

VOL 13, ISSUE 2 | SPRING 2018

JHN JOURNAL

a publication of the **Vickie and Jack Farber Institute for Neuroscience – Jefferson Health**



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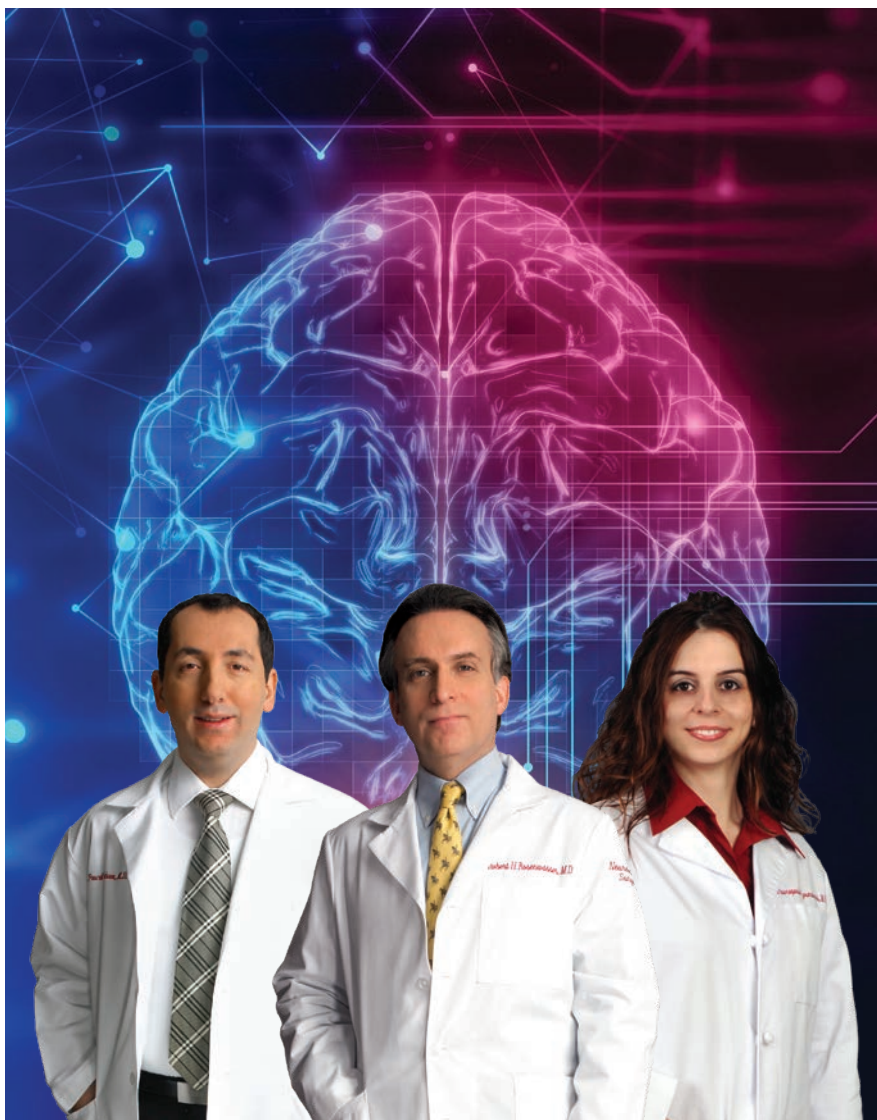


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Stavropoula Tjoumakaris, MD

Dear Colleague,

Last year proved to be an interesting and exciting time for endovascular neurosurgeons. The DAWN and DEFUSE-3 trials demonstrated what many of us have experienced for quite some time: endovascular treatment for ischemic stroke continues to be beneficial past the six hour window. At Jefferson, we've always implemented this theory into our treatment protocol to provide patients with the best chance for meaningful recovery.

Jefferson continues to be our area's leader in neurovascular care. Jefferson neurosurgeons provide endovascular procedures at four hospitals, including Jefferson Hospital for Neuroscience, the Delaware Valley's only hospital dedicated to the treatment of neurological disorders.

I also extend warmest welcomes to two of my newest colleagues. M. Reid Gooch, MD, joins us after completing his residency and endovascular fellowship at Albany Medical Center. Nabeel Herial, MD, MPH, joins after completing a vascular neurology fellowship at the University of California, San Diego and interventional neurology training at both CentraCare Health and Jefferson. The addition of Drs. Gooch and Herial will allow us to continue to provide state-of-the-art endovascular care for our community, particularly in light of research that supports expanding its use.

We are happy to share some of our research in the current issue of the *JHN Journal*.

Sincerely,

Stavropoula Tjoumakaris, MD, FAANS

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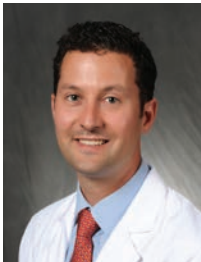
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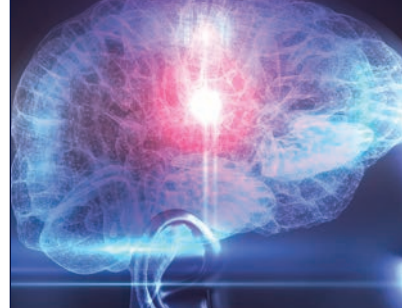
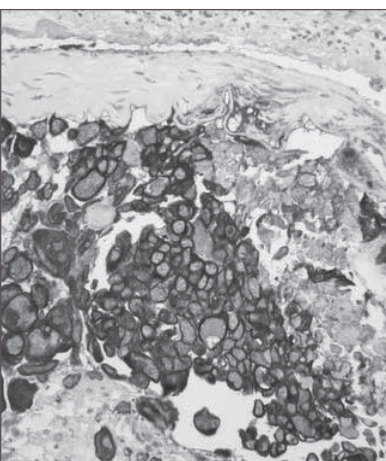
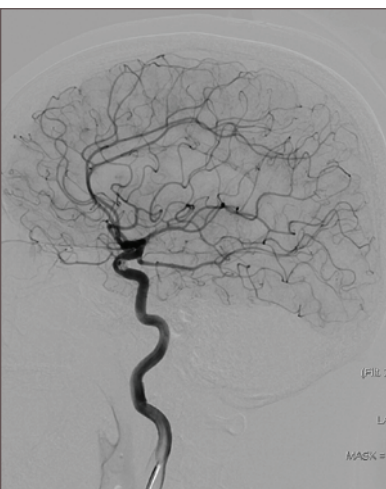


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A Systems Thinking Approach to Redesigning the Patient Experience to Reduce 30 Day Hospital Readmission

William Flounders, MBA; Justin Gates, MBA; Steven Heffner, MBA; Michael J. Lawler BS, RN, MSN, FNP-BC, MBA; Julie Pardini, MBA; Maureen DePrince, RN, BA, CCRN, SCRNP; Robert Rosenwasser, MD, MBA, FACS, FAHA

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INTRODUCTION

The cost of medical care is spiraling out of control, and one of the many reasons is lack of preventative care, poor communication to the patient and primary caregiver(s) both in an inpatient and outpatient setting. There are potentially many reasons for this cost escalation, one of the drivers of this cost is 30 day readmission after a hospitalization and this is what was examined in this analysis.

The purpose of this paper in particular is to share what has been learned using a systems thinking approach to hospital readmissions and the patient experience. It is critical to understand the problems that occurred in the past. In addition, we will explain the methodology utilized and bring awareness to the iterative process. We will also demonstrate a suggested redesigned model.

It is clear that the current system of medical care within the United States is expensive, wasteful and has failed in preventative care and promotion of wellness. Therefore, it is critical to change directions instead of the same paradigm (Old Street to go down Change Boulevard.)

The methodology utilized to dissect the problem was approached by employing the elements of systems thinking; looking at emergent properties, the importance of asking questions, problem dissolution, and listening and additional dialogue with key stakeholders. In addition, constant iteration and communication was important in developing functional models.

Emergent Properties (Figure 1)

Infeasible parts on their own do not yield the ideal but together they must create a feasible whole. Importance of asking questions is that the right questions must



Figure 1.

be asked and answered. Problem dissolution is solving the problem about applying redesigned solution to the problem after deconstruction has taken place. Listening, the more one listens, the more one will understand the problems and get to the "why." Constant iteration is essential and involves incremental change for continuous improvement. Communication without the ability to effectively and efficiently communicate, a vicious cycle continues. Good models - find the right breadth (scope and boundaries) and depth and (level of detail) for its intended purpose.

Constraints exist and are universal, but it is essential to solve problems within the constraints and understand which ones can be modified in which ones cannot.

A systems thinking framework involves the agenda, the context, opinions, and mental models in shared learning.

It is important to define the system boundaries and as figure 2 illustrates, new boundaries are created and changed in order to conform to the system.

There is not one correct mix, there are multiple levers to pull which include physician, patient and family unit, payor, policy maker, care delivery team and provider, and the financial aspect of delivering medical care.

It is important to remember the focus and time for review is essential. Currently the healthcare delivery model is in a significant transition and historically the system within the United States has been a volume-based model which is clearly shifting to a value based model. Value is defined as health outcomes divided by the cost of delivering the outcomes and revenue transition. The transition exists where these index curves are changing from volume-based to value-based and is illustrated in figure 3.

Hospital readmissions are a symptom of disease and these make up the "mess" as defined within a systems thinking

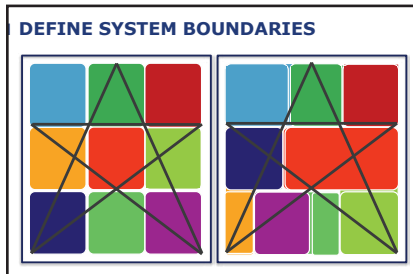


Figure 2.

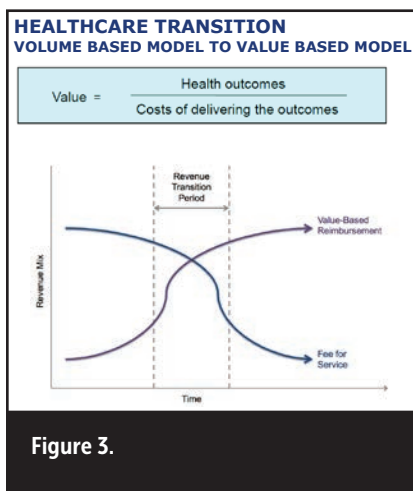


Figure 3.

context. (Ref J. Gharajedaghi). Walter Cronkite, a well-known and respected news journalist 50 years ago indicated that America's healthcare system is neither healthy, caring, nor a system. The impact is enormous and the cost to society of 30-day readmissions are crushing the system. The goal is that savings would be generated by a new paradigm and used for wellness and disease prevention. The project scope and mission in this model was to deconstruct the current system and develop a refined and iterative model to reduce the hospital readmissions for neurovascular events which include hemorrhagic stroke and ruptured intracranial aneurysms, two diagnoses that are extremely costly to the current system (Figure 4).

As alluded to, hospital readmissions are symptom of the disease as figure 5 illustrates. Readmissions account for 24 billion USD in the Medicare program, 8.1 billion USD in privately insured patients, 7.6 billion USD in the Medicaid

HOSPITAL READMISSIONS "SYMPTOM OF THE DISEASE / MESS"



"America's health care system is neither healthy, caring, nor a system."

Walter Cronkite, News Journalist, 50 years ago.

Impact: Enormous Cost to Society for 30-day readmission

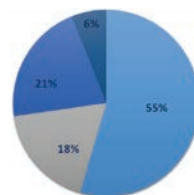
Goal: Savings could be used for wellness and prevention

Project Scope: Neurovascular Events
(Hemorrhagic stroke & ruptured aneurysm)

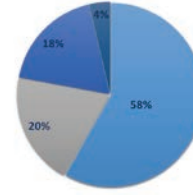
Figure 4.

HOSPITAL READMISSIONS Symptom of the "Disease"

% Readmission



% Cost (Billion USD)



Patient Category	Number readmissions (Million)	Cost (Billion USD)
Medicare program	1.8	24
Privately insured Patient	0.6	8.1
Medicaid Patient	0.7	7.6
Uninsured Patients	0.2	1.5
Total	3.3	41.2

Figure 5.

population and over 1.5 billion USD in uninsured patients. The total number of readmissions in 2016 was 3.3 million for an annual cost of 41.2 billion USD. As the figure 5 illustrates, not only the cost but the percent are largest in the Medicare population.

