INNOVATIONS in pharmacy

Volume 8 | Number 4 Article 5

11-7-2017

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Risk Factor Management with Guideline-Based Medications for Prevention of Recurrent Ischemic Stroke: A Retrospective Chart Review

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ABSTRACT

Background: *Implementation of new practice guidelines for stroke prevention has decreased the number of patients experiencing recurrent stroke. Clinical trials show antihypertensives, high-intensity statins, and antithrombotics to be beneficial after stroke.* ***Objective:*** *The objective of this study was to determine if recurrent stroke patients were discharged on guideline-based medications for secondary stroke prevention, and to identify potential errors in appropriate prescribing of medications.* ***Methods:*** *A retrospective chart review was conducted at a community hospital and included patients 19 years and older diagnosed with their second, third, or fourth stroke (transient ischemic attack or cerebrovascular accident). Descriptive statistics were used to describe collected information. Collected data included relevant patient demographics, diagnosis, past medical history, medications, and readmission rates. The primary objective was the percentage of patients appropriately discharged on guideline-based secondary stroke prevention medications. Appropriate treatment was based upon the 2010 and 2014 American Heart Association/American Stroke Association Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack.* ***Results:*** *A total of 124 charts were reviewed, 106 charts met the inclusion criteria. Guideline-based and appropriate medication-use was initiated in 9% and 4% of patients with noncardioembolic and cardioembolic stroke, respectively. Therapy deemed not guideline-based, but appropriate was initiated in 20% and 9% of patients with noncardioembolic and cardioembolic stroke, respectively. Errors in appropriate prescribing of secondary prevention medications were related to statins and antihypertensives.* ***Conclusion:*** *Better adherence to preventative recurrent stroke measures is needed at the time of patient discharge.*

Keywords: ischemic stroke, recurrent stroke, recurrent stroke prevention, secondary stroke prevention

BACKGROUND

Stroke is the second leading cause of death in the world, the fourth leading cause of death in the United States, and the leading cause of long-term disability.[1] The American Heart Association (AHA) reported in 2015 that higher rates of stroke exist among older adults, people with lower education, African-Americans, and people who live in the southeastern United States.[1] Stroke mortality is 20% higher in the stroke belt, including Alabama, than in the rest of the population, and this mortality rate doubles from 22% in primary stroke to 44% in recurrent stroke.[1,2] The annual rate of recurrent stroke is projected to decline from 5% in the 2000s to a little over 2% in the 2010s.[1] This decline may be attributed to the improvement in treatment options for secondary stroke prevention.[3]

Stroke recurrence not only increases the risk of death, but also increases disability and dependence on health services.[4] Of the 80% of stroke survivors that return post-stroke discharge, about half require permanent or temporary help from other people.[5] Close family members, e.g. spouses or children, are usually the caregivers for patients, and one-half of these family caregivers experience a high level of burden one year after their loved one's stroke.[5] A projected 3.4 million additional people will experience a new or recurrent stroke from 2012 to 2030, and the total direct medical stroke-related costs are projected to triple from $72 billion to $184 billion.[1,6] With the increased emotional and economic burden of stroke in the United States and internationally, aggressive treatment of stroke risk factors is imperative.

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Medication Management

Medications that significantly lower ischemic stroke risk include antihypertensives, HMG-CoA Reductase inhibitors (statins), antiplatelets, and anticoagulants.[3] According to the 2010 and 2014 American Heart Association/American Stroke Association (AHA/ASA) secondary stroke prevention guidelines, management of hypertension and dyslipidemia, as well as use of antithrombotic therapy, are beneficial for secondary stroke prevention. Initiation or resumption of antihypertensives is recommended following stroke to achieve blood pressure levels of <140 mmHg systolic and <90 mmHg diastolic.[7,8] Lowering blood pressure is associated with significant reductions in stroke, myocardial infarctions, and total vascular events.[9] Recommendations for antihypertensive therapy regimens are limited, but available data suggest use of diuretics with or without angiotensin-converting enzyme inhibitors (ACE inhibitors).[7,8] The treatment of dyslipidemia includes statins, which prevent secondary stroke by decreasing the progression

and promoting the regression of carotid artery plaques.[10] The recommendation for dyslipidemia therapy in secondary stroke prevention is use of high-intensity statins (HI statins) to decrease low-density lipoprotein cholesterol (LDL-C) blood levels by about 50% with a goal LDL<70 mg/dL.[11]

