Effect of Dual Antiplatelet Therapy on Gastric Mucosa in Stroke Patients (Endoscopic Evaluation)

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Abstract

Introduction: Our study was conducted prospectively on twenty patients with acute non-hemorrhagic cerebro-vascular stroke in the period from December 2007 to December 2008 aiming at evaluating and comparing gastric complications of dual antiplatelet therapy Vs Monoantiplatelet therapy using upper GI endoscopy.

Methods: Patients were divided into 2 equal groups (Group A, maintained on Aspocid 150mg & group B maintained on Aspocid 150mg plus Clopidogrel 75mg). Both groups were maintained on antiplatelets for 1 week and evaluated endoscopically twice, according to Rypins grading of gastric mucosa [1], once upon admission and another follow-up after a week of initiating antiplatelet therapy to detect gastric complications.

Results: There was no significant difference as regard age of both groups (p-value 0.496). Sex had non significant difference (p-value 0.65). There was a non significant difference between the two groups regarding diabetes mellitus, hypertension, smoking, previous CVA and dyslipidemia. A non significant difference between both groups regarding neurological findings (p-value 0.82). Regarding Glasgow Coma Scale (GCS), there was non significant difference between the two groups (p-value 0.125). A non significant difference between the two groups regarding presence of gastric symptoms (p-value 0.582). As regards previous usage of antiplatelets, there was a significant difference between the two groups (p-value 0.007). In Group A, Ninety percent of patients had the same endoscopic findings (grading 0-3) at day 0 and day 7 and only 10% of patients deteriorated, regarding endoscopic findings, from grade 0 to grade 7. In group B, Forty percent of patients had the same endoscopic gastric findings (grading 0-4) and 60% deteriorated-10% of them progressed from grade 1 to 7,10% progressed from grade 2 to 7,20% progressed from grade 3 to 7,10% progressed from grade 0 to 3 and 10% progressed from grade 3 to 6. There was statistically significant difference in both groups with a p-value 0.0198 that indicated that gastric complication increased markedly with usage of dual antiplatelets drugs in relation to Monoantiplatelet drugs. A non significant difference between the two groups regarding the outcome (mortality) (p-value 1.0).

Conclusion: The combination of dual antiplatelet therapy (Aspirin & clopidogrel) increased gastric complications in comparison to Monoantiplatelet therapy (Aspirin) alone and so it is not recommended.

Key Words: Aspirin – Clopidogrel – Cerebrovascular stroke – Upper endoscopy.

Introduction

STROKE is the third leading cause of death in the United States. It is the leading cause of adult disability in the United States and Europe. It is the number two cause of death world-wide and may soon become the leading cause of death worldwide [1]. Risk factors for stroke include advanced age, hypertension (high blood pressure), previous stroke or transient ischemic attack (TIA), diabetes, high cholesterol, cigarette smoking, atrial fibrillation, estrogen-containing forms of hormonal contraception, migraine with aura, and thrombophilia (a tendency to thrombosis), patent foramen ovale and several rarer disorders. High blood pressure is the most important modifiable risk factor of stroke.

Currently, antiplatelet agents are recommended for the prevention of recurrent ischemic vascular events [2]. Although these agents are primarily used as monotherapy, recent data suggest that outcomes can be improved with dual antiplatelet therapy.

Antiplatelets are drugs that decrease platelet aggregation and inhibit thrombus formation. They are effective in the arterial circulation, where anticoagulants have little effect. They are widely used in primary and secondary prevention of thrombotic cerebro-vascular or cardiovascular disease. Low doses of aspirin are recommended for the prevention of stroke, and myocardial infarction in patients with either diagnosed coronary artery disease or who have an elevated risk of cardiovascular disease.
Clopidogrel reduces the risk of serious vascular events among high-risk patients by about 10% as compared with aspirin. It is as safe as aspirin, but much more expensive.

The suppression of gastro-duodenal mucosal prostaglandin synthesis is one of the important mechanisms of mucosal damage by acetyl salicylic acid [3]. Serious GI ulcer complications are 2- to 4-fold more common in patients who take 75 to 300mg/d of aspirin compared with controls. During a 4-year period in the United Kingdom Transient Ischemic Attack study, GI complications in patients taking aspirin ranged from mild dyspepsia (31%) to life-threatening bleeding and GI erosions or ulcerations and perforation (8%) [4].

Both European and American guidelines recommend the use of antiplatelets drugs in patients with established coronary heart disease and other atherosclerotic diseases [5].