THE PROBLEM

In 2012, Center for Medicare Services believed providers with excess readmissions were providing low quality care and the proposed remedy at that time, was financial punishment to the professional and technical components of healthcare delivery. In 2013, there was a 1% penalty; 2014, a 2% penalty; in 2015, a 3% penalty. That is, not only would physicians and

hospitals not be paid for care delivered but in addition, a penalty would be paid to CMS, (Center for Medicare Services). In the United States, 82% of hospitals were affected by this penalty.

The simplified "Map of the Mess" as figure 6 illustrates, includes several vicious cycles that have been identified between the policy maker and misaligned incentives, between the payor and the patient, and between the patient and the policy maker. Avoidable unplanned readmissions are due to many factors including secondary care (such as inadequate or inappropriate rehabilitation) which is suboptimal and the poor communication of the event and post-hospital discharge planning and education and

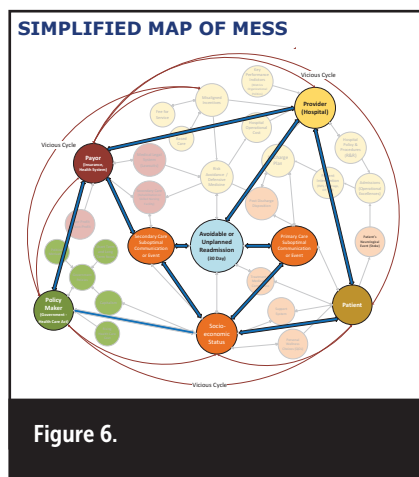


Figure 6.

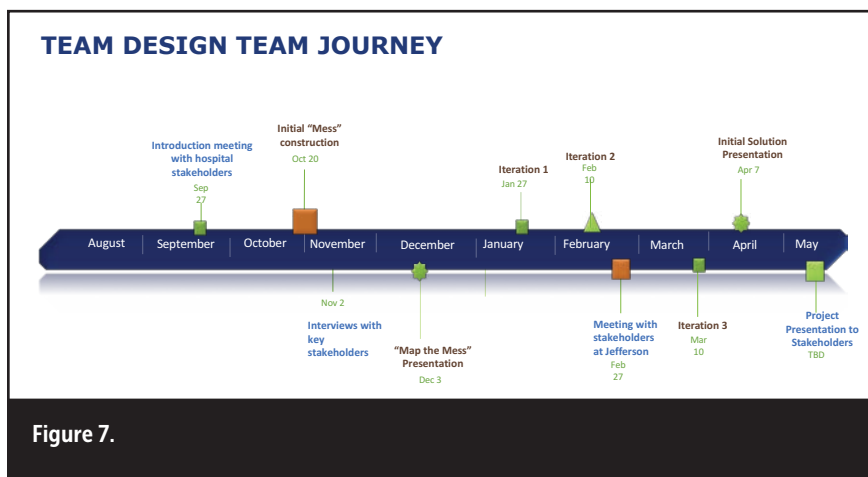


Figure 7.

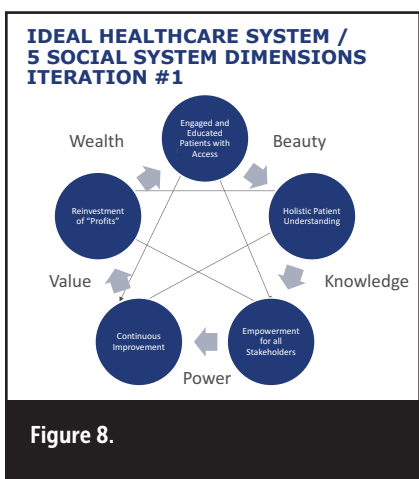


Figure 8.

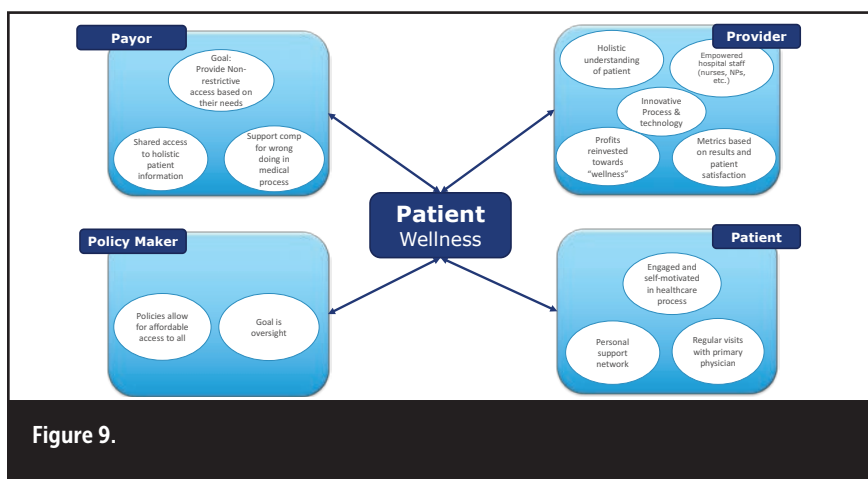


Figure 9.

sub-optimal primary care and communication of the event. This is affected by the socioeconomic status the individual and as the figure 6 illustrates, there are many interconnected variables.

Pathway to Potential Solutions

A winning healthcare formula starts with solving the right problems plus idealized design. Figure 7 illustrates the timeline which the investigators embarked upon to examine the problem, and to proceed with problem dissolution and reconstruction. On September 27th, there was an introduction meeting with hospital stakeholders. October 20th, the initial "mess" construction began. On November 2nd, interviews with key stakeholders performed by members of the research team. December 3rd, "Map of the Mess" was presented for consideration, criticism, and comment.

Once that had been accomplished, the 1st iteration was completed on January 27th, the 2nd iteration was completed on February 10th. After the 2nd iteration, there was a 2nd meeting with hospital stakeholders involved with this project on February 27th. This led to iteration #3 and on March 10th with the initial solution presentation on April 7th and complete project presentation and recommendations in May of 2017.

The common thread identified in problem dissolution was inefficient and inadequate communication as major drivers of hospital readmission. An additional factor was the significant impact of risk avoidance by healthcare providers influencing behavior and decisions. That is "easiest and safest" decision is to readmit the patient.

Based on these findings, the traditional care process for this subgroup of neurological patients was entirely deconstructed. Design specifications included a primary endpoint of reduction in 30-day readmission, a secondary endpoint of reduced cost to the system and a tertiary endpoint to improve patient outcome.

The ideal healthcare system using systems thinking definitions and methodology involve the 5 social system dimensions including wealth, beauty, knowledge, power, and value. They are illustrated in figure 8. Patients were engaged and educated, patients with access to information, holistic patient understanding, empowerment for all stakeholders, leading to continuous improvement and reinvestment of profits into wellness, disease

IDEALIZED DESIGN CONSTRAINTS

- Political environment & legal system
- Government regulations uncertainties
- Reimbursement models [private, public payer (Medicare, Medicaid)]
- Knowledge needs, continuous educational experiences at every patient touchpoint
- Culture in the healthcare system (Hospital, primary/secondary care)
- Healthcare team, patient, and patient family unit knowledge and behavioral

Figure 10.

LAYERED CONSTRAINTS

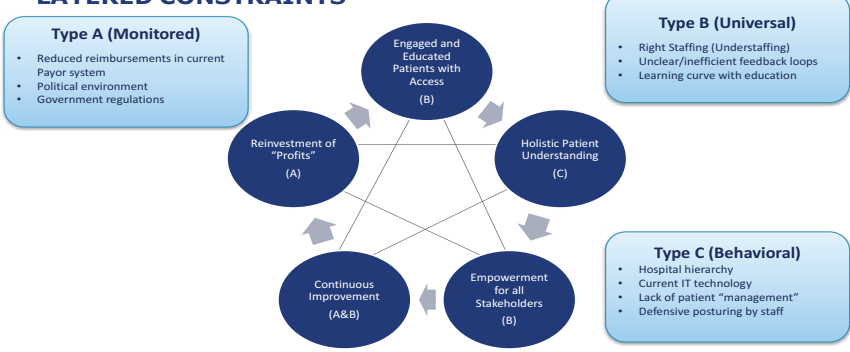


Figure 11.

prevention, education, and improved communication.

The patient wellness involved multiple categories but the 4 areas in particular intersecting are the payor, the policy maker, the provider, and the patient.

Concerning the payor, the goal is to provide nonrestrictive access based on patients' needs, shared access to holistic patient information, and support compensation of financial remuneration for medical errors.

The provider needs to have a holistic understanding of the patient, empowered hospital staff such as nurse practitioners and physician's assistants. There is need for development of innovative process and technologies and profit should/would be reinvested toward improving wellness. Metrics should also be based

on levels of patient satisfaction.

The patient should be engaged and self-motivated in healthcare process with regular visits with the primary care physician and to implement a personal support network.

The policy maker needs to develop policies which allow for affordable access to medical care to all individuals and the goal is oversight (Figure 9).

Idealized Design Constraints (Figure 10)

Any idealized design does have constraints and the constraints are:

1. Political environment and legal system.
2. Government regulations and uncertainties.

3. Reimbursement models, whether private, public payor such as Medicare or Medicaid.
4. Knowledge needs and continuous educational experiences and every patient touch point in the system.
5. The culture in the healthcare system must be changed, not only within the hospital but in primary and secondary care regarding communication to all stakeholders.
6. Healthcare team, the patient, and the patient's family unit knowledge and behavioral constraints exist and must be dealt with accordingly.

Layered Constraints (Figure 11)

The layered constraints consist of 3 types. Type A, Type B, and Type C. Type A constraint is a monitored constraint with reduced reimbursements in the current payer system, the political environment and government regulations. Type B are universal constraints such as does a right staffing ratio exist, unclear and inefficient feedback loops and certainly there is a learning curve with education. Type C constraints which are behavioral deal with the hospital hierarchy, the current IT backbone, and lack of patient management. In addition, there is often defensive posturing by the staff which needs to be altered. As the figure 11 illustrates, a reinvestment of profits will lead to engaged and educated patients with access to care and holistic understanding of the patient. This allows empowerment for all stakeholders with continuous improvement and a virtuous cycle is created.

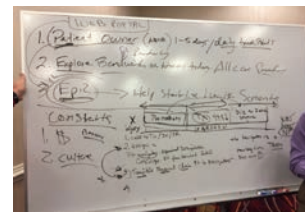
Iteration #2 involved the 2nd meeting with stakeholders at Thomas Jefferson University Hospital and Jefferson Hospital for Neuroscience (Figure 12). The "Patient/Owner managing team" is Value. Nationally accessible patient history is Knowledge as such would be utilized with an electronic medical record. Physicians and stakeholders should be empowered which is Power along that spectrum. Again, Wealth involves aligning government and payor incentives. Beauty in systems context, is utilizing technology to engage all stakeholders and caregivers to and for the patient.

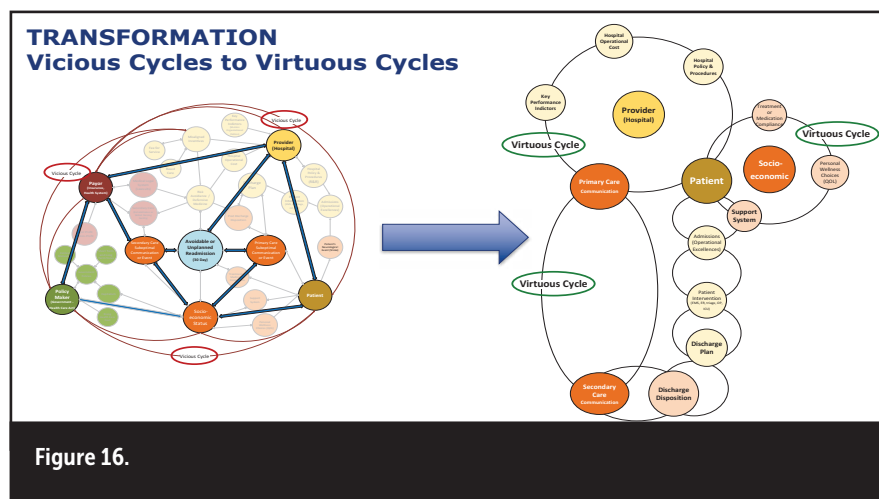
Iteration #3 (Figure 13) was to develop a patient technology platform that provides all previous medical history, real-time interactions from all touch points and suggested and recommended treatment pathways. A single dedicated resource (Patient Navigator System) for all patients that move through the system is critical and creates a “community of care network”.