Antithrombotic therapy is indicated in all ischemic strokes, with the selection of therapy dependent on the type of stroke experienced. Two of the types of stroke that may occur are noncardioembolic and cardioembolic.[12,13] Antiplatelet therapy is indicated for all ischemic strokes, but if the stroke is cardioembolic in nature, oral anticoagulation therapy may be indicated instead.[7,8] The goal of antithrombotic therapy is to prevent the formation of future clots, and as a result, future strokes. Other modifiable risk factors for secondary stroke prevention such as smoking cessation, diabetes management, and weight loss, are addressed in the guidelines but were not addressed in this study.

OBJECTIVE

The purpose of this study was to determine if recurrent stroke patients were discharged on guideline-based medications for secondary stroke prevention at a community hospital, and to identify errors in prescribing of these preventative medications.

METHODS

Study Design

A retrospective chart review was conducted at a small community hospital outside of Birmingham, Alabama. Approval for this retrospective chart review was obtained from the Samford University Institutional Review and the Baptist Health System Human Research Review Boards (IRB # S-1076). A waiver of informed consent was obtained due to the scope and retrospective nature of the study. The study involved reviewing charts of patients at least nineteen years old who were diagnosed with their second, third, or fourth stroke (transient ischemic attack or cerebrovascular accident) between May 30, 2010 and May 30, 2015. Patients who did not have complete documentation, expired prior to discharge, or were discharged on comfort measures only were excluded from the study. The following data was collected: age, gender, weight, race, number of stroke, medications on admission and discharge, relevant laboratory values and allergies, location and length of stay in hospital, and if readmitted for stroke within thirty days after discharge.

The primary objective measured was the percentage of patients discharged on guideline-based stroke prevention medications. Secondary objectives measured included patients discharged on medications that were appropriate, but not guideline-based, and percentages of each class of secondary stroke prevention medications patients were discharged on. Once data was collected, descriptive statistics including averages and percentages were used to analyze the data.

Defining the Criteria

Data collected on patients' discharge medications was compared to the recommended medications for each modifiable risk factor and type of stroke. Appropriate guideline-based treatment was based upon the 2010 and 2014 AHA/ASA Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. The recording of medications on admission and discharge was focused on the following classes of medications: diuretics (loop, thiazide, thiazide-like, or potassium-sparing classes), ACE inhibitors (any agent in class), statins (high-intensity), antiplatelets (aspirin, aspirin and extended-release dipyridamole, clopidogrel, or ticlodipine), and anticoagulants (warfarin, rivaroxaban, dabigatran, or apixaban).

Additional criteria for dyslipidemia and antithrombotic treatment were considered. ASA/AHA guidelines for the treatment of dyslipidemia in secondary stroke prevention recommend use of high-intensity statins, but the guidelines defer to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Blood Cholesterol Guidelines for patients with ischemic stroke and other comorbid clinical atherosclerotic cardiovascular disease (ASCVD).[7,8,14] The ACC/AHA guidelines further define criteria for statin therapy in secondary stroke prevention. For adults ≤75 years old with clinical ASCVD not currently on statin therapy or are on a low- or moderate-intensity statin, a high-intensity statin should be started.[14] For patients where a high-intensity statin is intolerable or contraindicated, or for patients >75 years old, a moderate-intensity statin may be used.[14] Recommendations for antithrombotic treatment are antiplatelet therapy unless anticoagulation is indicated.[7,8] Combination treatment with an antiplatelet and an anticoagulant may be indicated for some patients, e.g. those with clinically apparent coronary artery disease, especially after a myocardial infarction or stent placement.[8]

