# Research

# The Comparison of TOAST, CCS, and ASCO Etiological Classifications in Ischemic Stroke Patients

İskemik İnme Hastalarında TOAST, CCS ve ASCO Etiyolojik Sınıflamalarının Karşılaştırılması

Anıl Özkaya[1], Hacı Ali Erdoğan[2], İbrahim Acır[2], Murat Çabalar[3], Vildan Yayla[2]

[1]Mardin State Hospital, Clinic of Neurology, Mardin, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey
[3]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Neurology, Istanbul, Turkey

## ABSTRACT

**Objective:** Classifications of stroke etiology is generally based on lesion pathology and ischemic stroke or hemorrhage were two main groups. Nowadays, most common classification is Trial of Org 10172 in Acute Stroke Treatment (TOAST) which was published in 1993. After the TOAST classification system, Causative Classification of Stroke System (CCS), Atherothrombosis, Small vessel disease, Cardiac causes, and Other uncommon causes (ASCO) classification systems were developed. The purpose of the study is to discuss whether CCS or ASCO systems can be replaced for TOAST classification system which is most commonly used to determine the stroke etiology. And to determine whether the number of patients can be decreased in an unidentified cause of the etiology group according to TOAST by these CCS or ASCO systems.

**Methods:** Three hundred acute ischemic stroke patients hospitalized at Bakırköy Dr. Sadi Konuk Training and Research Hospital between 01.01.2016 and 30.06.2016 were evaluated retrospectively and they were assessed based on their neurological examination, laboratory findings and sub-types of stroke were identified according to TOAST, CCS, and ASCO etiology classifications. Results were compared based on TOAST, CCS, and ASCO. For comparison, obvious reasons for TOAST, obvious and potential reasons for CCS, and first and second evidence were used.

**Results:** The mean age of 300 patients (176 male-124 female) was 67.13±14.19 years. No significant differences were detected between TOAST, CCS and ASCO systems for detecting etiological subtypes; large artery atherosclerosis, small artery disease, other determined causes or undetermined causes but significant differences were found between ASCO and CCS in determining cardioembolic subtype (p=0.002). Correlation analysis showed high and significant correlations between TOAST and CCS (r=0.765) and TOAST and ASCO (r=0.731). The correlation between CCS and ASCO (r=0.928).

**Conclusion:** The traditional TOAST classification system, in use for a long time in determining stroke etiology, cannot be updated but it still maintains its practicality and availability compared to the new classification systems CCS and ASCO. There was no significant decrease in the number of patients in an undetermined etiology subgroup by CCS and ASCO compared to TOAST. As far as our results are concerned, CCS and ASCO systems have not superiority on TOAST.

**Keywords:** Ischemic stroke, etiological classification, TOAST

## ÖZ

**Amaç:** İnme etiyolojisine yönelik sınıflamalar, genellikle lezyonun patolojisine göre yapılmış ve tüm inmeler iskemi veya hemoraji olmak üzere iki ana gruba ayrılmıştır. Günümüzde en yaygın kullanılan sınıflama 1993 yılında yayınlanan Akut İnme Tedavisinde Organizasyon Çalışması 10172 (TOAST) sınıflamasıdır. TOAST sınıflamasından hareketle daha sonraki dönemde İnme Sisteminin Nedensel Sınıflandırması (CCS), Aterotromboz, Küçük damar hastalığı, Kardiyak sebepler ve Diğer nadir sebepler (ASCO) sistemleri geliştirilmiştir. Bu çalışmanın amacı, inmenin etiyolojik nedenini belirlerken yaygın olarak kullanılan TOAST sınıflama sistemi yerini daha sonradan yapılan CCS veya ASCO sistemlerinin alıp alamayacağını göstermek ve TOAST'nin zayıf yönü olan nedeni belirlenemeyen etiyoloji grubundaki hasta sıklığını azaltıp azaltmadığını belirlemektir.

