3 anterior cerebral, and 2 anterior choroidal artery), posterior circulation in 8 patients (3 posterior cerebral, 4 basilar, 1 superior cerebellar, 1 anterior inferior cerebellar, 1 posterior inferior cerebellar artery), and both areas in 2 patients.

Four patients (8.9%) had previously presented to other emergency wards for the same symptoms. All of these patients were aged less than 60 years, and two presented to us within the first 24 hours of initial discharge with symptoms of severe vertigo, ataxia, and vomiting, without accompanying loss of muscle strength; the third presented with severe headache during pregnancy, the fourth patient presented to us within the first 48 hours of initial discharge with symptoms of isolated impairment of speech and dysphagia. One of these patients died of posterior

Table 1. Clinical features of patients diagnose acute ischemic stroke at Besni State Hospital	ed as having
Age, median (IQD)	75 (66-80)
Female/male ratio (n)	1.25 (25/20)
Site of presentation, n (%)	
Emergency room	31 (75.6)
Outpatient's clinic	11 (24.4)
Timing of presentation, n (%)	
0-1 hours	10 (22.2)
1-3 hours	10 (22.2)
3-4.5 hours	2 (4.4)
4.5-24 hours	18 (40)
24 <hours< td=""><td>5 (11.1)</td></hours<>	5 (11.1)
Severity of stroke at presentation (by the NIH n (%)	ISS score),
Mild	22 (48.9)
Moderate	14 (31.1)
Moderate-severe	3 (6.7)
Severe	6 (13.3)
Number of referred patients, n (%)	
From emergency ward	10 (22)
Post-hospitalization	8 (18)
Risk factors* n, (%)	
HT	21 (60)
DM	10 (28.6)
HL	9 (25.7)
CAD	13 (37.13)
Smoking	7 (20)
Previous CVD	4 (11.5)
CCS classification*, n (%)	
Embolic	13 (37.1)
Large artery	7 (20)
Small vessel	3 (8.6)
Cryptogenic	11 (31.4)
Other	1 (2.9)
Need to perform angioplasty *, n (%)	2 (5.7)
Mortality*, n (%)	
Referred	13/18 (72)
Not referred	8/27 (30)

*n=35 (internalized patients), IQD: Interquartile distance, NIHSS: National Institutes of Health Stroke Scale, HT: Hypertension, DM: Diabetes mellitus, HL: Hyperlipidemia, CAD: Coronary artery disease, CVD: Cerebrovascular disease, CCS: Causative classification of stroke system infarction during hospitalization at our clinic, and the other died of disseminated sinus vein thrombosis at the referred stroke center. Thrombus was identified at the origin of the vertebral artery in one patient and treated with heparin infusion at our clinic. The patient who presented with acute dysarthria and dysphagia had four small embolic infarctions in the left centrum semiovale.

Etiologic examinations including ECG were performed in all 35 patients, transthoracic ECHO in 32 patients, brain and cervical CT angiography in 19 patients, and carotid-vertebral artery Doppler USG in the nine patients internalized with ischemic stroke. According to the CCS, the strokes were classified as embolic in 37% (n=13), large artery atherosclerosis in 20% (n=7). small vessel disease in 8.6% (n=3), and arterial dissection in 2.9% (n=1) of the patients; the etiology remained unknown in 31.4% (n=11) of the patients. Three out of 13 patients with embolic etiology accepted warfarin therapy; however, treatment could not continue in one patient because of urinary hemorrhage and drug incompliance in two patients. One patient, who was already on warfarin during the incident, continued treatment, another was put on dabigatran therapy. The remaining patients received antiaggregative therapy. Two patients with critical stenosis at the origin of internal carotid were referred to neighboring provinces for angioplasty.

Risk factors included hypertension in 60%, diabetes mellitus in 28.6%, hyperlipidemia in 25.7%, CAD in 37.1%, smoking in 20%, and previous history of cerebrovascular disease in 11.5% of the patients.

Analysis of the one-year survival data revealed that 13 out of the 18 patients referred to external centers had died (10 from the emergency room, 8 upon worsening during hospitalization). Among the remaining 27 patients, two died of cerebellar infarction and truncal middle cerebral artery infarction during hospitalization, and six died within one year of discharge. Kaplan-Meier analysis indicated that the one-month, three-month, and twelve-month survival rates were 82.2%, 57.8%, and 53.3%, respectively (Figure 3).