To determine if a patient was on guideline-based and appropriate medications, they had to be on all of the recommended medications, depending on the type of ischemic stroke. For example, a patient who experienced a noncardioembolic stroke would need to be on a diuretic with or without an ACE inhibitor, a high-intensity statin, and an antiplatelet. For a patient who experienced a cardioembolic stroke, he or she had to be on a diuretic with or without an ACE inhibitor, a high-intensity statin, an oral anticoagulant with or without an antiplatelet depending on other comorbid conditions. For a patient with allergies or contraindications to the recommended medications (e.g. angioedema with an ACE inhibitor, impaired renal function as a result of or preventing use of a diuretic, or myopathy from a statin), the investigators' clinical judgement was used to determine if the regimen he or she was discharged on was appropriate, even if not guideline-based. If a patient was not on the guideline-based medications, and there were no documented contraindications, he or she

was considered to be discharged on a regimen that was not guideline-based.

RESULTS

Data collection and analysis was conducted from the electronic health record at a small community hospital. Analysis was conducted using descriptive statistics. Nominal data, including the number of patients who were discharged on appropriate preventative medications, were analyzed using proportions.

A total of 124 patient charts were reviewed, and 105 patients were included in the analysis. The excluded patients did not meet inclusion criteria and were therefore removed from analysis. Of the 105 patients, 82 experienced a noncardioembolic stroke and 23 experienced a cardioembolic stroke. The majority of patients were admitted with their second stroke (84%). The patients in the study were 68 years old on average, 54% male, and 83% white (Table 1).

Guideline-based and appropriate medication use was initiated at discharge in 8% and 4% of patients with noncardioembolic and cardioembolic stroke, respectively. Therapy deemed not guideline-based, but appropriate was initiated in 20% and 9% of patients with noncardioembolic and cardioembolic stroke, respectively (Table 2). At discharge, 70 to 90% of patients who were admitted with their second, third, or fourth stroke were on inappropriate secondary prevention treatment. Errors in prescribing at discharge for noncardioembolic and cardioembolic strokes were largely related to antihypertensive and high-intensity statin use. Evaluation of antihypertensive use reveals that 15% of patients with noncardioembolic stroke and 26% of patients with cardioembolic stroke were discharged on a diuretic plus an ACE inhibitor; 13% and 4% were discharged on a diuretic only. Use of an ACE inhibitor without a diuretic was used in 52% and 65% of patients with noncardioembolic and cardioembolic strokes, respectively. Of note, 16 patients were discharged on an angiotensin II receptor blocker (ARB) in place of an ACE inhibitor. The use of high-intensity statins was 26% in patients with noncardioembolic stroke and 17% in patients with cardioembolic stroke. Appropriate use of moderate-intensity statins in place of high-intensity statins was initiated in 13 patients overall.

Antithrombotic therapy was prescribed the the vast majority of patients with 95% of patients receiving an antiplatelet if they had a noncardioembolic stroke, and 96% of patients receving an oral anticoagulant if they had a cardioembolic stroke. Of note, in patients with a cardioembolic stroke, 18 were prescribed an oral anticoagulant plus an antiplatelet. Of those 18 patients, only 10 had documented indications of atrial fibrillation and coronary artery disease. All percentages of medication class-specific use are listed in Tables 5 and 6 and Figures 1 and 2.

DISCUSSION

The findings in this study reveal that a sample of patients in this community hospital were not discharged on guideline-based or appropriate medications for secondary stroke prevention. The majority of deviations in prescribing from guidelines are related to hypertension and dyslipidemia management. While some clinicians may argue that guidelines serve to provide guidance to practitioners and are not a set of rules to adhere to, there is ample evidence to promote current guidelines for management post-stroke as “best practices”. Evidence to support guideline recommendations for post-stroke pharmacotherapy management is discussed in the sections below.