**Gereç ve Yöntem:** Akut inme tanısı ile Bakırköy Dr Sadi Konuk Eğitim ve Araştırma Hastanesi'ne 01.01.2016-30.06.2016 tarihleri arasında yatışı yapılan 300 hasta epikrizleri ve tetkikleriyle birlikte değerlendirildi ve TOAST, CCS ve ASCO etiyolojik sınıflamalarına göre gruplandırılmış, inme

alt tipleri belirlenmiş ve çıkan sonuçlar birbirleri ile karşılaştırılmıştır. Karşılaştırmalar için TOAST sınıflamasında bariz nedenler, CCS sınıflamasında bariz ve olası nedenler, ASCO sınıflaması için birinci ve ikinci derecede kanıtlar alındı.

**Bulgular:** Değerlendirmeye alınan 300 hastanın (176 erkek, 124 kadın) yaş ortalaması 67,13±14,19 yıl idi. İnme etiyolojik alt tiplerinden büyük arter aterosklerozu, küçük damar hastalığı, diğer etiyolojiler ve nedeni belirlenemeyen etiyolojileri belirlemede TOAST, CCS ve ASCO arasında anlamlı farklılık saptanmadı. Kardiyoembolik alt sınıfı belirlemede ASCO ve CCS arasında anlamlı farklılık mevcuttu (p=0,002). Korelasyon analizleri ile TOAST ile CCS arasında ileri düzeyde (r=0,765), TOAST ile ASCO arasında ileri düzeyde uyumluluk (r=0,731) gözlenirken CCS ve ASCO arasındaki ilişki mükemmele yakın düzeyde anlamlı idi (r=0,928).

**Sonuç:** İnme etiyolojisini belirlemede uzun süreden beri kullanılan geleneksel TOAST sınıflama sistemi, daha yeni sistemler olan CCS ve ASCO ile karşılaştırıldığında güncelleme imkanı olmadığı halde pratikliğini ve kullanılabilirliğini koruduğu düşünüldü. TOAST ile nedeni belirlenemeyen etiyoloji alt grubundaki hasta sayısında CCS ve ASCO ile anlamlı bir azalma gözlenmedi. Sonuçlarımıza bakıldığında CCS ve ASCO sistemi TOAST'ye göre bir üstünlük getirememiştir.

**Anahtar Kelimeler:** İskemik inme, etiyolojik sınıflama, TOAST

## INTRODUCTION

One of the traditional and most frequently used methods for stroke etiological classification, Trial of ORG 10172 in Acute Stroke Treatment (TOAST) sub-divides clinical data of stroke according to the formation mechanisms. In this classification, because it is impossible to determine which group is appropriate for patients who have more than one reason for stroke, many patients are evaluated within the undetermined group. The Causative Classification of Stroke (CCS), a web-based system organized by Harvard University, was created to reduce the limitations of the traditional TOAST system and reduce the unclassified group rate (1,2). It also creates a common language among physicians while determining the etiology and has a high level of compatibility among practitioners. Atherothrombosis, Small vessel disease, Cardiac causes, and Other uncommon causes (ASCO) classification is a phenotypic system that classifies stroke patients according to the composition of their etiological characteristics. Also, the ASCO system lists all etiologies that may be responsible for stroke pathophysiology (1-4). This study aims to compare the subtypes of these three classifications with each other, to prevent the inclusion of many patients to the undetermined group and to investigate whether the number of patients in this group will be affected.

## METHODS

In our study, patients who were followed up at Bakırköy Dr. Sadi Konuk Training and Research Hospital Neurology Clinic between January 1, 2016 and June 30, 2016 with the diagnosis of ischemic stroke were included. Anamnesis, histories, physical and neurological examination findings, imaging methods, and all other examinations performed for etiology were analyzed for all 300 patients. All patients participated in the study and their legal heirs were informed and consent were obtained. Exclusion criteria were; hemorrhagic stroke, patients under 18 years, and the doubt in the diagnosis of ischemic stroke. This study, with protocol number 2017/144, was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee decision no 2017-06-32 (date: 19.06.2017).