Timing of presentation

2270	2270	470	40%	11%
220/	220/	404	400/	110/

■ 0-1 hour, n=10 ■ 1-3 hour, n=10 ■ 3-4,5 hour, n=2 ■ 4,5-24 hour, n=18 ■ 24< hour, n=5

Figure 1. Timing of presentation in acute ischemic stroke patients (n=45)

NIHSS scores in patients presenting in the first 3 hours

50%		30%	5%	15%
0-4 (Mild), n=10	≣ 5-15 (Moderate), n=6	■ 16-20 (Moderate-severe), n=1	21-42 (Severe), n=3

Figure 2. National Institutes of Health Stroke Scale scores of patients with acute ischemic stroke presenting in the first three hours (n=20) *NIHSS: National Institutes of Health Stroke Scale*

Discussion

The most important results of our study were that 44.4% of the patients with acute ischemic stroke presented within the first three hours and 48.9% presented within the first 4.5 hours of stroke incident (Figure 1). Half of all patients who presented in the first three hours had mild stroke, the other half had moderate to severe stroke (Figure 2). Accordingly, secondary healthcare centers appear to be suitable candidates for the administration of thrombolytic therapy on condition that they provide proper terms and organization.

Despite their limited facilities, county and peripheral hospitals receive the first admissions of the majority of stroke patients, nationwide. Theoretically, it is feasible to administer thrombolytic therapy at an even higher rate compared with stroke centers because of the shorter time to arrive at these centers. This problem is valid worldwide and several strategies have been developed to resolve it. For instance, the number of stroke centers has been increased by the government, telemedicine networks have been established, and start-and-refer strategy has been recruited in some centers (11,12,13,14,15,16). These recent approaches have increased the rates of thrombolytic therapy in the related parts of countries and improved prognostic data.

The rates of thrombolytic administration are known to be rather low in patients with acute ischemic stroke in our country (9). Potential causes of this might include problems common to all countries as well as our country-specific problems, including an insufficient number of stroke centers and experienced specialists trained at stroke centers, absence of a government policy, and prosecution of the process solely by physicians' efforts, absence of a counterpart matching the risks of thrombolytic therapy with regard to the performance system and relying on the total number of patients, and fear of physicians performing risky treatments due to the nationwide tension against physicians (Table 2).

Another aspect of the problem is that 55.6% (n=25) of the patients presented to the hospital in the late period. This stems from the fact that the population is not adequately informed of stroke (17). Literature studies have demonstrated that campaigns aimed at informing rural populations in particular, yielded positive results after the establishment of proper infrastructure (18,19).



Figure 3. One-year Kaplan-Meier survival curve

In our study, four patients' stroke was not diagnosed at their initial presentation to the emergency room. All of these patients with atypical presentation were aged less than 60 years, two presented to us with vertigo and vomiting, the third presented with isolated dysarthria and dysphagia, and the fourth presented with severe headache and vomiting. Two of these patients died in the

Table 2. Problems encountered in the approach to patients with acute ischemic stroke in our country and solution recommendations			
Problems	Solution recommendations		
Pre-hospital problems			
Delayed presentation of patients to hospital	Educating the population about stroke		
Hospital and organizational p	problems		
Insufficient number of stroke centers	Generalization of stroke centers		
Difficulty in communication between stroke centers and neighboring province-county hospitals	Establishment of protocols between stroke centers and neighboring province-county hospitals about the proper approach to stroke patient		
Disallowance to start thrombolytic therapy at secondary case province- county hospitals	Recruitment of telemedicine and/or start-and-refer applications		
Insufficient number of neurologists experienced in acute stroke	Increasing the number of neurologists trained at stroke centers		
Insecurity of physicians with respect to the potential complications of thrombolytic therapy	Removal of nationwide tension threatening physicians' lives with the efforts of the government		
Failure to recognize patients with atypical stroke in the emergency room	Organization of regular training sessions about stroke aimed at all physicians working at emergency wards		
Communication problems between physicians at county centers and province centers	Providing allowance and a friendly work space to newly graduated physicians by the Ministry of Health		
Post-hospitalization problems			
Non-adherence of rural population to warfarin therapy	Generalization of novel oral anticoagulants		
Difficulties in the post- discharge management of patients with dysphagia	Enhancing the facilities of centers providing swallowing rehabilitation and percutaneous gastrostomy		
Difficulties in the prevention and treatment of decubitus ulcers	Increasing the number of specialized centers providing decubitus ulcer management		
Difficulties in the management of bedridden patients severe deficits	Increasing the number of nursing homes		

early period of follow-up, the third was heparinized at an external center because of thrombus in the vertebral artery. Other than neurologists, emergency physicians should also note that patients with stroke might have atypical presentations in the absence of paresis or unconsciousness in order to achieve early diagnosis and save lives. Patients presenting with persistent vertigo and vomiting should alert physicians to obtain neurology consultation, and cerebral vein thrombosis as well as preeclampsia/eclampsia and migraine should be kept in mind in pregnant patients who present with severe headache, and a detailed neurologic examination should be performed. Training sessions aimed at emergency staff and family physicians might be significantly beneficial in achieving better recognition rates of atypical presentations and transient ischemic attacks (20,21).