Dyslipidemia and Hypertension Management

Before and during the development of the AHA/ASA stroke guidelines, new studies were conducted investigating effective management of dyslipidemia and hypertension after stroke. The landmark study illustrating benefit of high intensity statins was the SPARCL trial, which evaluated the use of atorvastatin 80 mg versus placebo.[15] Atorvastatin 80 mg reduced the overall risk of stroke despite an increased incidence of hemorrhagic stroke.[15] The most common adverse effect reported in the study was elevated liver enzymes.[15] Even with the potential for hepatic injury, high-intensity statins are recommended as tolerated, with a moderate-intensity statin used as a secondary option.[7,8,14] Furthermore, studies evaluating the use of moderate-intensity statins in secondary stroke prevention showed that individuals >75 years experienced a reduction in ASCVD events, compared with control. A moderate-intensity statin should be considered for individuals >75 years with clinical ASCVD, unless they are currently tolerating a high-intensity statin.[14] In this study, thirteen patients met the criteria for initial use of a moderate-intensity statin, but many patients were either continued or started on a moderate-intensity statin. Arnan et al published a study that addressed secondary stroke prevention in the elderly.[16] The investigators pointed out that stroke mortality increases with age, and the majority of strokes occur in those over 65 years of age. This finding correlates to those found in this study, as the average age of patients experiencing a recurrent stroke was 68 years old. They acknowledged the concern for adverse effects in the elderly and agreed with the recommendation of the 2013 ACC/AHA cholesterol guidelines. Overall, with the increased incidence and risk of poor outcomes, it is even more important to have close follow-up and management of elderly patients.

Studies evaluating hypertension management include the HOPE trial, the PROGRESS trial, the MOSES trial, and the PRoFESS trial.[17-22] The HOPE trial evaluated the use of ramipril versus placebo and revealed that despite a modest reduction in blood pressure, ramipril reduced the incidence of stroke and other vascular events over the four and a half years of the study.[18,19] The PROGRESS trial evaluated the use of perindopril versus placebo; indapamide could be added to the treatment regimen at physicians’ discretion as well.[20] Over the four year

study, the combination of an ACE inhibitor and diuretic produced a greater reduction in blood pressure, and a larger risk reduction versus the ACE inhibitor alone.

The MOSES trial sought to evaluate the benefit of eprosartan versus nitrendipine.[21] Over the two and a half year follow-up, there was a comparable decrease in blood pressure between the two groups, but the combined primary end point of cardiovascular and cerebrovascular events was significantly lower in the eprosartan group. In contrast, a few years later, the PRoFESS trial evaluated the use of telmisartan (ARB) versus placebo in a larger sample of patients.[22] After a two and half year follow-up, telmisartan did not significantly lower the rate of recurrent stroke. There is a need for more studies investigating the different therapy options for hypertension management post-stroke. One limitation to most studies is that African Americans and other racial-ethnic minorities are under-represented in the trials, even though these minorities are associated with a higher risk of stroke and other vascular diseases.[2] Therefore, it would be beneficial for future studies to investigate not only alternative regimens, but specific regimens for other patient populations.

Boan et al reported that up to 50% of strokes might be attributable to exposure to high blood pressure, and initiation of antihypertensives while in the hospital potentially improves both medication adherence and risk of recurrent vascular events. [17] In the study, investigators analyzed the use of antihypertensives one-year post-stroke hospitalization. A total of 270 patients were included. About 80% of the patients were discharged on antihypertensive therapy. Of those not discharged on antihypertensives, 26% were started on therapy prior to follow-up, whereas 74% were never started on therapy after hospital discharge. The study further subdivided the use of medications by class. About 30% of patients were discharged on a diuretic in the study, which correlated to the findings of this study. In another study conducted by the same investigators, the investigators reported that blood pressure remains poorly controlled throughout long-term follow up after stroke.[2] The study emphasized the overwhelming gray area surrounding lowering blood pressure for recurrent stroke prevention; when and how to lower blood pressure post-stroke, and if different regimens are beneficial in different groups of patients.[2]