Routine biochemical tests, hemogram, blood sedimentation rate and C-reactive protein, brain computed tomography and diffusion magnetic resonance (MR) imaging, electrocardiogram (ECG), transthoracic echocardiography (TTE), bilateral carotid-vertebral artery Doppler ultrasonography, cranial-cervical MR and MR angiographies have been selected for almost all patients. Transesophageal echocardiography (TEE), 24-hour rhythm holter examination, vasculitis tests, thrombophilia panel were performed on patients who needed advanced diagnosis. It was determined which subtypes of TOAST, CCS and ASCO etiological classifications are suitable for each patient. Obvious reasons for TOAST classification, obvious and possible reasons for CCS classification, first and second-degree evidence for ASCO classification were obtained for comparing classifications to each other. If any patient had two first-degree evidence in the ASCO classification, these patients were included in the group whose etiology could not be determined. If any patient had two or more definite etiologies according to the TOAST classification, these patients were also included in the group whose cause was not found. There are 4 subtypes normally defined in the ASCO classification, and the condition defined as ASCO-0 for cases in which the etiological cause cannot be determined. In our study, ASCO-0 was taken as the 5th subtype for comparison with TOAST and CCS.

### Statistical Analysis

Frequency and percentage were calculated for qualitative variables, and mean and standard deviation were calculated for quantitative variables. The Marginal Homogeneity test was used to compare the TOAST, CCS, and ASCO classification methods for classifying possible etiology subgroups of stroke. Bonferroni Corrected McNemar test was used for pairwise comparisons between methods. Spearman correlation analysis was performed for the correlation and Cramer's V correlation coefficient (r) was calculated.

## RESULTS

A total of 300 patients were included in the study and 124 patients were women (41.33%) and 176 patients (58.67%) were men. The mean age of the patients was found as 67.13±14.19 years. Hypertension in 191 (63.6%) of 300 patients, diabetes mellitus in 110 (36.6%), atrial fibrillation (AF) in 32 (10.6%), a history of stroke or transient ischemic attack (TIA) in 48 (16%), hyperlipidemia in 63 (21%), a history of coronary artery disease, metallic heart valve or heart failure in 89 (29.6%), a smoking history in 81 (27%), and other risk factors in 35 (11%, 6) were available. After imaging methods, 5 (1.6%) of 300 patients had the anterior cerebral artery area infarcts, 112 (37.3%) patients had the middle cerebral artery area infarcts, 21 (7%) patients had the posterior cerebral artery area infarcts, 68 (22.6%) patients had the vertebrobasilar area infarcts. And 30 (10%) patients had lacunar infarcts, 39 (13%) patients had multiple areas infarcts, and 17 (5.6%) patients had border zone infarcts. The TIA clinic was present in 8 patients, and no infarct area was observed in neuroimaging.

TOAST system was used when evaluating cardioembolic risk factors. Eighty nine patients with isolated AF, 22 patients with other major cardiac risks (dilated cardiomyopathy, atrial thrombus, mechanical heart valve, infective endocarditis, mitral stenosis, etc.) and 54 patients with minor cardiac risks (patent foramen ovale, mitral valve prolapse, hypokinetic left ventricular segment, bioprosthetic heart valve, etc.) was detected.

There was no significant difference between TOAST and CCS methods in determining the etiological subgroups of ischemic stroke (p=0.115) (Table 1).

No significant difference was found between TOAST and ASCO methods in determining the etiological subgroups of ischemic stroke (p=0.803) (Table 2).

There was a significant difference between CCS and ASCO methods in determining the etiological subgroups of ischemic stroke (p=0.033) (Table 3).

A significant difference was found between CCS and ASCO classification methods for cardioembolic etiologic causes of ischemic stroke (p=0.002) (Table 4).

One patient (2.8%) who was included in the large artery atherosclerosis subgroup in ASCO classification was included in the group of undetermined etiology in the CCS classification. Ten patients (9.71%) who was included in the cardioembolism subgroup in ASCO classification was included in the group of undetermined etiology in the CCS classification. Five patients (4.5%) were in the undetermined etiology subgroup according to ASCO classification were included in the small vessel disease group in the CCS classification (Table 5).