The path to a virtuous cycle involves understanding the mess, dissolution and multiple iterations and finally idealized design. This is illustrated in figure 14. The vicious cycles need to be removed and the key components of the provider which involves hospital, suboptimal primary care and secondary care, and the patient all ultimately can lead to an unplanned readmission and by dissolution and realignment, as is illustrated in figure 15 vicious cycles are converted to virtuous cycles as illustrated in figure 16. Virtuous cycles are developed between primary care involving communication and secondary care communication. Additional virtuous cycles involve treatment and medication compliance with personal wellness and involving a support system and a 3rd virtuous cycle identified, also involves primary care communication with key performance indicators, reduction of hospital and operational costs, simplification of hospital policy and procedures, which affect the patient in a positive manner. In summary, vicious cycles have been realigned and the dissolution process completed to reorganize and form virtuous cycles, (figure 17). Behind the virtuous cycles is the overall concept of patient care and overall wellness with a rapidly accumulated experience, rising process efficiency becomes better information and clinical data. This is then followed and implemented by more fully dedicated teams, more tailored services of facilities which leads to greater leverage in purchasing and rising capacity for sub specialization. This then allows to spread the cost of IT measurement and process improvement over a larger population i.e. a population health perspective. This becomes self-fulfilling leading to wider capabilities in the care cycle including patient education and engagement which then leads to faster

MEETING AT JEFFERSON ITERATION #2

- Patient “Owner/Managing team” (VALUE)
- Nationally accessible patient history (KNOWLEDGE)
- Physicians / stakeholders empowerment (POWER)
- Align Government / Payor incentives (WEALTH)
- Utilizing Technology to engage all stakeholders [caregivers to patient] (BEAUTY)

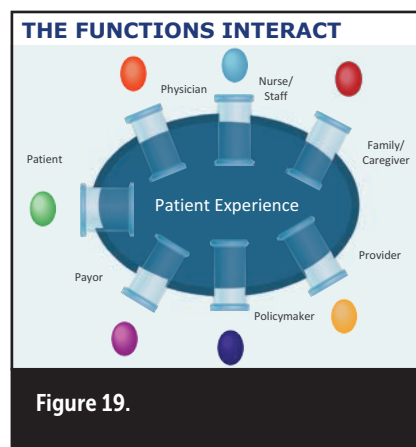
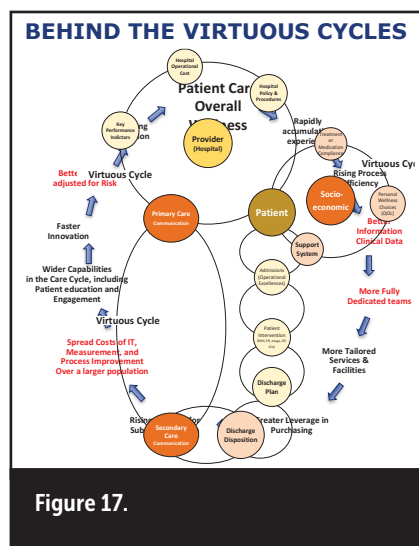




All of these functions interact (Figure 19). The 3 V's to sustainable success are taking a vicious cycle converting via dissolution to virtuous cycles which ultimately becomes a victorious situation, but it does not end here and the iterative processes must continue.

CONCLUSION

In summary, the tools of systems thinking were utilized to perform dissolution of an inadequate health care delivery system and to implement and design a new team construct. As William E. Demming is quoted, "managed care means managing the processes of care, not managing the physicians and nurses (Figure 20)."



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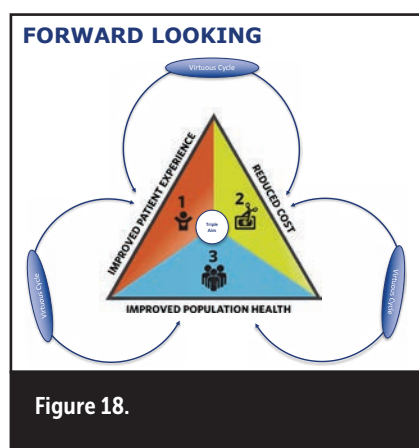
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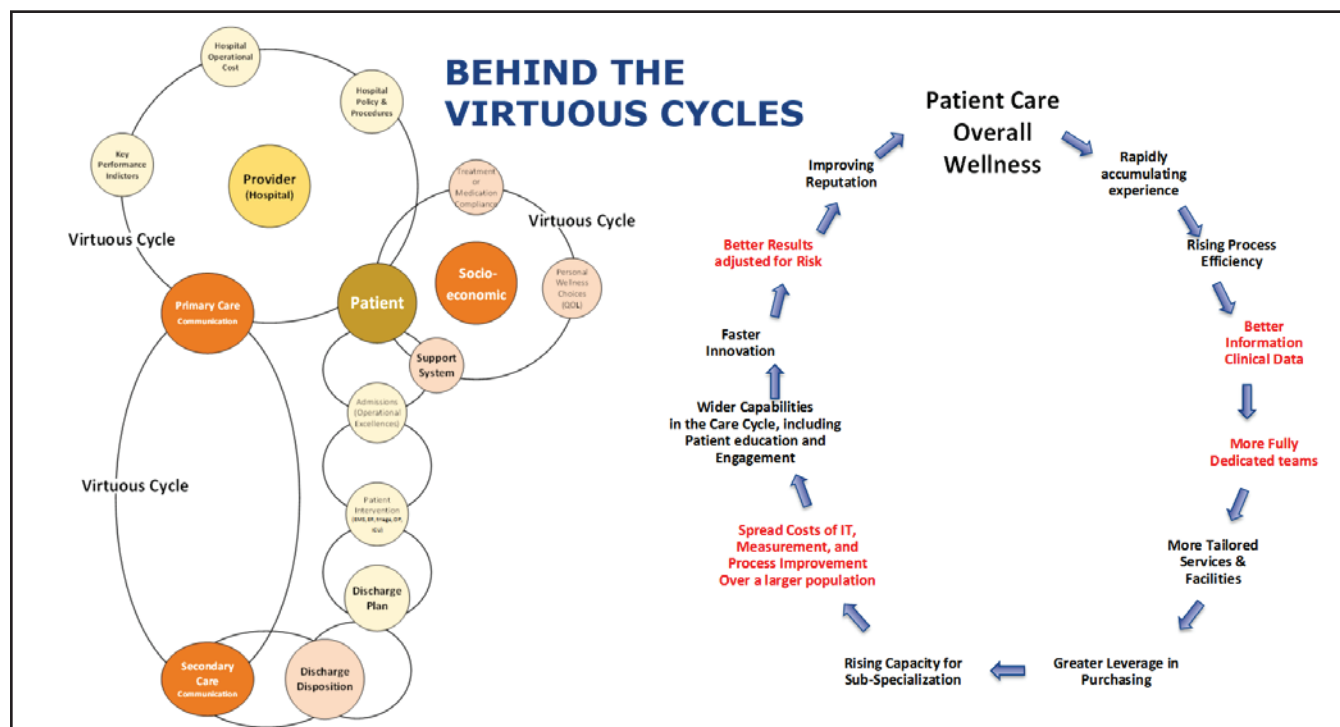
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Assessing a 600-mg Loading Dose of Clopidogrel 24 Hours Prior to Pipeline Embolization Device Treatment

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ABSTRACT

Background: Clopidogrel/aspirin antiplatelet therapy routinely is administered 7-10 days before pipeline aneurysm treatment. Our study assessed the safety and efficacy of a 600-mg loading dose of clopidogrel 24 hours before Pipeline Embolization Device (PED) treatment.

Methods: In this retrospective cohort study, we included patients treated with PED from October 2010 to May 2016. A total of 39.7% (n = 158) of patients were dispensed a loading dose of 650 mg of aspirin plus at least 600 mg of clopidogrel 24 hours preceding PED deployment, compared to 60.3% (n = 240) of patients who received 81-325 mg of aspirin daily for 10 days with 75 mg of clopidogrel daily preprocedurally. The mean follow-up was 15.8 months (standard deviation [SD] 12.4 months). modified Rankin Scale (mRS) was registered before the discharge and at each follow-up visit. To control confounding, we used multivariable logistic regression and propensity score conditioning.

Results: Of 398 patients, the proportion of female patients was ~16.5% (41/240) in both groups and shared the same mean of age ~56.46 years. ~12.2% (mean = 0.09; SD = 0.30) had a subarachnoid hemorrhage. 92% (mean = 0.29; SD = 0.70) from the pretreatment group and 85.7% (mean = 0.44; SD = 0.91) of the bolus group had a mRS ≤ 2 . In multivariate analysis, bolus did not affect the mRS score, P = 0.24. Seven patients had a long-term recurrence, 2 (0.83%; mean = 0.01; SD = 0.10) of which from the pretreatment group. In a multivariable logistic regression, bolus was not associated with a long-term recurrence rate (odds ratio [OR] 1.91; 95% confidence interval [CI] 0.27-13.50; P = 0.52) or with thromboembolic accidents (OR 0.99; 95% CI 0.96-1.03; P = 0.83) nor with hemorrhagic events (OR 1.00; 95% CI 0.97-1.03; P = 0.99). Three patients died: one who received a bolus had an acute subarachnoid hemorrhage. The mean mortality rate was parallel in both groups ~0.25 (SD = 0.16). Bolus was not associated with mortality (OR 1.11; 95% CI 0.26-4.65; P = 0.89). The same associations were present in propensity score-adjusted models.

Conclusions: In a cohort receiving PED, a 600-mg loading dose of clopidogrel should be safe and efficacious in those off the standard protocol or showing <30% platelet inhibition before treatment.

INTRODUCTION

Pipeline embolization device (PED; Covidien, Irvine, California, USA) has become an integral tool in the treatment of intracranial aneurysms. Since its approval by the Food and Drug Administration in 2011, studies have publicized remarkable occlusion rates with this endoluminal device.¹ Antiaggregation drugs are dispensed during and after the pipeline deployment procedure to reduce the likelihood of thromboembolic events.² A single loading dose of aspirin or clopidogrel is neither safe nor sufficient in reducing PED-related thromboembolic complications.³ Patients suffering from cerebrovascular aneurysms and selected for a flow diversion treatment should receive a dual antiplatelet

therapy (DAPT) of aspirin and clopidogrel for a minimum of 7-10 days before the intervention.⁴ Even at a high maintenance dose, patients continue to show variability in the degree of platelet inhibition.⁵

The key in approaching cerebral aneurysms is in assuring an optimal >50% platelet inhibition with the right choice of antiplatelet medication and by keeping the platelet-reactive units (PRUs) between 194 and 416 (adopted in our center).⁶ Although a standard 75-mg dose of clopidogrel produces an irreversible P2Y₁₂ platelet receptor blockade, its 72-hour delayed maximal action is one of its major limitations.⁷ A bolus of 600 mg of clopidogrel must be administered to overcome the previous limitation and achieve a rapid and more potent platelet inhibition within 24 hours before the pipeline deployment.⁸ The central aim of this study was to evaluate the safety and the efficacy of a 600-mg loading dose of clopidogrel when given 24 hours before PED deployment to protect patients from thromboembolic events during and after their procedure.

METHODS

Study Population

This was a retrospective cohort study of all patients undergoing a PED treatment for their cerebrovascular aneurysms in a tertiary referral center between October 2010 and May 2016. A total of 398 consecutive patients undergoing pipeline flow diversion were included. The mean age of the population was 56.46 years (min = 16 years, max = 81 years). Only 2 patients were minors at 16 and 17 years old. The study protocol was reviewed and approved by the institutional review board. Patient consent was not needed because of the retrospective nature of the study. A total of 23 of 398 patients presented with ruptured aneurysm.