The NEMESIS study in Australia examined blood pressure control at five years post-stroke.[23] About 450 patients were evaluated in the study, but only 300 of them had complete data (blood pressure measurement, medication records, and survey). Results showed that 82% of the patients were diagnosed with hypertension; 52% were controlled (90% on therapy), and 30% were uncontrolled (67% on therapy). Rashid et al conducted a systematic review of seven randomized clinical trials that evaluated lowering blood pressure for secondary stroke prevention.[9] The investigators reported that trials evaluating hypertension management recruited patients regardless of what their blood pressure was, and lowering the blood pressure resulted in decreased vascular events, including recurrent stroke. Blood pressure management compared to dyslipidemia management is a treat-to-goal recommendation versus a fixed-dose recommendation with high-intensity statins. Close management and follow-up with blood pressure control post-stroke is crucial.

Standardized Discharge Orders

Multiple studies have evaluated the use of standardized discharge orders as well as integrated care plans post-stroke. Currently there is insufficient evidence to support routine implementation of standardized discharge orders. Johnston et al. evaluated the use of standardized discharge orders at the hospital level for adherence to preventative measures six months post-discharge from an ischemic stroke.[24] The study evaluated the adherence to normalization of blood pressure, treatment with a statin, and treatment with anticoagulation among patients with atrial fibrillation; outcomes measured using documentation of prescription refills and achieving normal blood pressure after six months. The study did not evaluate the use of antiplatelets among patients because the investigators were unable to follow-up with prescription refills, as many patients received their antiplatelet over-the-counter. An estimated 3000 patients were included in this study. Overall, the implementation of standardized discharge orders resulted in greater adherence to the study's primary outcome measure, but the results were not statistically significant. The investigators concluded that even though there was no statistical significance in the study, standardized discharge orders were a focused, inexpensive intervention. A limitation of this study would be the lack of antiplatelet evaluation. Even though many patients receive their antiplatelet over-the-counter, i.e. aspirin in various doses, other antiplatelets, clopidogrel and aspirin-dipyridamole, are utilized post-stroke and are prescription only medications.

Another study by Wolfe et al evaluated the benefit of extensive patient education and team management of medications and risk factors.[4] The study also found no statistical significance; however, during the study, the United Kingdom Department of Health introduced quality and outcome measure strategies. Investigators believe these skewed the results, as the health care professionals were impacted by this change, and this was not accounted for in the original design of the study. A multicenter trial in Australia developed a standardized integrated care (IC) model for patients after a stroke.[25] This IC model targeted seven modifiable risk factors including blood pressure, cholesterol, atrial fibrillation, body mass index (BMI), smoking, alcohol intake, and physical activity. The IC model included optimization of pharmacotherapy and patient education, with counseling specific towards stroke risk factor modification. Over the year of the study, patients in the IC group, compared to the control group, met their goals for

systolic blood pressure and BMI and showed greater improvement in disability. One limitation of the study was rates of recurrent stroke were not evaluated.

Limitations and Challenges

Limitations of this study and analysis of results include incomplete documentation of contraindications to medications, economic factors and patient access to medications, patients receiving additional treatment at outside facility, and sample size when compared to similar published studies. Even with these limitations, the adherence to evidence-based practice was staggeringly low for patients admitted with recurrent ischemic stroke. Theoretical challenges for secondary prevention include lack of prioritization and consistency of secondary prevention follow-up and treatment by health care professionals.[26,27] Gaps in education and health literacy also exist between patients and physicians, which may create a poor environment for addressing patient concerns and decrease adherence to medications.[10] Finally, unlike previous studies, this study was conducted in a smaller community hospital, which may be more representative of "real-life" care experienced by patients in rural settings. Further studies would be necessary to identify the significance of disparities in guidelines versus care received in academic versus community hospital settings, as well as the reasons behind them.