Many trials suggested that dual antiplatelets therapy would prevent (20 to 30) ischemic events per 1000, at a cost of (1.7) severe bleeds and (7.6) moderate bleeds.

Material and Methods

Over a period of one year starting from December 2007 to December 2008 twenty patients were admitted to Critical Care Department, Cairo University with Acute Non-haemorrhagic cerebro-vascular stroke. Patients were divided into two equal groups A&B. Each consists of ten patients. Group A, represents patients who received Aspirin as a Monoantiplatelet therapy, Group B, represent patients who received Aspirin & Clopidogrel as a Dual antiplatelet therapy for 1 week in both groups.

Inclusion criteria:

All patients in the study were admitted to our department with Acute Non-hemorrhagic Cerebro-vascular Stroke and started oral Antiplatelet therapy within 24 to 48 hours.

Exclusion criteria:

1- Liver cirrhosis with bleeding esophageal varices.
2- Patients with a contraindication to Gastroscopy.
3- Bleeding tendency.
4- Patient with a contraindication to Antiplatelet therapy.
5- Congenital coagulopathy.

All patients were evaluated on admission by:

1- Full clinical assessment including history & general examination.
2- Full neurologic examination, Glasgow Coma Score (GCS) and CT brain (to exclude cerebral hemorrhage).
3- Laboratory assessment:
   - Complete blood picture (CBC), Renal function tests (Urea, Creatinine), Random blood sugar (RBS), Coagulation profile (PC, INR, PTT, PT), Liver function tests (SGPT, SGOT, T.Bil, D.Bil, Total protein and Serum albumin) and Cholesterol Level.
4- Abdominal ultrasound.
5- ECG and echocardiography.
6- Upper GIT endoscopy.

Patients had upper GI endoscopy in the day of admission before starting oral antiplatelets therapy with follow-up of symptoms (dyspepsia, epigastric pain), signs (Haematemesis) and laboratory abnormalities and another upper GI endoscopy was done one week later after starting Antiplatelet therapy to evaluate gastric mucosal changes (gastritis, gastric or duodenal ulcers) according to the following endoscopic grading.

Endoscopic grading of gastric lesions:

A Standard fiber-optic endoscope (Olympus GIF XQ-20 & XQ-30) was used and the procedure was done under sedation with midazolam or propofol for conscious patients and without sedation in comatose patients. Between each use, endoscope is disinfected using standard disinfection procedure.

Table (1): Endoscopic grading of gastric lesions [1].

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal mucosa.</td>
</tr>
<tr>
<td>1</td>
<td>Slight, diffuse hyperaemic changes.</td>
</tr>
<tr>
<td>2</td>
<td>Single hemorrhagic lesion.</td>
</tr>
<tr>
<td>3</td>
<td>2-5 hemorrhagic lesions.</td>
</tr>
<tr>
<td>4</td>
<td>6-10 hemorrhagic lesions partially confluent or Connected with areas of Patchy erythema.</td>
</tr>
<tr>
<td>5</td>
<td>Large areas of confluent hemorrhagic lesions and/or patchy erythema.</td>
</tr>
<tr>
<td>6</td>
<td>Erosions with white bases surrounded by erythematous edges.</td>
</tr>
<tr>
<td>7</td>
<td>Ulcer.</td>
</tr>
</tbody>
</table>

Limitations:

Problems of gastrointestinal function are usually not well diagnosed by endoscopy since motion or secretion of the gastrointestinal tract is not easily
inspected by Endoscopy. Nonetheless, findings such as excess fluid or poor motion of gut during endoscopy can be suggestive of disorders of function. Irritable bowel syndrome and functional dyspepsia is not diagnosed with upper GI endoscopy, but upper GI endoscopy may be helpful in excluding other diseases that mimic these common disorders.

Statistical methods:

- Data were summarized using mean & standard deviation for quantitative variables & percent for quantitative variables, compare between groups was done using chi-square for qualitative variables & independent samples t-test for normal distributed quantitative variables while quantitative variables not normally distributed were compared using non-parametrical Mann-Whitney test & Wilcoxon signed rank test.

- $p$-value <0.05 was considered statistically significant.

Results

A- Demographic data:

The mean age of the studied population was 66±10.193 years (nine patients were males and eleven were females). The age of all patients in the study ranged from 39 to 85 years. The mean age in the first group was 65±10.59 years. The mean age in the second group was 66±10.31 years. There was no significant value as regard age of both groups with $p$-value 0.496. As regards sex, there was no significant difference between the two groups with $p$-value 0.65.