Treatment Protocol

Patients treated with the PED were analyzed retrospectively and separated into two groups of standard of care treatment, i.e., 158 (39.7%) patients were administered a DAPT bolus of 650 mg of aspirin plus at least 600 mg of clopidogrel within the 24 hours preceding their procedure and 240 (60.3%) patients (227 with aspirin, 9 with coumadin, 4 with rivaroxaban) received the standard protocol of 81-325 mg of aspirin daily with 75 mg of clopidogrel daily for 7-10 days before their intervention. Patients included in both groups were recruited subsequent to an incidental finding of their aneurysm on routine neuroimaging or to a screening magnetic resonance angiography prescribed because of first-degree family history of aneurysms. Others had symptoms related to the aneurysm: worst headache of life, Horner syndrome, worsening headache, ophthalmoplegia, dizziness, tinnitus, blurry vision, diplopia, and retro-orbital pain. A total of 23 (5.8%) patients were admitted urgently and diagnosed with a subarachnoid hemorrhage (SAH) secondary to aneurysm rupture: 6 (26%) were pretreated with aspirin and clopidogrel, and 17 (74%) was administered a bolus of DAPT as described previously.

We regularly calculated the P2Y12 PRU score using P2Y12 assays (VerifyNow; Accumetrics, San Diego, California, USA) for all patients before the procedure. Prasugrel (n = 20) was considered if the patients were allergic, nonresponders, or resistant to clopidogrel. Resistance was defined with <30%, PRU <194 of platelets' P2Y12 receptor inhibition with antiplatelet drugs. Ticagrelor (n = 2) was adopted in patients labeled as non-responders or allergic to prasugrel. Patients with inhibition >90% had their procedure canceled, and clopidogrel was held until the platelet inhibition level fell below 90%. Patients were continued afterward on 75 mg of clopidogrel daily or 5-10 mg of prasugrel daily or 90 mg twice a day of ticagrelor daily. Vitals and neurologic examination were monitored in the intensive care unit, and patients were deescalated to the floor after 24 hours of clinical well-being. Prophylactic antiplatelet therapy was given as a minimum of 6 months to 1 year after the procedure, followed by aspirin indefinitely (Figure 1).

Outcome Variables

The key primary outcomes were thromboembolic event incidence (minor: transient deficit or asymptomatic stroke documented on diffusion-weighted imaging; major: clinically measurable deficit) including pre- and postprocedural thrombus formation and hemorrhagic accidents with subsequent tangible and concrete clinical deficit (not including the asymptomatic sulcal SAH as seen on routine postoperational computed tomography) after pipeline deployment. Early and late postprocedural hemorrhagic and thromboembolic events were included. Modified Rankin Scale (mRS) score, calculated and registered before the discharge of the patients and at each follow-up visit, mortality rates, intrapipeline stenosis due to overt neointimalization, postinterventional length of stay, and the long-term recurrence were all considered secondary outcomes.

Patient Follow-Up

Follow-up visits were scheduled with the senior author after 1, 3, 6, and 18 months after their discharge from

the institution. The efficacy and the safety of the aspirin/clopidogrel bolus dispensed within 24 hours preceding the pipeline treatment was evaluated on initial postoperative angiography. Cerebrovascular angiography (digital subtraction angiography) was required at the 6-month visit, and then patients were followed accordingly to evaluate for bleeding recurrence or vessel stenosis. Computed tomography scans of the head were compared and analyzed by the senior author to document any new or recurrent subarachnoid or intraparenchymal hemorrhage only if the patients developed new insidious symptoms. Medical charts were reviewed to determine whether any retroperitoneal, gastrointestinal, or genitourinary bleeding had occurred.

Exposure Variables

The primary exposure variable was the treatment (clopidogrel pretreatment vs. clopidogrel bolus). Covariates used for risk adjustment were age and sex. The comorbidities used for risk adjustment

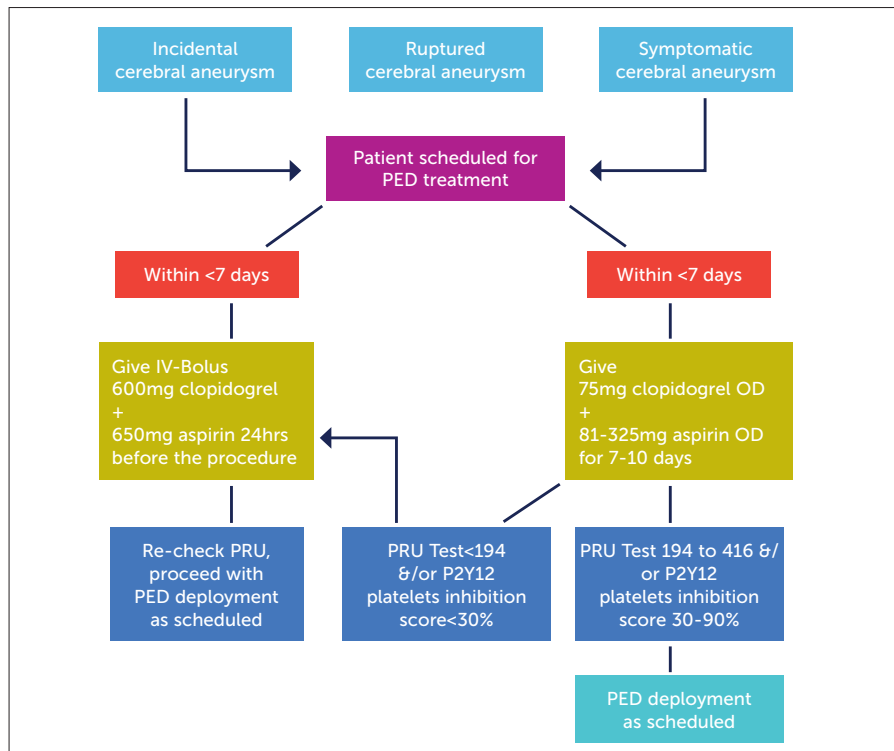


Figure 1. Decision tree graph of the antiaggregation Pipeline Embolization Device; PRU, platelet-reactive protocol adopted before pipeline deployment. PED, unit.

Table 1. Patient characteristics

	Bolus		p value
	Yes (n=158)	No (n=240)	
Age (years)	56.77 (13.70)	56.15 (13.04)	0.51
Male gender	84.2%	82.9%	0.30
Hypertension	0.53 (0.50)	0.49 (0.50)	0.83
Smoking	0.52 (0.50)	0.49 (0.50)	0.31
Aneurysm size (mm)	9.58 (6.84)	9.23 (6.04)	2.86
Previous SAH*	0.10 (0.30)	0.10 (0.23)	0.92
Adjunctive Coiling	0.12 (0.33)	0.04 (0.20)	0.75
Balloon use	0.07 (0.26)	0.07 (0.26)	0.90

*SAH, subarachnoid hemorrhage.

were hypertension, diabetes mellitus, smoking, previous SAH, aneurysm size, per-procedural balloon, previous coiling. This manuscript adheres to the Strengthening the Reporting of Observational studies in Epidemiology (i.e., STROBE) Statement: guidelines for reporting observational studies.

Statistical Analysis

For binary outcomes we used a multi-variable logistic regression, controlling for all the covariates mentioned previously. To control for clustering at the physician level, we used mixed effect models with physician as a random effects variable. For continuous outcomes, we used the corresponding linear regression analyses.

In an alternate way to control for confounding for binary outcomes, we used a propensity score adjusted logistic regression model. To derive the propensity of receiving a bolus, we developed a prediction model using logistic regression, based on all the covariates described previously. We subsequently used a logistic regression with adjustment (stratification) by quantiles (we chose the number of quantiles to be 10) of the propensity score. Operating physician was again used as a random effects variable.

Patients who were lost to follow-up were not included in the original analysis. In sensitivity analysis, all the aforementioned analyses were repeated using multiple imputations for the patients lost to follow-up.

Regression diagnostics were performed for all analyses. Given that the long-term recurrence was 2% in a study sample of 437 patients, we had an 80% power to detect a difference in long-term recurrence as small as 13.4%, at an α -level of 0.05. All probability values were the result of two sided tests. Stata version 13 (StataCorp, College Station, Texas, USA) was used for statistical analysis.

RESULTS

Demographic Characteristics

Between October 2010 and May 2016, 398 patients underwent treatment with PED in our institution. The proportion of female patients was 17.1% (41/240) in the pretreatment group and 15.8% (25/158) in the bolus group ($P = 0.30$). Patients in the pretreatment group shared a similar mean of age with the bolus group (56.15 years; 56.77 years), respectively ($P = 0.510$). The mean aneurysm size was 9.22 mm (standard deviation [SD] = 6.04) in the pretreatment group and 9.58 mm (SD = 6.84) in the bolus group ($P = 2.86$). The proportion of patients with a history of previous SAH (not presenting with acute SAH) was 11.7% (28/240; mean = 0.09; SD = 0.30) in the pretreatment group, whereas it was 12.7% (20/158; mean = 0.10; SD = 0.30) in the bolus group ($P = 0.92$). Likewise, both groups had the same average 1.21 (min = 1 PED, max = 4 PED) number of pipelines used per patient. The fraction of patients receiving adjunctive coiling was 4.6% (11/240; mean = 0.41;

SD = 0.19) in the pretreatment group versus 13.3% (20/158; mean = 0.12; SD = 0.33) in patients receiving the loading dose of antiaggregant medication ($P = 0.75$). Balloon angioplasty was needed in approximately 9.7% (22/240; 16/158) of patients in both groups ($P = 0.90$). Nine of 158 patients from the bolus group presented with aneurysm rupture and a subsequent SAH and required an immediate intervention with a loading dose of clopidogrel. A total of 139 of 158 patients were included because of nonresponsiveness or resistance to the standard 10 days DAPT antiaggregation protocol. The mean monthly follow-up for the patients was 15.8 months (SD = 12.36). A total of 398 patients were identified at our institution, and they constituted our study population. The characteristics of the cohort at baseline are disclosed in Table 1.

Safety of a Loading Dose of Clopidogrel

Thromboembolic Complications. Of 398 patients, 15 (6.3%; mean = 0.05; SD = 0.23) patients receiving the pretreatment protocol had thromboembolic complications, and 17 (10.8%; mean = 0.12; SD = 0.32) patients from the bolus group suffered from these complications (Table 2). A univariate analysis comparing the use of a bolus of clopidogrel with the thromboembolic complication rate did not show any correlation between the 2 variables (odds ratio [OR], 0.99; 95% confidence interval [CI] 0.96-1.03; $P = 0.83$). We found similar results in a multivariable mixed-effects logistic regression bolus (OR 0.99; 95% CI 0.96-1.03; $P = 0.81$) and a propensity score-adjusted model (OR 0.99; 95% CI 0.96-1.03; $P = 0.82$).

Hemorrhagic Complications. Of 398 patients, 9 (3.75%; mean = 0.25; SD = 0.16) (Table 2) patients receiving the pretreatment protocol had hemorrhagic complications, and 12 (7.6%; mean = 0.08; SD = 0.27) patients from the bolus group suffered from these complications. The mean of hemorrhagic complications in the global population was 0.48 (SD = 0.21). A univariate analysis comparing the use of a bolus of clopidogrel with the hemorrhagic complication rate did not show any correlation between the 2

variables (OR 0.99; 95% CI 0.97-1.03; $P = 0.87$). In a multivariable mixed-effects logistic regression, bolus (OR 1.00; 95% CI 0.97-1.03; $P = 0.99$) was not associated with an increased hemorrhagic event rate. We found similar results with the propensity score adjusted model (OR 0.99; 95% CI 0.96-1.03; $P = 0.87$).

Long-Term Recurrence. Of 398, 7 (1.76%; mean = 0.02; SD = 0.15) patients had a long-term recurrence: 2 (0.83%; mean = 0.01; SD = 0.10) from the pretreatment group versus 5 (3.16%; mean = 0.03; SD = 0.18) patients in the bolus group. A univariate analysis comparing the use of a bolus of clopidogrel to the long-term recurrence rate did not show any correlation between the 2 variables (OR 3.32; 95% CI 0.60-18.43; $P = 0.17$). In a multivariable mixed-effects logistic regression, bolus (OR 1.91; 95% CI 0.27-13.50; $P = 0.52$) was not associated with a long-term recurrence rate. This finding was consistent with the propensity score-adjusted model (OR 3.00; 95% CI 0.51-17.58; $P = 0.22$) (Table 3).