Four patients in need of referral were transferred to the stroke center at Malatya Turgut Özal Medical Center. Posterior fossa decompression surgery was performed to survive one of these patients. In the other case, a 28-week infant of the pregnant patient was rescued although the patient herself died despite decompression. Stroke centers are crucial for the maintenance of difficult stroke cases and for providing effective training for residents on stroke practices, and coordinating thrombolytic therapy administration. Increasing the nationwide number of stroke centers is therefore of uttermost significance (15). Although the embolic etiology was determined in a significant portion of our patients, warfarin therapy could only be initiated in a few, most of whom did not comply with the therapy. To a great extent this problem is caused by the difficulties encountered in the transfer of stroke patients for INR tests. The implementation of prescription allowance for novel oral anti-coagulants for physicians at SHs should enhance the rates of etiology-appropriate treatment among patients with stroke. In our study, seven (15.6%) patients had stroke at a young age (below 60 years) and therefore had to be referred to larger centers for further etiologic tests.

Literature studies have shown that one-year mortality rates were about 25-30% in larger centers (22,23,24). However, our results demonstrated that one-year mortality was 45% in our population. The higher death rates were associated with failure to initiate proper treatment, non-compliance to treatment following discharge, insufficient facilities to perform percutaneous gastrostomy operation in patients with dysphagia, and difficulties encountered in the proper maintenance of decubitus ulcers. Resolution of these problems should increase the rates of survival following discharge.

Conclusion

Consequently, similar to other countries, there are major deficits in the approach to patients with stroke in the neurologic practice of our country. These problems and our solution recommendations have been summarized in Table 2 in light of literature findings and our country-specific conditions (25,26,27,28). Patients with stroke will be able to receive better treatment should the necessary regulations be made.

Ethics

Ethics Committee Approval: This study was a non-invasive, descriptive clinical study and was based on retrospective, anonymous analysis of the data that was obtained during routine clinical work-up. Study was approved by the local committee.

Peer-review: Externally peer-reviewed.

Informed Consent: Informed consent was not obtained because of the retrospective nature of the study.

References

- Öztürk Ş. Serebrovasküler hastalık epidemiyolojisi ve risk faktörleri-Dünya ve Türkiye perspektifi. Turkish Journal of Geriatrics 2009;13:p51-58.
- 2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. American Heart Association Statistics, and S. Stroke Statistics, Heart disease and stroke statistics 2015 update: A report from the American Heart Association. Circulation 2015;131:e29-322.
- 3. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson LM, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C; Global Burden of Diseases, Injuries, Risk Factors Study 2010 (GBD 2010); GBD Stroke Experts Group. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. Lancet Glob Health 2013;1:e259-81.
- 4. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929-1935.
- Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, Millán M, Urra X, Cardona P, López-Cancio E, Tomasello A, Castaño C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Pérez M, Goyal M, Demchuk AM, von Kummer R, Gallofré M, Dávalos A; REVASCAT Trial Investigators.Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372:2296-306.
- Joubert J, Prentice LF, Moulin T, Liaw ST, Joubert LB, Preux PM, Ware D, Medeiros de Bustos E, McLean A. Stroke in rural areas and small communities. Stroke 2008;39:1920-1928.
- Gropen T, Magdon-Ismail Z, Day D, Melluzzo S, Schwamm LH; NECC Advisory Group. Regional implementation of the stroke systems of care model: recommendations of the northeast cerebrovascular consortium. Stroke 2009;40:1793-1802.
- Leira EC, Hess DC, Torner JC, Adams HP Jr. Rural-urban differences in acute stroke management practices: A modifiable disparity. Arch Neurol 2008;65:887-891.
- Kutluk K. Akut iskemik inmede intravenöz trombolitik tedavi: Sorumluluğumuzun farkında mıyız? Türk Serebrovasküler Hastalıklar Dergisi 2009;15:p.35-39.
- Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, Ayata C, Towfighi A, Smith EE, Chong JY, Koroshetz WJ, Sorensen AG. A computerized algorithm for etiologic classification of ischemic stroke: The Causative Classification of Stroke System. Stroke 2007;38:2979-2984.
- Müller-Barna P, Hubert GJ, Boy S, Bogdahn U, Wiedmann S, Heuschmann PU, Audebert HJ. Heuschmann, H.J. Audebert, TeleStroke units serving as a model of care in rural areas: 10-year experience of the TeleMedical project for integrative stroke care. Stroke 2014;45:2739-2744.
- Fassbender K, Balucani C, Walter S, Levine SR, Haass A, Grotta J. Streamlining of prehospital stroke management: The golden hour. Lancet Neurol 2013;12:585-596.