Table (2): Age, sex distribution in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65±10.59</td>
<td>66±10.31</td>
<td>0.496</td>
</tr>
<tr>
<td>Sex</td>
<td>50% males</td>
<td>40% males</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>50% females</td>
<td>60% females</td>
<td></td>
</tr>
</tbody>
</table>

B- Risk factors for ischemic cerebro-vascular stroke:

Table (3): Risk factors distribution for whole population.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Group A</th>
<th>Group B</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers/Non-smokers</td>
<td>4/16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>7 (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensives</td>
<td>11 (55%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemias</td>
<td>12 (60%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous CVA</td>
<td>4 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous usage of antiplatelets</td>
<td>10 (50%)</td>
<td></td>
<td></td>
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Baseline characteristics for both groups (Risk factors):

30% of group A patients were diabetics while in group B 40% were diabetics, with a non-significant $p$-value (1.0) between both groups. As regards hypertension, there was non significant difference between the two groups as in group A, 60% of patients were hypertensives and in group B, 50% of patients were hypertensives with $p$-value (1.0).
There was no significant difference between the two groups regarding Dyslipidemia as In group A, 60% of patients were Dyslipidemic and the same percentage in group B with \( p \)-value (1.0). Also, a non significant difference between the two groups as regards presence of previous CVA (cerebro-vascular accidents) as in group A & B 10% and 30% of patients had previous CVA respectively with \( p \)-value (0.58). Regarding smoking, a non significant difference between the two groups as In group A,20% of patients were cigarette smokers and the same percentage in group B with \( p \)-value (1.0).

C- Neurologic findings and neuro-imaging data:

There was no significant difference in the two groups regarding neurologic findings. In group A, 60% of patients had middle cerebral artery (MCA) affection, 20% had Posterior cerebral artery affection, 10% had anterior cerebral artery affection and 10% had vertebrobasilar artery affection (10%). In group B, 50% patients had middle cerebral artery (MCA) affection, 20% had posterior cerebral artery affection, 30% had anterior cerebral artery affection. \( p \)-value was (0.82).

Regarding Glasgow Coma Scale (GCS), there was no significant difference between the two groups as In group A, 10% of patients had GCS 11, 10% had GCS 12, 10% had GCS 14 and 70% had GCS 15. In group B, 20% of patients had GCS 7, 40% had GCS 11 and 40% had GCS 15. \( p \)-value was (0.125).

There was no significant difference between the two groups regarding CT brain findings as In group A, 60% of patients had cerebral infarction in the Middle cerebral artery (MCA) territory, 10% had infarction at anterior cerebral artery territory, 30% had infarction at Posterior cerebral & Vertebrobasilar arteries territories. In group B, 50% of patients had cerebral infarction at middle cerebral artery (MCA) territory, 30% had infarction at the Anterior cerebral artery territory and 20% had infarction at the posterior cerebral & vertebrobasilar arteries territories (\( p \)-value = 0.7).

D- Selected gastric symptomatology and endoscopic findings:

There was no significant difference between the two groups regarding presence of gastric symptoms: Regarding upper gastrointestinal manifestations patients were classified according to selected gastric symptoms into symptomatic (epigastric pain, Haematemesis) and asymptomatic. Other gastric symptoms (Nausea, vomiting, dyspepsia, heart burn) were included but they were rare and had no significance.

In group A, 10% of patients were symptomatic (Epigastric pain and haematemesis) and in group B, 30% of patients were symptomatic-10% of them had haematemesis and the other 20% had Epigastric pain. \( p \)-value was (0.582).

Regarding endoscopic gastrointestinal findings, Patients had two upper GI Endoscopies; the first was done at day of admission (day 0) and the other follow-up endoscope was done after one week. Patients were classified according to gastric findings into grades from (0-7) according to Rypins E, et al. [1].

a- The admission endoscopy findings (day 0):

In group A, 60% of patients had grade 0 (normal mucosa), 30% had grade 2 (single hemorrhagic lesion) and 10% had grade 3 (2-5 hemorrhagic lesions). In group B, 30% of patients had grade 0 (normal mucosa), 10% had grade 1 (slight diffuse hyperaemic changes), 10% had grade 2 (single hemorrhagic lesion) and 50% had grade 3 (2-5 hemorrhagic lesions). \( p \)-value was (0.165).