## DISCUSSION

TOAST classification system is the most widely used system in clinics thanks to its practicality, on the other hand, its important disadvantage is that includes patients with more than one etiology into the undetermined group. Nowadays with current technology, more than one possible etiology in the stroke mechanism can be determined, so approximately half of the stroke patients are included in the undetermined etiology group. Another disadvantage of this classification is, when a positive etiology is found, the TOAST etiological subclass of the patient is determined, other investigations are not performed so maybe a possible second cause is missed. Here, the etiological subtypes in the TOAST system are determined at a low-reliability level (1,2).

The web-based CCS system, which is one of the modern classification systems, has been developed to reduce the

**Table 1.** Comparison of TOAST and CCS etiological classification systems

| | TOAST | | CCS | | |
| --- | --- | --- | --- | --- | --- |
| | n | % | n | % | p* |
| 1 | 54 | 18 | 47 | 15.67 | 0.115 |
| 2 | 99 | 33 | 93 | 31 | - |
| 3 | 23 | 7.67 | 31 | 10.33 | - |
| 4 | 11 | 3.67 | 12 | 4 | - |
| 5 | 113 | 37.67 | 117 | 39 | - |

*Marginal homogeneity test, TOAST: Trial of Org 10172 in Acute Stroke Treatment, CCS: Causative Classification of Stroke System, 1- Large artery atherosclerosis, 2- Cardioembolism, 3- Small vessel disease, 4- Other etiology, 5- Undetermined etiology

**Table 2.** Comparison of TOAST and ASCO etiological classification systems

| | TOAST | | ASCO | | |
| --- | --- | --- | --- | --- | --- |
| | n | % | n | % | p* |
| 1 | 54 | 18 | 48 | 16 | 0.803 |
| 2 | 99 | 33 | 103 | 34.33 | - |
| 3 | 23 | 7.67 | 26 | 8.67 | - |
| 4 | 11 | 3.67 | 12 | 4 | - |
| 5 | 113 | 37.67 | 111 | 37 | - |

*Marginal homogeneity test, TOAST: Trial of Org 10172 in Acute Stroke Treatment, ASCO: Atherothrombosis, Small vessel disease, Cardiac causes, and Other uncommon causes, 1- Large artery atherosclerosis, 2- Cardioembolism, 3- Small vessel disease, 4- Other etiology, 5- Undetermined etiology

limitations of the TOAST system and to reduce the rate of undetermined groups. Reliability studies conducted by Ay et al. (2,3) and by Arsava et al. (4) showed that especially the CCS classification was used safely in stroke patients.

The ASCO classification makes a phenotypic classification by grading all causes of stroke, and thus all etiological causes are classified according to the degree of evidence. The reliability of the ASCO system has not been well-known yet (5).

The fact that TOAST and CCS systems depend on the reason but the ASCO system is a phenotypic system creates difficulties in terms of comparison with each other. To make a meaningful comparison, 'obvious and clear causes' etiologies in CCS (possible etiologies were not taken), first and second-degree evidence in ASCO were taken (3rd-degree evidences were not obtained). Similarly, the inclusion criteria were limited in previous studies, which makes it possible to compare the classifications with each other (6,7).

In our study, there was no significant difference between subtypes of CCS and TOAST such as large artery atherosclerosis (p=0.189), cardioembolism (p=0.146), small vessel disease (p=0.02), other etiologies (p=1.00) and undetermined etiologies (p=0.572). The fact that being no significant difference between undetermined etiologies contradicts the purpose of the CCS system. Because the CCS classification has been created with the aim of reducing the undetermined etiology of the TOAST system. Our study showed that instead of the TOAST system, also the CCS system can be applied in daily practice. Lanfranconi and Markus (8), by comparing TOAST and CCS systems in 2012, found both classification systems in high compatible with each other, as we also found.