- Meyer BC, Raman R, Hemmen T, Obler R, Zivin JA, Rao R, Thomas RG, Lyden PD. Efficacy of site-independent telemedicine in the Stroke DOC trial: A randomised, blinded, prospective study. Lancet Neurol 2008;7:787-795.
- Sheth KN, Smith EE, Grau-Sepulveda MV, Kleindorfer D, Fonarow GC, Schwamm LH. Drip and ship thrombolytic therapy for acute ischemic stroke: Use, temporal trends, and outcomes. Stroke 2015;46:732-739.
- Kim J, Hwang YH, Kim JT, Choi NC, Kang SY, Cha JK, Ha YS, Shin DI, Kim S, Lim BH. Establishment of government-initiated comprehensive stroke centers for acute ischemic stroke management in South Korea. Stroke 2014;45:2391-2396.
- Tekle WG, Chaudhry SA, Hassan AE, Rodriguez GJ, Suri MF, Qureshi AI. Drip-and-ship thrombolytic treatment paradigm among acute ischemic stroke patients in the United States. Stroke 2012;43:1971-1974.
- Kim YS, Park SS, Bae HJ, Heo JH, Kwon SU, Lee BC, Lee SH, Oh CW, Yoon BW. Public awareness of stroke in Korea: a population-based national survey. Stroke 2012;43:1146-1149.
- Boden-Albala B, Edwards DF, St Clair S, Wing JJ, Fernandez S, Gibbons MC, Hsia AW, Morgenstern LB, Kidwell CS. Methodology for a community-based stroke preparedness intervention: The Acute Stroke Program of Interventions Addressing Racial and Ethnic Disparities Study. Stroke 2014;45:2047-2052.
- Nickles A, Fiedler J, Roberts S, Lyon-Callo S, Hurst R, Reeves M. Compliance with the stroke education performance measure in the Michigan Paul Coverdell National Acute Stroke Registry. Stroke 2013;44:1459-1462.
- Massengo SA, Cisse M, Guiziou C, Leray E, Rajabally YA, Edan G. Knowledge of TIA among general practitioners and emergency department physicians. A questionnaire survey in a French semi-rural area. Clin Neurol Neurosurg 2013;115:1457-1463.

- 21. Navarrete-Navarro P, Murillo-Cabeza F, Bono-de-Seras R, Rodriguez-Romero R, Rodriguez-Zarallo A, Vazquez-Mata G. Development of an acute ischemic stroke management course for hospital physicians in emergency departments and intensive care units. Eur J Emerg Med 2012;19:108-111.
- Cabral NL, Muller M, Franco SC, Longo A, Moro C, Nagel V, Liberato RB, Garcia AC, Venancio VG, Gonçalves AR. Three-year survival and recurrence after first-ever stroke: The Joinville stroke registry. BMC Neurol 2015;15:70.
- Brønnum-Hansen H, Davidsen M, Thorvaldsen P; Danish MONICA Study Group. Long-term survival and causes of death after stroke. Stroke 2001;32:2131-2136.
- Sun Y, Lee SH, Heng BH, Chin VS. 5-year survival and rehospitalization due to stroke recurrence among patients with hemorrhagic or ischemic strokes in Singapore. BMC Neurol 2013;13:133.
- 25. Shultis W, Graff R, Chamie C, Hart C, Louangketh P, McNamara M, Okon N, Tirschwell D. Striking rural-urban disparities observed in acute stroke care capacity and services in the pacific northwest: Implications and recommendations. Stroke 2010;41:2278-2282.
- 26. Alberts MJ, Wechsler LR, Jensen ME, Latchaw RE, Crocco TJ, George MG, Baranski J, Bass RR, Ruff RL, Huang J, Mancini B, Gregory T, Gress D, Emr M, Warren M, Walker MD. Formation and function of acute stroke-ready hospitals within a stroke system of care recommendations from the brain attack coalition. Stroke 2013;44:3382-3393.
- 27. Brainin M, Teuschl Y, Kalra L. Acute treatment and long-term management of stroke in developing countries. Lancet Neurol 2007;6:553-561.
- Okon NJ, Fogle CC, McNamara MJ, Oser CS, Dietrich DW, Gohdes D, Harwell TS, Rodriguez DV, Helgerson SD. Statewide efforts to narrow the rural-urban gap in acute stroke care. Am J Prev Med 2010;39:329-333.