There is much room for improvement in risk factor management among secondary stroke patients. Studies acknowledge that patients with risk factors for stroke typically do not follow physicians' suggestions regarding lifestyle modifications and adherence to medications for prevention.[10] Achieving a comprehensive patient education and medication management plan post-stroke would likely improve patients' understanding of their disease state, the importance of secondary prevention, and how to manage their risk factors. These tasks could be completed by healthcare professionals such as pharmacists, who are increasingly available in hospital settings to assist in transitions of care, medication reconciliation, and patient education, and who are trained specifically to manage complex medication regimens and improve patient education on medication use.

CONCLUSION

Significant opportunities for improvement in secondary stroke prevention prior to hospital discharge exist in this setting of a community hospital. Secondary prevention of stroke through optimized pharmacotherapy is crucial in order to promote the best possible patient outcomes. Standardized care plans are one potential option to promote better adherence to practice guidelines for post-stroke patient management, in addition to discharge orders and increased patient counseling which are focused and inexpensive interventions that can improve adherence to secondary stroke prevention measures. Further research is needed to compare the difference in guideline-driven care received by patients in community versus academic hospitals, and to identify effective solutions in both settings.

Acknowledgements: None

Conflict of interest: We declare no conflicts of interest or financial interests that the authors or members of their immediate families have in any product or service discussed in the manuscript, including grants (pending or received), employment, gifts, stock holdings or options, honoraria, consultancies, expert testimony, patents and royalties.

Funding/support: None

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APPENDIX

Table 1. Patient Demographics

Patient Demographics	
Characteristic	No. (%)
Mean Age (yrs)	68 ± 11
Gender	
Male	57 (54%)
Female	48 (46%)
Race	
White	87 (83%)
African American	17 (16%)
Hispanic	1 (1%)
Relevant disease states	
Chronic kidney disease/renal insufficiency	27 (26%)
Atrial fibrillation	20 (19%)
Atrial fibrillation + coronary artery disease	12 (11%)
Documented allergies/intolerances to recommended medications (anaphylaxis, myopathy, drug-induced electrolyte imbalances, etc.)	
On admission	9 (9%)
New onset intolerances at discharge	8 (8%)
Total Strokes (n=105)	
Noncardioembolic Stroke	82 (78%)
Cardioembolic Stroke	23 (22%)
#Stroke for Patient	
Second	88 (84%)
Third	11 (10%)
Fourth	6 (6%)
Readmission for stroke within 30 days	4 (4%)

Table 2. Appropriate Medication Use

Appropriate Medication Use		
	No. (%)	No. (%)
	Noncardioembolic	Cardioembolic
Guideline-based; appropriate	7 (8%)	1 (4%)
Not guideline-based; appropriate	16 (20%)	2 (9%)
Not guideline-based; not appropriate	59 (72%)	20 (87%)

Table 3. Overall Breakdown of Medication Use

Overall Breakdown of Medication Use		
	Patients Prescribed (%)	Patients Prescribed (%)
	Noncardioembolic	Cardioembolic
Diuretic	23 (28%)	7 (30%)
Diuretic only	11 (13%)	1 (4%)
Diuretic + ACEi	12 (15%)	6 (26%)
ACE inhibitor (ACEi)	43 (52%)	15 (65%)
High Intensity Statin	21 (26%)	4 (17%)
Antiplatelet	78 (95%)	19 (83%)
Oral Anticoagulant (OAC)	----	22 (96%)