Mortality. Of 398 patients, 9 patients expired: 6 patients died from various non-PED related events such as severe sepsis (1), malignant hypertension with a large middle cerebral artery infarct (1), severe gastro-intestinal complication (1), and non-reported (3). Only three patients were announced dead secondary to cerebrovascular complications: one patient from the bolus group died from acute SAH, and two patients from the pretreatment group died from severe intraparenchymal hemorrhage. The mean of mortality rate in the global population was 0.02 (SD = 0.15), 0.25 (SD = 0.16) in the pretreatment group, and 0.26 (SD = 0.16) in the bolus group (Table 2). A univariate analysis comparing the use of a bolus of clopidogrel to the mortality rate did not show any correlation between the two variables (OR 0.99; 95% CI 0.77-1.30; $P = 0.95$). In a multivariable mixed-effects logistic regression, bolus (OR 1.11; 95% CI 0.26-4.65; $P = 0.89$) was not associated with an increased mortality rate. This finding persisted in a propensity

score-adjusted model (OR 0.99; 95% CI 0.89-1.11; $P = 0.92$).

Efficacy of the Loading Dose of Clopidogrel

Intrapipeline Stenosis. Of 398 patients, 27 (6.8%; mean = 0.75; SD = 0.26) had an intra-PED stenosis with 17 (7.08%; mean = 0.72; SD = 0.26) in the pretreatment group and 10 (6.32%; mean = 0.76; SD = 0.27) in the bolus group. A univariate analysis comparing the use of a bolus of clopidogrel with the intrapipeline stenosis rate did not show any correlation between the two variables (OR 1.07; 95% CI 0.45-2.55; $P = 0.88$). In a multivariate mixed-effects logistic regression, bolus (OR, 0.90; 95% CI 0.36-2.30; $P = 0.89$) was not associated with higher intra-PED stenosis rate. This was coherent with the propensity score-adjusted model. (OR 0.92; 95% CI 0.37-2.34; $P = 0.88$).

Latest Clinical Status. In the global population, the mean mRS was 0.36 (SD = 0.79); it was 0.44 (SD = 0.91) in the bolus group and 0.29 (SD = 0.70) in the pretreatment group. A total of 87.8% of the global population, 92% of the pretreatment group and 85.7% of the bolus group had a mRS 2. In a multivariate analysis were the latest mRS is a dependent variable, bolus did not affect the latest mRS score, $P = 0.24$ (Table 3).

Postinterventional Hospital Stay. In the global population, the mean postoperative hospital stay was 1.86 days (SD = 2.96); 1.69 days (SD = 2.81) in the pretreatment group and 2.11 days (SD = 3.2) in the bolus group. In a multivariate analysis in which the postinterventional stay is a dependent variable, bolus did not affect the postoperative hospital stay, $P = 0.64$.

Table 2. Mean Value and Standard Deviation of Outcomes

Outcomes	Pre-treatment mean(SD*)	Bolus mean(SD*)	Total mean(SD*)
Long-term recurrence	.11 (0.10)	.34 (0.2)	.21 (0.14)
Intra-PED stenosis	.07 (0.26) n=17	0.07 (0.26) n=10	.07 (0.26)
Thromboembolic acc.	.54 (0.23) n=2	.12 (0.32) n=5	.07 (0.26)
Hemorrhagic acc.	.25 (0.16)	.10 (0.28)	.41 (0.28)
Mortality	.25 (0.16)	.25 (0.16)	.02 (0.15)
Length of stay(days)	1.69 (2.81)	2.11 (3.2)	1.86 (2.96)
mRS at last follow-up	.44 (0.91)	.29 (0.7)	.36 (0.79)

*SD, standard deviation; PED, Pipeline Embolization Device; acc., accident; mRS, modified Rankin Scale.

Table 3. Association Between Outcomes and Clopidogrel Bolus

Models	Long-term recurrence OR*(CI95%) p value		Intra-PED stenosis OR*(CI95%) p value		Thromboembolic OR*(CI95%) p value		Hemorrhagic OR*(CI95%) p value		Mortality OR*(CI95%) p value	
Multi-variable logistic regression	1.91 (.27 to 13.50)	0.517	0.90 (.36 to 2.29)	0.83	0.99 (.96 to 1.03)	0.81	1.00 (.97 to 1.03)	0.99	1.11 (.26 to 4.65)	0.89
Propensity score	3.00 (.513 to 17.58)	0.22	0.928 (.37 to 2.34)	0.88	0.99 (.96 to 1.03)	0.82	0.99 (.97 to 1.03)	0.87	0.99 (.89 to 1.11)	0.92

*OR, odds ratio; CI, confidence interval.

DISCUSSION

Using a retrospective cohort of patients treated for their cerebrovascular aneurysm(s), we did not find any association between a clopidogrel 600-mg loading dose and increased mortality rate, thromboembolic accidents, long-term recurrence, intrapipeline stenosis, hemorrhagic events, mRS on last follow-up, and postoperational length of stay. The elevated risk of acute and delayed thromboembolic complications associated with the PED necessitates the use of antiplatelet therapy.⁹ The use of DAPT instead of aspirin alone has been the most commonly used trend after being translated from the cardiology literature.¹⁰ Nevertheless, there is no standard protocol to define the dose, duration, and the combination of the antiplatelet drugs used in the setting of PED placement.¹¹

In our study, 10.8% of patients in the bolus group suffered from thromboembolic complications compared with 6.3% of the maintenance group. A total of 17 patients from the bolus group manifested with thromboembolic events within less than 1-month follow-up: only 4 of them had a major permanent neurologic deficit ranging from extremity weakness to complete hemiparesis, whereas the other 13 patients had minor transient neurologic symptoms, such as visual floaters, minimal limb weakness, and numbness or speech difficulty, that completely resolved on latest follow-up (mRS <1). The latter results are somehow predictable as they reflect the pharmacodynamic properties of clopidogrel. Platelet function assays done *ex vivo* revealed a measurable antiplatelet effect starting within 60 minutes and reaching a maximum of antiplatelet inhibition 2 hours after the 600-mg loading dose of clopidogrel.¹²⁻¹⁴ The rates of thromboembolic events seen in the clopidogrel bolus group would be precipitated by the complex pathophysiology of thromboembolic events even when the patient is under an optimal antiplatelet regimen. This clopidogrel regimen would be addressing one single step in the primary hemostasis (platelet aggregation) process and sometimes might turn out to be insufficient for complete and definite protection of the patient from these complications.

The rate of hemorrhagic complications in the clopidogrel bolus group was 7.6% compared with 3.75% in the clopidogrel pretreatment maintenance dose. Leung et al.¹⁵ suggested that patients with acute ischemic strokes receiving clopidogrel loading doses within 24 hours of symptom onset did not have a greater rate of new serious bleeding events compared with patients who did not receive loading doses. Nonetheless, we will wait the results of the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke trial to confirm the safety of clopidogrel dosing in this group.¹⁶ Nonetheless, 4 patients receiving bolus precipitated intracerebral hemorrhage postprocedurally. One died, and 3 had small right temporal and frontal bleeding, who ended up having minimal neurologic sequelae (mRS 2). Eight other patients from the same group manifested SAH postprocedurally. Three had minor SAH with minimal neurosequelae (mRS 2) on latest follow-up, and the remaining 5 patients died subsequently due to major SAH: 2 of them died the first week after their intervention, and the last 3 died 1 or 2 months postprocedurally. Even if our statistical analysis does not show any significant difference in hemorrhagic complication between both groups, it is noteworthy to emphasize the greater rate of hemorrhagic events in the bolus group. Whether the clopidogrel loading dose increased the rate of hemorrhage in our series cannot be inferred from our descriptive study design, and further prospective studies are needed for to confirm these observations.

To our knowledge, there is only one study reflecting a head-to-head comparison between clopidogrel pretreatment protocol and high loading dose in cardiovascular literature, as percutaneous coronary intervention (PCI) is almost always done during emergencies.¹⁷ In this randomized, double-blinded, clinical trial, Nguyen et al.¹⁷ compared different maintenance doses of clopidogrel given a week before PCI (75 mg once daily vs. 150 mg once daily after 300-mg loading dose each) and loading doses (300 mg vs. 600 mg) given 1 day before the procedure. They concluded that a loading standard dose of 300 mg of clopidogrel followed by a 150-mg daily maintenance dose given a week before PCI achieved better platelet inhibition and low reactivity

than the 300-mg loading dose given 24 hours before the procedure. However, the 600-mg loading dose given a day before PCI was not statistically inferior to the 300-mg/150-mg daily maintenance dose.

The results from the Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA-8 RELOAD-ACS) trial have shown a statistically significant advantage of reloading patients with acute coronary syndrome who were already on chronic clopidogrel therapy (75 mg) with a loading dose of 600 mg of clopidogrel before PCI.¹⁸ The reloading strategy was associated with a 66% relative risk reduction of 30-day major adverse cardiac events.¹⁸ Whether this additional advantage is due exclusively to added inhibition of platelet aggregation is not well established. A study conducted by Patti et al.¹⁹ indicates that a clopidogrel loading dose (600 mg or 300 mg) before PCI decreases procedural P-selectin levels. P-selectin is a marker of platelet activation and may directly contribute to the stability of platelet aggregates.²⁰ It also may be partly responsible for mechanisms linking inflammation and thrombosis.²¹ This may suggest that the benefits of the loading dose strategy are not just exclusive to the inhibition of adenosine diphosphate-induced platelet aggregation. Many other studies demonstrated the advantage of giving a high-loading dose (600 mg) of clopidogrel before PCI compared with the standard 300-mg dose.^{19,22-24} Also, the clinical trial done by Nguyen et al. did not show any superiority of an even high pretreatment maintenance dose of clopidogrel preceded by 300-mg bolus 1 week before PCI compared with the 600-mg loading dose 1 day before the procedure.¹⁷ It is also noteworthy to mention that in our study population, <20% of the patients were female, and our overall aneurysm distribution by sex was not typically skewed towards males. We do not know how this finding could have affected our results. Further prospective studies are needed to uncover a possible association between sex and pipeline treatment complications.

Whether all these results infer superiority of the 600-mg loading dose of clopidogrel before PED to the 75-mg maintenance dose given a week before

the procedure cannot be determined at this time. Most of the studies in which authors compared the efficacy and safety of different doses of clonidogrel were extrapolated from cardiac studies and cannot be directly translated to cerebrovascular settings. Also, no head-to-head comparison was done between the 1-week pretreatment maintenance dose of clonidogrel with the 600-mg loading dose 24 hours before PED. This comparison was not done in the present study, and no definite conclusions can be derived at this point. Our study is the first descriptive observational study that compared the different outcomes between the 600-mg loading dose and the pretreatment 75-mg maintenance dose used in patients undergoing PED. Our study remains limited by the retrospective nature of the data collection: the patients were not selected randomly for bolus versus pretreatment. Such a limitation must be addressed in further large prospective studies. Although no direct clinical suggestions can be derived from this study, we believe it is a first step towards higher-evidence studies to come out with a standard regimen of DAPT.

CONCLUSIONS

Aspirin/clonidogrel DAPT routinely is recommended for patients 7e10 days before receiving neurovascular PED treatment. Nevertheless, patients presenting with ruptured aneurysms, those who could have not received a standard 10 days DAPT protocol, or those showing nonsatisfactory platelet inhibition at admission can be selected for an acute antiaggregation protocol: a 600-mg loading dose of clonidogrel might be safe and efficacious in reaching the optimal platelet inhibition within 24 hours of the pipeline deployment.

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A Case Report and Overview of Familial Cerebral Cavernous Malformation Pathogenesis in an Adult Patient

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OBJECTIVE

We present a case of a 39 year-old woman who presented with a solitary cavernous malformation hemorrhage without any other lesions, and subsequently presented several months later with a new hemorrhage from a de novo lesion. We discuss mechanisms of paradominant inheritance and haploinsufficiency to describe phenotype expression of familial cavernous malformations.

CASE DESCRIPTION

The patient presented with unremitting headaches, who had a known history of a solitary cerebral cavernous malformation (CCM) for which she underwent resection several months prior with no evidence of any other CCM lesions seen on post-operative MRI. She has no history of whole brain radiation, family history of cavernous malformations, or prior head trauma. During this hospital visit, she was found to have developed two new lesions in the left fronto-parietal lobe and cerebellum. She was treated with surgical resection of the left frontoparietal lesion, and recovered fully. It is of interest that a patient approaching her fourth decade of life would start to develop formation of multiple de novo cavernous malformations, especially with an absent family history. Paradominant Inheritance and haploinsufficiency are two proposed models of inheritance that can be related to this patient's disease progression.