Fig. (3): Endoscopic findings at day 0 in both groups.

b- Follow-up endoscopy (day 7):

In group A, 30% of patients had grade 0 (normal mucosa), 20% had grade 1 (slight diffuse hyperaemic changes), 40% had grade 3 (2-5 hemorrhagic lesions) and 10% had grade 7 (Ulcer). Ninety percent of patients had the same endoscopic findings (grading 0-3) at day 0 and day 7 and only 10% of patients deteriorated, regarding endoscopic findings, from grade 0 to grade 7.

In group B, 20% of patients had grade 1 (slight diffuse hyperaemic changes), 10% had grade 3 (2-5 hemorrhagic lesions), 20% had grade 4 (6-10 hemorrhagic lesions partially confluent), 10% had
grade 6 (Erosions with white bases surrounded by erythematous edges) and 40% had grade 7 (Ulcer). Forty percent of patients had the same endoscopic gastric findings (grading 0-4) and 60% deteriorated-10% of them progressed from grade 1 to 7, 10% progressed from grade 2 to 7, 20% progressed from grade 3 to 7, 10% progressed from grade 0 to 3 and 10% progressed from grade 3 to 6.

There was statistically significant difference in both groups with a $p$-value 0.0198 that indicated that gastric complication increased markedly with usage of dual antiplatelets drugs in relation to Monoantiplatelet drugs.

There was no significant difference between the two groups regarding the outcome (mortality) as in group A, 90% of patients were Survivors and in group B, 80% were Survivors with a $p$-value (1.0).

**Discussion**

Age is an important risk factor with the relative increase beginning at age 60 years and rising in a non-linear fashion, but in our study, there was a non-significant difference between both groups as regards mean age $65 \pm 10.59$ years & $66 \pm 10.31$ years in group A & B respectively and there was no significant relation between Age and upper gastrointestinal complications in patients receiving antiplatelets therapy with a $p$-value ($>0.05$).

Gender is a less important concern, although the risk of stroke between men is slightly higher than that of women [6]. Similar to Hernandez-Diaz S, et al. [7] our results showed that risk of gastrointestinal complications was equal in both males and females (50% Vs. 50%) and there was insignificant relation in both groups with $p$-value >0.05.

Regarding risk factors for cerebro-vascular stroke, we studied Hypertension, Diabetes, Dyslipidemia, Previous use of antiplatelets and smoking in both groups and their specific relation with gastric complications in stroke patients.

In our study there was non-significant difference in both study groups regarding risk factors. Meta-analyses of randomized controlled trials confirm an approximate 30% to 40% stroke risk reduction with BP lowering [8,9].

Although a wealth of data from a variety of sources support the importance of treatment of hypertension for primary cardiovascular disease prevention in general and in stroke in particular, only limited data directly address the role of BP treatment in secondary prevention among persons with stroke or TIA [9].

In our study, there was a non-significant difference between both groups as regards hypertension as 60% & 50% of patients in group A & B respectively were hypertensives but with a non significant $p$-value (1.0) as regards gastric complications.

Diabetes is estimated to affect 8% of the adult population [10] and it is frequently encountered in stroke care. Diabetes is known as a clear risk factor for stroke [11]. In a community-based stroke study, the Oxfordshire Stroke Project, diabetes was 1 of 2 factors independently associated with stroke recurrence ($p$-value 0.01) and investigators estimated that 9.1% of the recurrent strokes were attributable to diabetes [12]. Furthermore, diabetes has been shown to be a strong determinant for the presence of multiple lacunar infarcts in 2 different stroke cohorts [13].

In our study, although 30% & 40% of patients in group A & B respectively were diabetics, there was a non significant difference in both groups regarding diabetes mellitus and there was a non significant relation regarding gastric complications ($p$-value 1.0).

Hypercholesterolemia and hyper-lipidemia are not as well established as risk factors for first or recurrent stroke in contrast to what is seen in cardiac disease [14,15]. Overall, prior observational cohort studies have shown only a weakly positive
association for cholesterol level and risk of ischemic stroke or no clear relationship between plasma cholesterol and total stroke, and stroke risk reduction in statin trials may be primarily for nonfatal stroke [16]. Recent clinical trial data suggest, however, that stroke may be reduced by the administration of statin agents in persons with CHD [17]. The risk reductions with statins were beyond that expected solely through cholesterol reductions and have led to the consideration of other potential beneficial mechanisms.

The recommendation in very-high-risk persons is to aim for an LDL-C of 70mg/dL [18]. Very-high-risk patients are those who have established cardiovascular disease plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglycerides 200mg/dL with low HDL cholesterol (40mg/dL), and (4) patients with acute coronary syndromes.