When comparing TOAST and ASCO etiological classifications, no significant difference was found between

subgroups. The 103 patients (34.33%) in the study were included in the cardioembolic subgroup in the ASCO classification, and this rate is slightly above the rate of cardioembolism etiology (20%-30%) mentioned in the literature (9). The reason for this is the higher number of coronary artery diseases in our patient population with

**Table 3.** Comparison of CCS and ASCO etiological classification systems

| | CCS | | ASCO | | |
|---|---|---|---|---|---|
| | n | % | n | % | p* |
| 1 | 47 | 15.7 | 48 | 16 | 0.033 |
| 2 | 93 | 31 | 103 | 34.3 | - |
| 3 | 31 | 10.3 | 26 | 8.67 | - |
| 4 | 12 | 4 | 12 | 4 | - |
| 5 | 117 | 39 | 111 | 37 | - |

*Marginal homogeneity test, CCS: Causative Classification of Stroke System, ASCO: Atherothrombosis, Small vessel disease, Cardiac causes, and Other uncommon causes, 1- Large artery atherosclerosis, 2- Cardioembolism, 3- Small vessel disease, 4- Other etiology, 5- Undetermined etiology

**Table 4.** Binary comparisons between CCS and ASCO classifications

| | CCS | | ASCO | | | |
|---|---|---|---|---|---|---|
| | n | % | n | % | % Dif. | p* |
| 1 | 47 | 15.7 | 48 | 16 | 0.33 | 1 |
| 2 | 93 | 31 | 103 | 34.3 | 3.33 | **0** |
| 3 | 31 | 10.3 | 26 | 8.67 | -1.66 | 0.06 |
| 4 | 12 | 4 | 12 | 4 | 0 | 1 |
| 5 | 117 | 39 | 111 | 37 | -2 | 0.21 |

*McNemar test with Bonferroni Correction, CCS: Causative Classification of Stroke System, ASCO: Atherothrombosis, Small vessel disease, Cardiac causes, and Other uncommon causes, Dif.: Difference, 1- Large artery atherosclerosis, 2- Cardioembolism, 3- Small vessel disease, 4- Other etiology, 5- Undetermined etiology

**Table 5.** Cross comparison of CCS and ASCO

| | | ASCO | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | | 2 | | 3 | | 4 | | 5 | |
| | | n | % | n | % | n | % | n | % | n | % |
| CCS | 1 | 47 | 97.92 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2 | 0 | 0 | 93 | 90.29 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3 | 0 | 0 | 0 | 0 | 26 | 100 | 0 | 0 | 5 | 4.5 |
| | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 12 | 100 | 0 | 0 |
| | 5 | 1 | 2.08 | 10 | 9.71 | 0 | 0 | 0 | 0 | 106 | 95.5 |

CCS: Causative Classification of Stroke System, ASCO: Atherothrombosis, Small vessel disease, Cardiac causes, and Other uncommon causes, 1- Large artery atherosclerosis, 2- Cardioembolism, 3- Small vessel disease, 4- Other etiology, 5- Undetermined etiology

a mean age of 67.13±14.19 years. As a result, ejection fractions were below 35% in TTE and ASCO classification have included this in the cardioembolism group as first-degree evidence. Montero et al. (10), in their recent study, emphasized that the rate of undetermined stroke decreased and the frequency of cardioembolism increased in ASCO classification compared to TOAST, and this is also supporting our study.

A significant difference was found between CCS and ASCO etiological classifications in terms of the cardioembolic subgroup (p=0.002). ASCO evaluates "ejection fraction below 35%" as first-degree evidence, "having apical akinesia in the left ventricle despite ejection fraction above 35%" as second-degree evidence, "having a history of myocardial infarction and multiple infarcts on both anterior and posterior systems" as another evidence. All these expanded criteria may have led to this significant difference. These criteria are not categorized as 'obvious or clear' according to CCS but are categorized as 'possible'. As stated before in our study, the first and second-degree evidence levels of ASCO and the obvious and clear degrees of CCS were accepted as etiological reasons for each group.