CONCLUSION

The case illustrates an atypical clinical course of a patient with familial cerebral cavernous malformations with delayed formation of de novo lesions.

INTRODUCTION

Cerebral Cavernous Malformation is a vascular disease of the brain with solitary and familial mechanisms.¹ The patient of interest presented to the hospital with headaches and a past history of CCM one year prior, with new hypodense lesions on a head CT scan, most likely cavernous malformations. The possibility of hereditary CCM development during adulthood and lesion multiplicity through the mechanisms of paradominant inheritance and haplo-insufficiency is described. Understanding these modes of inheritance as well as the genetic pathology can aid in genetic counseling as well as developing disease modifying treatments apart from surveillance and surgery.

CASE

The patient is a 39 year-old female with a history of a solitary cavernous malformation for which she underwent a left parieto-occipital craniotomy for resection in 2016. At that time, a post-operative MRI did not reveal any other lesions suspicious for cavernous malformations (including GRE sequence). She presented to an outside hospital with

an unremitting headache starting one-week prior. She describes the headache as bifrontal and similar to a headache she had during her prior presentation. She rated the pain as an 8 out of 10. A head CT was performed and a new left frontoparietal intraparenchymal hemorrhage was discovered separate from her previous resection site. When the patient was admitted to our institution for further care and evaluation.

Other than her previous craniotomy for a hemorrhagic cavernous malformation, she has no other significant surgical history. Her family medical history is pertinent for hypertension in her mother. She was not taking any medications, and claims not to smoke, drink alcohol, or use illicit substances. An MRI was performed after her resection in 2016, which did not demonstrate new lesions.

Her physical exam demonstrated that she was awake, alert, and oriented to person, place, and time. She had no gross cognitive or neurologic deficits; cranial nerve testing of CN II-XII showed normal functioning, her strength was 5/5 in upper and lower extremities, and her sensation was intact. Her gait was normal, without disturbances; she did not demonstrate pronator drift. An MRI was performed, revealing new lesions in the right cerebellum as well as left frontoparietal lesion.

The patient was brought to the OR for resection of the lesion the following day. She underwent a left frontoparietal craniotomy and resection of the lesion without complications. Her post-operative recovery had no complications and she was discharged from the hospital on post-operative day³.

DISCUSSION

Cerebral cavernous malformations (CCM) are low flow, vascular malformations of vessel-like channels, filled with blood in

various stages of degradation. They lack the smooth muscle support of normal vessels without any intervening brain parenchyma, and are generally clustered and dilated.^{1,2} Cavernous malformations account for 5 to 15% percent of all vascular malformations in the CNS, and are prone to rupture due to stressors or changes in blood pressure.² Cavernous malformations can be hereditary (familial) or sporadic, and are usually discovered through a symptomatic presentation of hemorrhage.² The most common presenting symptoms include headache, seizures, and focal neurologic deficits; seizures are the most common symptom in 40-60% of presenting cavernous malformations. The presence of multiple lesions seen on a cerebral magnetic-resonance image is indicative of the familial form of the disease, and 20-50% of affected individuals will develop symptoms between the second and fifth decade of life.³

We report a patient approaching her 4th decade of life with a history of one prior symptomatic cavernous malformation the previous year, presenting now for a separate symptomatic, actively bleeding cavernous malformation. Following her previous resection in 2016, post-operative MRI did not reveal new lesions or disease foci. Now, CT and MRI reveals two distinct lesions, newly developed within a year's time, reflecting an atypical clinical course of the familial form of cerebral cavernous malformation disease.

Familial Cerebral Cavernous Malformation Development

Familial or hereditary CCM occurs from mutations involving 3 loci: CCM1, CCM2, and CCM3. CCM1 mutations account for roughly 70% of familial cerebral cavernous malformations.⁴ It is proposed that the various mutations within these genes might affect angiogenesis and endothelial cell morphogenesis, deteriorating vascular stability.⁴ There are close to one hundred CCM1 mutations that contribute to disease development.⁵ In a 2007 review, Brouillard and Viskula described numerous roles the CCM1 locus plays in cerebral vascular development, as well as its possible significance in arterial-venous differentiation. The main pathogenesis

from a CCM1 mutation is derived from the KRIT1 gene, that is suggested to play a role in cell adhesion and migration, directly influencing the endothelial cells which form and support vasculature.⁵ CCM2 is described as playing a role akin to that of CCM1, especially in the sequestration and signaling of the KRIT1 involved pathway. This acts through the MGC4607 gene, malcavernin; it has been shown that both loci can act together in a CCM1/2 complex to influence vascular development.⁶ CCM3 can be described as "tumor suppressor like," where deletions in CCM3 can lead to proliferation and resistance to apoptosis, shown by Louvi et al in a mouse model.⁷ A zebrafish model by Yoruk et al further supports that the CCM3 model behaves separately from the CCM1/2 pathway, and even contributes to a phenotypically different pattern of vascular development.⁸ Furthermore, their study showed CCM3 worked in conjunction with GCKIII, which can be implicated in pharmaceutical therapy.

Originally, Zabramski et al described familial cavernous malformation as a dynamic disease, with families exhibiting similar symptomatology among generations.⁹ Our patient, however, did not recall family members with her disease or symptomatology. It is possible that family members had asymptomatic lesions, as Zabramski's research points out that actively bleeding cavernomas are most likely to be symptomatic and discovered. In addition, Denier et al had demonstrated that CCM3 genotypes generally had less familial expression of the disease. Though it is understood which genes play a role in disease development, the underlying mechanism of expression is not concretely understood (See figure 1).

De novo Cerebral Cavernous Malformation

De novo cavernomas have been reported to have underlying risk factors, such as cranial radiation, coexistent vascular malformations, and hormonal factors. Head injury, reactive angiogenesis, and viral infections can also play a role in producing cavernomas.¹⁰ However, their exact pathogenesis remains unknown. Gross' meta-analyses proposed that de novo CCMs develop from developmental venous anomalies (DVA), venous stasis,

and resultant microhemorrhage due to venous hypertension.¹ Nearly half of sporadic CCMs are associated with an adjacent DVA; in contrast, hereditary CCMs develop in near absence of DVAs.³

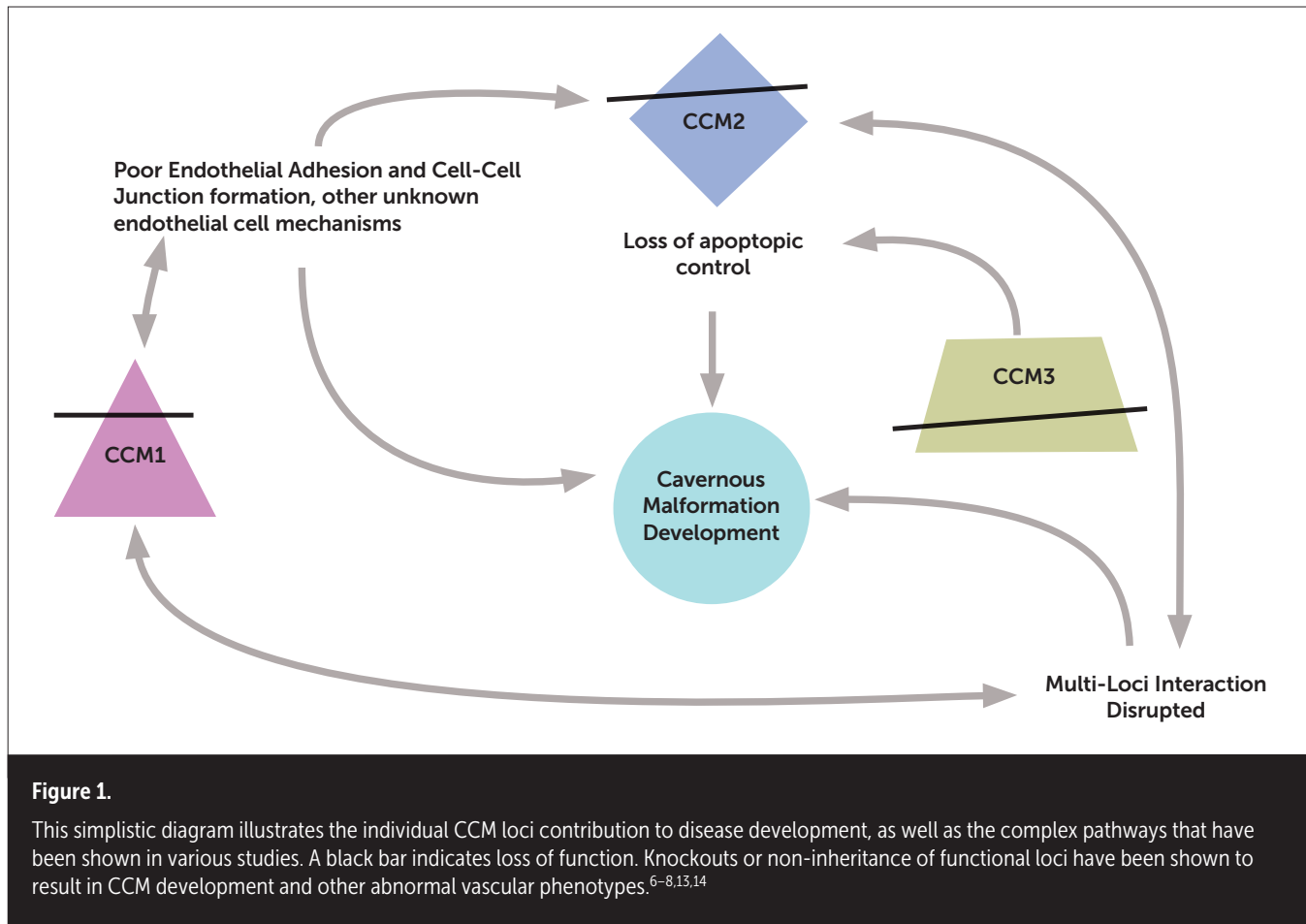
Our patient had no history of cavernous malformation until her first occurrence one year prior to this presentation. In between that time and now, two new cavernous malformations formed. Her work up and medical history did not have any associated DVA or other vascular abnormality. The question remains to why she had developed a symptomatic cavernoma close to four decades into her life, and then two more within a year's time. There are several cases of multifocal sporadic lesions, where CCM mutations accounted for roughly 60% of observed pathologic findings.¹¹ Bacigaluppi's review et al sheds light on various molecular pathways that are responsible for vascular development and pathologic variations in cerebral cavernous malformation.³ Two of the foremost theories on the inheritance of this disease, as well as other vascular malformation pathologies are those of paradominant inheritance and haploinsufficiency.

Haploinsufficiency

Haploinsufficiency is defined by non-inheritance of a gene or loss of function mutation that leads to insufficient genetic expression of a wild-type phenotype. Diseases such as Angelmann syndrome and Ehlers-Danlos Syndrome are characteristic of haploinsufficiency. It has been proposed that haploinsufficiency manifests through various ways in CCM, such as inadequate protein production for endothelial junction formation, causing the pseudovascular formation characteristic of CCM.¹² Though this can be seen as an adequate explanation for disease mechanism, it would not fit the presentation of our patient as haploinsufficiency would indicate disease progression since birth, which was not the case here.

Paradominant Inheritance:

Paradominant inheritance mimics the two hit hypothesis initially described by Knudson to describe the tumor suppressor gene mechanism.³ Paradominant inheritance constitutes a congenital inheritance of a nonfunctional gene, and



then a somatic second hit during life. However, the patient preserves a normal phenotype until the second hit is sequestered, thus the "paradominance." Though there are 3 CCM genes, a loss of function by two hit mechanism to any one gene can lead to lesion development.^{3,5,13} Furthermore, it has been pointed out that one hit to any gene can express vascular abnormalities, such as weakened endothelial vascular lining.⁶ These genetic disruptions can come to light through any trauma, injury, or radiation the brain vasculature. See figure 2.