Table 4. Medication Use within Each Outcome

Medication Use Within Each Outcome		
	Patients Prescribed (%)	Patients Prescribed (%)
	Noncardioembolic	**Cardioembolic**
Guideline-based; appropriate	**7 (9%)**	**1 (4%)**
Diuretic	7	1
ACE inhibitor (ACEi)	5	1
High Intensity Statin	6	1
Antiplatelet	7	1
Oral Anticoagulant (OAC)	----	1
Not guideline-based; appropriate	**16 (20%)**	**2 (9%)**
Diuretic	4	0
ACE inhibitor (ACEi)	10	2
High Intensity Statin	7	0
Antiplatelet	15	2
Oral Anticoagulant (OAC)	----	2
Not guideline-based; not appropriate	**59 (72%)**	**20 (87%)**
Diuretic	12	6
ACE inhibitor (ACEi)	31	13
High Intensity Statin	8	3
Antiplatelet	57	16
Oral Anticoagulant (OAC)	----	19

Figure 1. Medication Use in Noncardioembolic Stroke

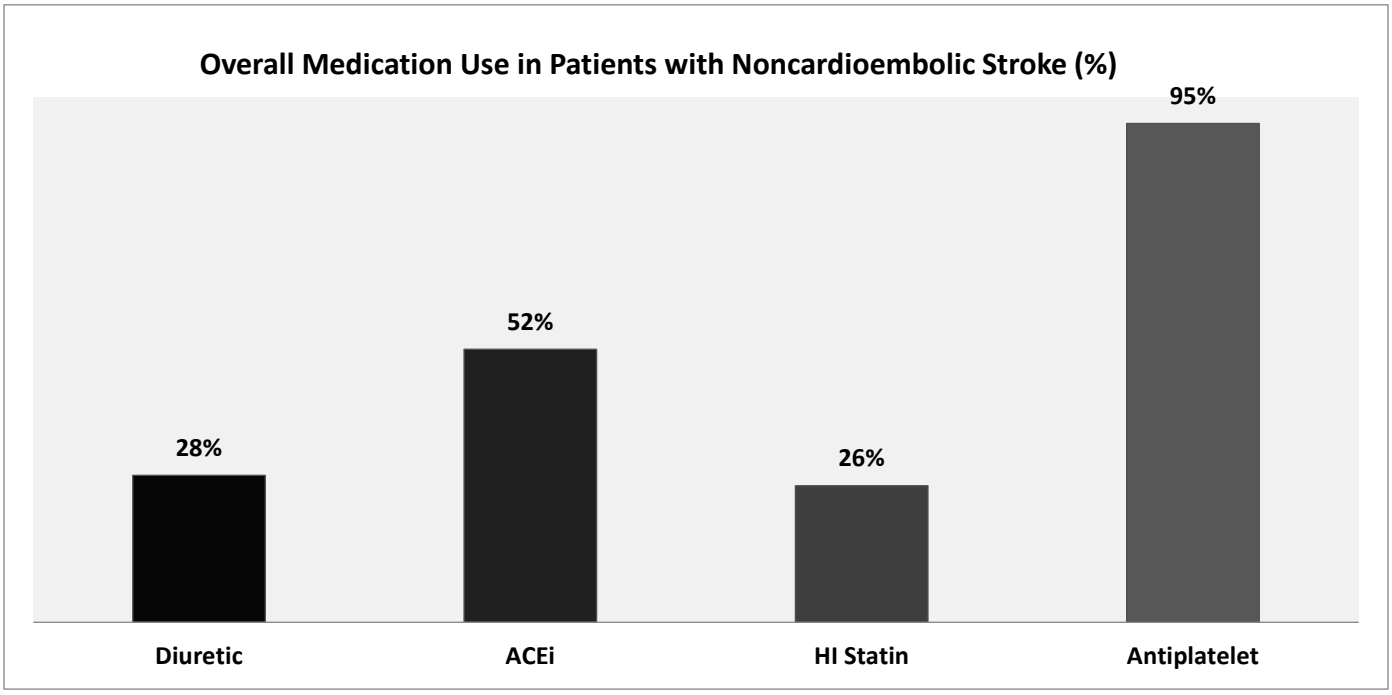

Figure 2. Medication Use in Cardioembolic Stroke