In agreement with our results, 60% of patients were dyslipidemias with a non-significant difference between both groups regarding dyslipidemia and there was a non significant increase as regards gastric complications (p-value 1.0).

There is strong and convincing evidence that cigarette smoking is a major independent risk factor for ischemic stroke [19]. The risk associated with smoking is present at all ages, in both sexes, and among different racial/ethnic groups [20]. In a metanalysis, smoking has been shown to be associated with a doubling of risk among smokers compared with nonsmokers. The pathological pathway contributing to increased risk includes changes in blood dynamics [21] and vascular stenosis [22].

In our study, only 20% of patients were smokers with a non-significant difference in both groups regarding smoking and there was a non-significant increase as regards presence of gastric complications (p-value 1.0).

The efficacy of aspirin in the secondary prevention of MI and stroke has been demonstrated in the Antiplatelet Trialists’ Collaboration (ATC) meta-analysis [23] and several large-scale clinical trials including the International Stroke Trial (IST) [24] the Chinese Acute Stroke Trial (CAST) [25] and the Second International Study of Infarct Survival (ISIS-2) [26]. Data from IST showed that early initiation of aspirin (median time to randomization, 19 hours) in 19,435 patients with acute stroke reduced both the risk of stroke recurrence and mortality [24].

Among elderly patients, dose reduction does not appear to reduce antithrombotic benefits; however, dose escalation seems to increase bleeding complications [27].

The ACC and AHA recommend lowering the dose from 325 to 81mg among those with a high risk of Upper Gastro Intestinal Events [28].

The American Academy of Neurology (AAN) and American Stroke Association (ASA) have published recommendations regarding the importance of antithrombotic agents in reducing early stroke recurrence (4 weeks after the first event) [29]. These guidelines state that aspirin reduces risk of early recurrent ischemic stroke when given within 48 hrs after stroke onset but increases risk of hemorrhagic stroke (absolute risk reduction, 0.7%). Although Antiplatelets agents have been shown useful for preventing recurrent stroke or stroke after TIAs, efficacy in the treatment of acute ischemic stroke has not been demonstrated.

The use of low-dose aspirin is associated with a 2- to 4-fold increased risk of Upper Gastro Intestinal Events [4] which is not reduced by the use of buffered or enteric-coated preparations [30].

This similar to our study as previous usage of Aspirin had a significant increase as regards development of gastric complications (p-value 0.007).

Clopidogrel is an appropriate alternative to aspirin since it is at least as safe as aspirin. This preference for clopidogrel in the management of recent MI, stroke, and TIA is consistent with the recommendations from the American College of Chest Physicians and the American Heart Association Stroke Council [31,32]. When Clopidogrel was compared with aspirin in a systematic review of four randomized controlled trials (n=22,656) involving patients with a history of recent ischemic stroke or TIA, recent MI, or symptomatic PAD, a modest but significant reduction (9%) in the odds of developing acute MI, stroke, or vascular death was shown with the ADP receptor antagonists [33].

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial found an 8.7% relative-risk reduction (5.32% versus 5.83%) in the composite endpoint of ischemic stroke, MI, and vascular death in favor of clopidogrel versus aspirin (p=0.043) in patients with a recent ischemic stroke, recent MI, or established PAD [3]. It remains unclear whether clopidogrel exerts an independent injurious effect on the GI mucosa, or whether it merely induces bleeding in already damaged mucosa via its antiplatelet effects. Observational
studies have suggested that PPI co-therapy is beneficial to reduce the risk of Clopidogrel monotherapy as well [34].

An in vitro study suggested that haemostasis depends on pH and the stability of the platelet plug [35], antiplatelet drugs may negate the haemostatic effect of a PPI by impairing platelet-plug formation.

Our study agreed with Bhatt, et al. [36] in the part of early excess bleeding with dual antiplatelets, who noted that the benefit in preventing ischemic events is greatest early after treatment began and in patients with a recent previous ischemic event, and the bleeding excess is also greatest early, with more bleeding seen with dual antiplatelets therapy compared with aspirin alone.

Dr Paul Armstrong pointed that those with more than one vascular bed affected had worse outcomes and amplification of antithrombitics is beneficial, and patients with recent MI or stroke (less than 30 days) are at greatest risk and derive a greater benefit, this reinforcing CURE trial. In terms of safety, while there was no significant difference in the rate of severe bleeding between the Clopidogrel-plus aspirin arm and the Aspirin alone arm (1.7% Vs. 1.5%), there was a significant increase in moderate bleeding, including GI bleeding, with the combination antiplatelets therapy (2.0% Vs. 1.3%).