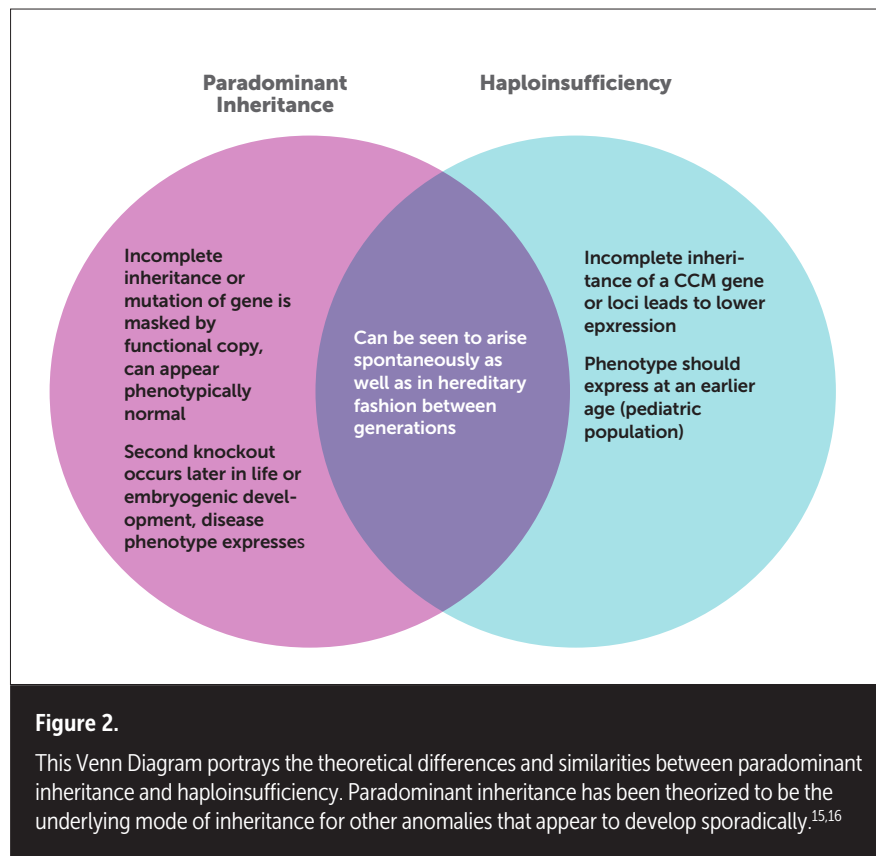
Paradominant inheritance could shed light on our patient's disease development as she has no prior evidence of CCM development apart from her prior presentation; her rapid multifocal lesion development imitates similar disease processes of tumor suppressor genes, such as breast tumor multiplicity in BRCA mutations. It should be understood that

there is difference between paradominant inheritance and two hit mechanism; the two hit mechanism conveys the disease is autosomal dominant and shows partial penetrance after one hit, while a two hit would show full penetrance.

This patient's development of CCM lesions in the absence of venous anomalies, alongside the manifestation of new lesions in a short period of time mimic a pathologic mechanism resembling that of paradominant inheritance. Her generation of multiple lesions after a year's time could indicate that a second gene was compromised in the past few years, fulfilling a two-hit mechanism. Further genetic testing on tissue sample can illuminate which CCM mutations led to her disease, and could further illuminate the variations in CCM1, CCM2, and CCM3 pathogenesis.

CONCLUSION

Here we have presented the case of a 39 year-old female who was diagnosed and treated for a de novo formation of a symptomatic cavernous malformation, with only one prior cavernous malformation one year prior. The acuity of lesion genesis and her late presentation of the disease can address the reasoning toward the pathogenesis of familial cavernous malformation as resembling a two-hit mechanism, resembling similarities with paradominant inheritance, with the second gene knockout occurring recently. Further genetic analysis of this patient and her family could possibly illuminate her mutations and inheritance pattern.



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Clinical Applications of the Pipeline Embolization Device

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Flow diverters (FDs) are being used with increasing frequency, especially to target large and complex aneurysms not amenable to treatment with conventional endovascular methods.^{8,10,11,26} The Pipeline embolization device (PED) is the first FD approved by the FDA following the results of the PUFs trial for the management of large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments. Although initially indicated for a limited type of aneurysms, the use of the PED is being extended for the management of a variety of aneurysms in different settings.^{5-7,9} The main factors that are considered in deciding if an aneurysm is suitable for treatment with the PED include aneurysm size, location, geometry and shape and rupture status.¹⁶ Studies have shown a high technical success rate, a high rate of aneurysm occlusion accompanied by low recurrence and re-treatment rates.^{10,12,20} Current evidence also supports the PED as a safe device associated with low morbidity and mortality.^{10,21,23,27} Although treatment failure with flow diversion has been reported, the characteristics of these aneurysms with persistent filling have not been well established. Furthermore, the course of these aneurysms remains a topic of uncertainty. The initial thrombosis caused by FDs does not result in immediate cure of the aneurysm rather FDs act as a scaffold for endothelial overgrowth at the aneurysm neck resulting intra-aneurysmal flow stasis and thrombosis while promoting remodeling of the parent vessel and parent vessel reconstruction which results in gradual occlusion of the aneurysm.²²

Prior literature on the efficacy of PED have shown a high complete aneurysm occlusion rate, with most studies reporting occlusion rates > 80%^{3,13} and this compares favorably to endovascular coil embolization, where the reported complete occlusion rate is 66% (ISAT).⁴ Recurrence after successful PED treatment has not been reported with the available short- and medium-term data. This is in contrast to high recurrence rates with coiling (9-34% at 12 months) that increases with large, giant, wide-necked, and nonsaccular aneurysms that are the target for PED treatment.¹ The retreatment rate is much lower with PED treatment as compared to coiling in ISAT (17.4%).⁴ Flow diverters seem to be more effective than the conventional endovascular techniques in select cases.

Aneurysm location in the distal anterior circulation (PCOM artery, anterior choroidal artery and MCA) is a significant predictor of persistent aneurysm. Parent vessels for such aneurysms are usually small, and aneurysms often arise at major branch points. In addition, the A1 segment of the ACA and M1 segment of the MCA are rich in lenticulo-striate perforators, and covering these areas with PEDs could theoretically increase the risk of perforator strokes with neurological deficits. These factors render PED delivery and deployment more difficult. Also, PEDs (with available sizes from 2.5 to 5 mm) are in general designed for parent vessels that are larger than the caliber of distal anterior circulation vessels. In a small vessel, the device may be elongated and the stent pores may become larger which may impair the flow diversion effect

and lower the chances of aneurysm thrombosis. This may affect the reliability of PED deployment in smaller distal vessels. However, there are some distal anterior circulation aneurysms that are morphologically challenging for either traditional microsurgical or endovascular approaches, and the use of PEDs may have an advantage in these cases. In these cases, placing a single, long flow diverter stent and avoiding telescoping of multiple devices along perforator-rich segments can reduce the risk of perforator occlusion.

The PED was originally approved for the treatment of aneurysms proximal to the PCOM artery.¹⁴ PCOM aneurysms are among the most frequently encountered cerebral aneurysms. A fetal PCOM artery is an end vessel with no distal collaterals. Since fetal PCOM arteries represent the only supply to the PCA, care should be taken when treating PCOM aneurysms incorporating a fetal variant.¹⁹ In fact, fetal PCOM artery aneurysms are often treated surgically since endovascular therapy is thought to cause a higher treatment risk.¹⁹ Several reports have suggested that flow diversion for fetal PCOM aneurysms is ineffective and does not lead to aneurysm occlusion and has high potential for serious complications.^{17,19} Aneurysms arising from a fetal PCOM are less likely to be occluded even after placement of a flow diverter due to the high flow and the high physiological demand for this artery which maintains pressure gradient across the ostium.¹⁴ PCOM aneurysms with a fetal PCA are better to be treated with microsurgical clipping.¹⁸ Attempting flow diversion may add procedural risks and make surgical clipping even more technically complex.

MCA aneurysms represent the third most common cause of subarachnoid hemorrhage and almost 1/5 of unruptured aneurysms.²⁴ The majority of MCA aneurysms arise at the level of the bifurcation tend to be wide-necked, incorporate one

or more side branch vessels and tend to have an unfavorable anatomical configuration.¹⁵ Wide-necked MCA bifurcation lesions have been classically treated with microsurgery with excellent results. Traditional endovascular approaches can sometimes be challenging with a risk of occluding branch vessels as well as the risk of coil herniation. Flow diversion for MCA aneurysms should be considered when other surgical or endovascular approaches are not an option or do not offer superior outcomes and for lesions that persist after previous surgery or endovascular treatment.²⁶ Clinical data should demonstrate better or similar results than clipping to challenge surgical intervention, with current occlusion rates from clipping reported to be >90% in most studies.²⁵

Stent placement negatively affects the safety and efficacy of the PED in the management of recurrent aneurysms. The rate of complete aneurysm occlusion is lower in previously stented aneurysms (50–65%) with potential for a higher complication rate (14.3%) and technical failure rate.²⁸ If a stent was placed initially, recurrence would be less eligible for PED treatment and might require surgical clipping to achieve aneurysm occlusion. The presence of a previous stent may: reduce the hemodynamic effect of the PED, disrupt the process of wall apposition of the PED to the parent vessel, preventing the endothelialization process inhibiting complete aneurysm occlusion, complicate the navigation of the delivery catheter into position and the actual deployment of the PED and because the PED should be deployed distal to the stent, the distal end of the PED may “catch” on the previously placed stent, which may cause anchoring and stretching of the device, leading to less effective results. It is important to note that patients of advanced age can have a weaker neo-intimal response and therefore may have higher odds of incomplete aneurysm occlusion.

The majority of cases require the placement of only one PED, and a single PED should be usually placed as there was no difference in aneurysm occlusion when more than 1 device were deployed.²⁹ Coiling and flow diversion have been shown to be complementary, rather than

competitive modalities for intracranial aneurysm treatment.³ Using coils along with the PED in select cases can be more effective with a higher occlusion rate and lower retreatment rate, by promoting endosaccular thrombosis and providing a mechanical scaffold.

The PED is indicated for large and giant aneurysms.⁴ However, large and giant aneurysms represent a small fraction of all cerebral aneurysms with the majority of aneurysms in the general population being <10 mm in size. Traditional endovascular strategies including coiling and stent-assisted coiling are usually used for small aneurysms (≤ 7 mm). Some retrospective studies have demonstrated high occlusion rates (75–90%) and low complication rates (<5%) with treating these small aneurysms.¹⁰ In experienced centers the PED is demonstrating a better efficacy profile and a similar safety profile to coiling of smaller aneurysms.¹⁰ With the increasing use of the PED for the treatment of small, simple aneurysms, the question arises as to whether the use of this device routinely, or even as a first line treatment for these aneurysms is as safe and effective as the current standard endovascular techniques. This needs to be further studied

Good clinical outcomes have been reported with flow diversion of saccular or non-symptomatic fusiform posterior circulation aneurysms.³ Treatment with the PED may be a preferable alternative to open surgical treatment for these aneurysms. Because of the large number of perforating vessels in the posterior circulation that supply vital brainstem structures, complex aneurysm anatomy, and aneurysm location, flow diversion should be used with caution. Aneurysm morphology and presentation are critical factors to consider when selecting posterior circulation aneurysms for treatment with the PED.³⁰

Device deployment is successful in 95% to 100% of cases (99% in PUFs).² Selection of the appropriate diameter and length of the device is essential to ensure proper device function and to minimize the chance for unanticipated stent shortening or migration. (*FDA-Summary of Safety and Effectiveness of Data, PED, P100018*) The delivery catheter

must recross the PED over the delivery wire to recapture the distal coil tip after complete stent deployment. Up to 50% foreshortening is expected when fully deployed compared with 1.5%–7.1% and 1.8%–5.4% foreshortening in Wingspan® and Neuroform® 3 stents. (*Bench testing conducted by Boston Scientific*)

There is a potential risk of an endoleak-like phenomenon with implantation of an undersized device, which results in poor wall apposition. Similarly, implantation of an oversized device may result in poor coverage of the lesion because of an incomplete compaction of the strands.³¹ When a branch vessel is incorporated into the target aneurysm, its runoff can potentially contribute to persistent filling of the aneurysm by the very same physiological processes theoretically responsible for the preservation of jailed branch vessels and perforators arising from normal segments. One may expect that final closure of such aneurysms would require concomitant occlusion of the associated branch.

While the PED can allow for treatment of large, wide-necked aneurysms with high efficacy, aneurysm location, previous treatment, patient age and the use of concomitant coiling may influence treatment outcomes.

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The Use of Prasugrel and Ticagrelor in Pipeline Flow Diversion

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ABSTRACT

Background: Despite the routine clopidogrel/aspirin anti-platelet therapy, complications like thromboembolism, continue to be encountered with PED. We studied the safety and the efficacy of prasugrel in the management of clopidogrel non-responders treated for intracranial aneurysms.