Cardioembolic etiology was found in 99 patients (33.00%) according to TOAST, 93 patients (31.00%) according to CCS and 103 patients (34.33%) according to ASCO among 300 patients who were evaluated. The reason for the higher rate of cardioembolic etiology compared to the literature may be the increased tests performed for cardiac examination thus more cardiac reasons may be determined. For example, 24-hour rhythm holter examination and transesophageal echocardiography are now more frequently performed in patients who were evaluated only with ECG and TTE in the past. In our study, paroxysmal AF was detected in 12 patients with the 24-hour rhythm holter and atrial thrombus was detected in 2 patients with TEE, and they were included in the cardioembolic subgroup instead of the undetermined group.

Twenty three cases (7.67%) according to TOAST, 31 cases (10.33%) according to CCS, 26 cases (8.67%) according to ASCO were classified as small vessel disease, and a significant correlation between them was detected. The presence of hypertension in patients with infarction of deep branch arteries, is a criterion of small artery disease according to TOAST. In our study, lacunar or deep branch infarcts were found in some patients without hypertension. The lower number of patients in TOAST can be explained by this.

To the undetermined etiology group, 113 patients (37.67%) according to TOAST, 117 patients (39.00%) according to CCS,

111 patients (37.00%) according to ASCO were included, and no significant difference was observed between them in paired comparisons. In our study, among the etiological subtypes, 'undetermined etiology group' was the group with the most patients. It was thought that the reason for this might be that the etiological examinations were normal at approximately 25%, two or more etiologies were found that could cause stroke in 6%-7% of the patients, and some patients were transferred to the intensive care unit or lost during follow-up.

## CONCLUSION

Compared to the newer systems CCS and ASCO, the TOAST classification system maintains its practicality and usability. According to the statistical results, CCS and ASCO systems could not provide any innovation according to TOAST. Considering the importance of the stroke etiology subtype in the clinical follow-up and in determining the treatment strategy, maybe different classifications will be needed.

### ETHICS

**Ethics Committee Approval:** This study, with protocol number 2017/144, was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee decision no 2017-06-32 (date: 19.06.2017).

**Informed Consent:** All patients participated in the study and their legal heirs were informed and consent were obtained.

### Authorship Contributions

Surgical and Medical Practices: A.Ö., Concept: V.Y., Design: V.Y., M.Ç., Data Collection or Processing: A.Ö., H.A.E., Analysis or Interpretation: H.A.E., İ.A., Literature Search: M.Ç., İ.A., Writing: A.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

## REFERENCES

1. Ay H. Etiologic Classification in Ischemic Stroke. Turk J Neurol 2011;17:1-6.
2. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke 2007;38:2979-84.
3. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. Ann Neurol 2005;58:688-97.
4. Arsava EM, Ballabio E, Benner T, Cole JW, Delgado-Martinez MP, Dichgans M, et al. The Causative Classification of Stroke system:

an international reliability and optimization study. Neurology 2010;75:1277-84.

5. Saatci I. İnmede görüntüleme yöntemleri. Balkan S. (Editör) Serebrovasküler hastalıklar'da. Ankara: Güneş Kitabevi; 2005. p. 207-42.

6. Marnane M, Duggan CA, Sheehan OC, Merwick A, Hannon N, Curtin D, et al. Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O, and causative classification system: direct comparison in the North Dublin population stroke study. Stroke 2010;41:1579-86.

7. Desai JA, Abuzinadah AR, Imoukhuede O, Bernbaum ML, Modi J, Demchuk AM, et al. Etiologic classification of TIA and minor stroke by A-S-C-O and causative classification system as compared to TOAST reduces the proportion of patients categorized as cause undetermined. Cerebrovasc Dis 2014;38:121-6.

8. Lanfranconi S, Markus HS. Stroke subtyping for genetic association studies? A comparison of the CCS and TOAST classifications. Int J Stroke 2013;8:626-31.

9. Özeren A, Kutluk K (ed). Klinik yaklaşım ve sınıflama. İskemikinme. Nobel Kitabevi: 2004. p. 61-73.

10. Montero MV, Pastor AG, Cano BC, García PS, Mohedano AI, Otero FD, et al. The A-S-C-O classification identifies cardioembolic phenotypes in a high proportion of embolic stroke of undetermined source (ESUS). J Neurol Sci 2016;367:32-3