Hand in hand with our study, we found that there were no significant increase in severe bleeding and there was only a significant increase in gastric complications with the combination of antiplatelets therapy (p-value 0.0198).

In line with this, they report that the CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) and CREDO (Clopidogrel for Reduction of Events During Observation) trials suggested that dual antiplatelets therapy would prevent (20 to 30) ischemic events per 1000, at a cost of (1.7) severe bleeds and (7.6) moderate bleeds.

Similar to our study, Data from the CURE [37], MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients) [38] and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) Studies [36] provide confirmatory evidence that combined ASA and Clopidogrel therapy is associated with significantly increased risk of Upper gastrointestinal events & complications when compared with either agent alone in patients at high risk of bleeding who require a stent, a bare-metal stent, with its shorter requisite duration of dual antiplatelet therapy, may be preferable [39]. Concomitant use of clopidogrel and an NSAID (including low-dose ASA) has been associated with impaired healing of asymptomatic ulcers and disruption of platelet aggregation [40] with a consequent increase in serious Upper gastrointestinal events (OR 7.4; 95% CI: 3.5 to 15) [41].

Aspirin and Clopidogrel Results of randomized controlled trials in patients with coronary manifestations of Atherothrombosis have shown the sustained benefit of Clopidogrel when added to aspirin [37]. These trials provided the rationale for further investigation to determine whether the combination of aspirin and Clopidogrel can reduce the risk of recurrent ischemic vascular events in patients who have sustained a TIA or ischemic stroke.

The Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) study compared Clopidogrel monotherapy (75mg) with Clopidogrel and aspirin (75mg) in patients who have had a recent stroke or TIA [38]. The primary end point was a composite of stroke, acute MI, vascular death, or rehospitalization for an acute ischemic event during the 18-month treatment period. The study showed that Clopidogrel-aspirin combination therapy did not produce a significantly greater reduction in major vascular events than Clopidogrel alone. Of more concern was a significant increase in life-threatening hemorrhage-up to a 1.3% absolute risk increase-in patients who took the Clopidogrel-aspirin combination (2.6% Vs. 1.3% in the Clopidogrel-alone group).

This study was followed by the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial [36]. A total of 15,603 patients with either clinically evident cardiovascular disease or multiple cardiovascular risk factors received Clopidogrel (75mg) in combination with low-dose aspirin (75 to 162mg) or low-dose aspirin alone over a 28-month period. There was no overall difference in the primary end point of MI, stroke, or death from cardiovascular causes, and there was a significant increased risk of moderate to severe bleeding in the group who received aspirin-Clopidogrel combination (3.8%) compared with the group who received aspirin alone (2.6%).

Both the CHARISMA and MATCH trials suggest that the combination of Clopidogrel and aspirin does not provide greater benefit than aspirin or Clopidogrel alone and increases the risk of bleeding. Thus, the combination is not recommended at this time.
Our results agreed with the above mentioned studies in which patients who received dual antiplatelets (Clopidogrel combined with low dose aspirin 75mg) had higher risk of gastric complications than those who received Monoantiplalet therapy (low dose aspirin 75mg) (70% Vs. 10%) with a \( p \)-value 0.0198.

In agree with our study, the incidence of gastric changes was conversely correlated with the level of consciousness with a non-significant \( p \)-value (0.82). While some patients in the clear and awake group showed gastric changes, some patients in the semi-comatose to comatose group did not show gastric changes. In general, the location of these cerebral lesions was far from the hypothalamus, and the influence upon the hypothalamus might be mild [42,43].

**Conclusion:**

We concluded that:

- Age is an important risk factor for CVA but has nosignificant relation with gastrointestinal complications.
- Risk of CVA was equal between males and females with a non significant relation with gastric complications.
- Hypertension is an important risk factor for CVA but has non-significant relation with gastric complications.
- The only independent risk factor that had a statistically significant difference as regards developing gastric complications was the previous usage of antiplatelet therapy.
- Neurological findings, Glasgow Coma Scale and Radiological findings had nosignificant relation to gastric complications.
- The combination of Clopidogrel and aspirin does not provide greater benefit than aspirin or Clopidogrel alone and increases the risk of bleeding. Thus, the combination is not recommended at this time.
- The use of Clopidogrel alone to reduce GI bleeding as an alternative to aspirin is not a safe strategy.

**References**

Amr El-Hadidy, et al.