Methods: 437 consecutive neurosurgery patients were identified between January 2011 and May 2016. Patients allergic or having <30% platelet-inhibition with a daily 75mg of clopidogrel were dispensed 10mg of prasugrel daily (n=20) or 90mg of ticagrelor twice daily (n=2). The average follow-up was 15.8 months (SD=12.4 months). Patient clinical well being was evaluated with the modified Rankin Scale (mRS) registered before the discharge and at each follow-up visit. To control confounding we used multivariable mixed-effects logistic regression and propensity score conditioning.

Results: 26 of 437(5.9%) patients (mean of age 56.3 years; 62 women [14,2%]) presented with a sub-arachnoid hemorrhage. 1 patient was allergic to clopidogrel and prasugrel simultaneously. All the patients receiving prasugrel (n=22) had a mRS<2 on their latest follow-up visit (mean=0.67; SD=1.15). In a multivariate analysis, clopidogrel did not affect the mRS on last follow-up, p=0.14. Multivariable logistic regression showed that clopidogrel was not associated with an increased long-term recurrence rate (odds ratio[OR], 0.17; 95%Confidence Interval [CI95%], 0.01-2.70; p=0.21) neither with an increased thromboembolic accident rate (OR, 0.46; CI95%, 0.12-1.67; p=0.36) nor with an increased hemorrhagic event rate (OR, 0.39; CI95%,0.91-1.64; p=0.20). None of the patients receiving prasugrel deceased or had a long-term recurrence nor a hemorrhagic event, only 1 patient suffered from mild aphasia subsequent to a thromboembolic event. 3 patients on clopidogrel passed during the study: (2) from acute SAH and (1) from intra-parenchymal hemorrhage. Clopidogrel was not associated with an increased mortality rate (OR, 2.18; CI95%,0.11-43.27; p=0.61). The same associations were present in propensity score adjusted models.

Conclusion: In a cohort of patients treated with PED for their intracranial aneurysms, prasugrel (10mg/day) is a safe alternative to clopidogrel resistant, allergic or non-responders.

INTRODUCTION

Since the 2011 FDA approval, PED has been a favored option in treating cerebral aneurysm(s).¹⁵ The PED is a self-expanding stent with 30-35% metal surface area coverage that diverts blood flow from the aneurysm lumen to the downstream arteries causing aneurysm sac thrombosis.³ However, there is a window period until full luminal endothelialization of the PED occurs, during which the patient is at a high risk of thromboembolic events.^{11,2,13} The use of Dual Anti-Platelet Therapy (DAPT) with aspirin and clopidogrel has been recommended for preventing thrombotic and hemorrhagic complications that occur after the deployment of PEDs.¹² However, Delgado Almandoz JE et al. demonstrated that thromboembolic complications continue to be encountered, particularly with PED, despite the routine DAPT. Approximately 30% of patients exhibit anti-platelet resistance.¹ Insufficient platelet inhibition in CYP2C19 heterozygotes causes this variability in the response to clopidogrel. Several centers have replaced clopidogrel with different anti-aggregation drugs like prasugrel or ticagrelor in the management of these resistant cases.^{5,14} Prasugrel and Ticagrelor achieve more potent and rapid inhibition of platelet aggregation and decreased inter-subject response variability.^{6,8} In our Study, we identified all the patients that were resistant to clopidogrel. They were dispensed prasugrel or ticagrelor in order to achieve the optimal platelet inhibition. This allowed them to undertake their flow diverting stent treatment. We demonstrate the safety and efficacy of prasugrel and ticagrelor as alternative antiplatelet agents whilst dispensed in conjunction with aspirin in clopidogrel non-responders.

Table 1. Association between outcomes and clopidogrel

Model	Long-term recurrence		Intra-PED stenosis		Thromboembolic Complications		Hemorrhagic Complications		Mortality	
	OR(CI95%)	p value	OR(CI95%)	p value	OR(CI95%)	p value	OR(CI95%)	p value	OR(CI95%)	p value
Multi-variable regression	0.17(0.01 to 2.70)	0.21	0.44(0.09 to 2.15)	0.31	0.46(0.12 to 1.67)	0.24	0.39(0.91 to 1.64)	0.20	2.18(0.11 to 43.27)	0.61
Propensity score adjustment	0.26(0.22 to 3.03)	0.28	0.46(0.09 to 2.44)	0.37	0.39(0.11 to 1.41)	0.82	0.33(0.08 to 1.37)	0.13	0.73(0.75 to 7.17)	0.79

METHODS

Cohort creation

We performed a retrospective cohort study of all patients undergoing treatment of cerebral aneurysms with flow diverting stents in a tertiary referral center between January 2011 and May 2016. The Institutional Review Board reviewed and approved the study protocol. All patients received a pipeline embolization device (PED; Covidien, Irvine, California). The characteristics of the cohort at the baseline can be seen in Table 1.

Treatment protocol

In our institution, patients are pretreated with 75mg of clopidogrel daily and at least 81mg of aspirin *daily* for 10 days before their PED deployment. Some patients presenting for their intervention without having received the appropriate 10 days DAPT were loaded with 325-650mg of aspirin and a bolus of anti-aggregate drug (600mg of clopidogrel or 40-60mg of prasugrel or 90mg of ticagrelor) within less than 24 hours to their intervention. We routinely calculated the P2Y12 platelet inhibition assay (VerifyNow; Accumetrics, San Diego, California) for all the patients before the procedure. Prasugrel was considered when patients are allergic, non-responders or resistant to clopidogrel. Resistance was defined as having (<30%) of platelets P2Y12 receptor inhibition. 22 patients among the 437 did not have a significant platelet inhibition (<30%) with clopidogrel, they constituted our population. Ticagrelor was the final alternative for those whose P2Y12 platelet inhibition was still not satisfactory with prasugrel. Patients were continued after the operation on 75mg of clopidogrel daily or 10mg of prasugrel

daily or 90mg of Ticagrelor twice daily. Prophylactic anti-platelets therapy was given as a minimum of 6 months to 1 year following the procedure.

Outcome variables

The key primary outcome was the patients' Modified Rankin Scale which was calculated and registered before the discharge of the patients and at each follow-up visit. Mortality, thromboembolic events and DSA documented hemorrhagic accidents, following the aneurysm's pipeline treatment, were considered primary outcomes. Secondary outcomes were the post interventional length of stay and the long-term recurrence.

Patient Follow Up

Patients were scheduled for a follow up visit with the senior author after 1, 3, 6 and 18 months following their discharge from the institution.

The efficacy and the safety of the prophylactic DAPT post pipeline treatment were evaluated on initial post-operative angiography and follow-up angiography when available. Cerebrovascular Angiography (digital subtraction angiography DSA) was required at their 6 months visit and then patients were followed accordingly to evaluate for bleeding recurrence or vessel stenosis. Additional information on the number of PED used for initial treatment and on the stent migration were all collected during the follow up (Table 1). Head computed tomography scans were compared and analyzed by the senior author to document any new or recurrent subarachnoid or intra-parenchymal hemorrhage, only if the patients were to develop new insidious symptoms. Medical charts

were reviewed to determine whether any retroperitoneal, gastrointestinal, or genitourinary bleeding had occurred.

Exposure variables

The primary exposure variable was the treatment (prasugrel or ticagrelor vs clopidogrel).

Covariates used for risk adjustment were age and gender. The comorbidities used for risk adjustment were: hypertension, diabetes mellitus, smoking, previous sub arachnoid hemorrhage, aneurysm size, per-procedural balloon, previous coiling.

Statistical analysis

To investigate the association of clopidogrel exposure and our outcome measures we used several methods to address confounding. Initially, for binary outcomes we used a multivariable logistic regression controlling for all the covariates mentioned above. In order to control for clustering at the physician level, we employed mixed effect models with physician as a random effects variable. For continuous outcomes, we used the corresponding linear regression analyses.

In an alternate way to control for confounding for binary outcomes we employed a propensity score adjusted logistic regression model. To derive the propensity of receiving clopidogrel we developed a prediction model using logistic regression, based on all the covariates described above. We subsequently employed a logistic regression with adjustment (stratification) by quantiles (we chose the number of quantiles to be 10) of the propensity score. Operating physician was again used as a random effects variable.

Table 2. Patient characteristics

	Clopidogrel		Prasugrel - Ticagrelor	
	374		22	
No	Mean	SD	Mean	SD
Age (years)	56.25	13.29	57.31	13.55
Sex	1.15	0.36	1.23	0.43
Hypertension	0.51	0.50	0.54	0.51
Smoking	0.50	0.50	0.65	0.49
Aneurysm size (mm)	9.11	5.87	12.93	10.93
Previous SAH	0.10	0.30	0.15	0.37
Adjunctive Coiling	0.74	0.26	0.08	0.27
Stent migration	0.01	0.09	0.04	0.19
Number of stents per patient	1.21	0.56	1.32	0.57
mRS on last follow up	0.32	0.75	0.67	1.15

Patients who were lost to follow up were not included in the original analysis. In sensitivity analysis, all the above analyses were repeated using multiple imputations for the patients lost to follow up. We created 5 imputed datasets. The directions of the observed associations did not change and these results are not reported further.

Regression diagnostics were performed for all analyses. Given that the long-term recurrence was 2% in a study sample of 437 patients, we had an 80% power to detect a difference in long-term recurrence as small as 13.4%, at an α -level of 0.05. All probability values were the result of two sided tests. Stata version 13 (StataCorp, College Station, TX) was used for statistical analysis.

RESULTS

Demographic characteristics

Between 2011 and 2016, a total of 437 patients (mean of age 56.3 years; 62 women [14,2%]) underwent treatment with PED in our institution. 26 (5.9%) patients presented with an acute sub-arachnoid hemorrhage (SAH). 374 received clopidogrel [361 with aspirin, 9 with Coumadin, 4 with rivaroxaban], 20 (4.6%; Mean= 0.047; SD= 0.2117)

received prasugrel and 2 received ticagrelor (Mean=0.0074; SD= 0.0858). 7 patients were lost for follow-up after their intervention (6 from the clopidogrel group and 1 from the prasugrel group). 1 patient was reported allergic to clopidogrel and prasugrel. (Table 1)

Efficacy of prasugrel and ticagrelor

a. Intra-pipeline stenosis

Of 369 patients receiving clopidogrel, 23(6.1%) of the patients had an intra-PED stenosis.

In the group of patients receiving prasugrel & ticagrelor the mean of intra-pipeline stenosis was 0.117(SD=0.33), only 2 patients had an intra-pipeline stenosis: 1(5%) receiving prasugrel the other ticagrelor. The mean of intra-pipeline stenosis with patients receiving clopidogrel was 0.071(6.7%; SD=0.26). A univariate analysis of the effect of clopidogrel on the thromboembolic complication rate did not show any correlation between the two variables (OR, 0.58; CI95%, 0.12 to 2.70; p=0.48). In a multivariable mixed-effects logistic regression, clopidogrel was not associated with an increased

intra-pipeline stenosis (OR, 0.44; CI95%,0.08 to 2.15; p=0.31). This was coherent with the propensity score adjusted model. (OR, 0.46; CI95%, 0.088 to 2.44; p=0.37).

b. Long term recurrence

None of the 22 patients receiving prasugrel or ticagrelor had a long term recurrence. Of 374 patients receiving clopidogrel, 1,6% suffered from a long term recurrence rate with a mean of 0.02(SD=0.13). A univariate analysis of the effect of clopidogrel on the long term recurrence rate does not show any correlation between the two variables (OR, 0.27; CI95%, 0.03 to 2.41; p=0.24). In a multivariable mixed-effects logistic regression, clopidogrel was not associated with an increased long term recurrence (OR, 0.17; CI95%, 0.01 to 2.70; p=0.21). This was consistent with the propensity score adjusted model (OR, 0.26; CI95%, 0.02 to 3.03; p=0.28). (Table.2)

Safety of prasugrel and ticagrelor

c. Post PED complications

Of 22 patients receiving prasugrel and ticagrelor the mean of post-procedural complications is 0.19 (SD=0.40), only 1 patient developed an arterio-venous V3 fistula and 1 other patient had an ophtalmoplegia and a ptosis of the left eye. Of 374 patients receiving Clopidogrel, the mean post PED complications was 0.53(SD=0.23). A univariate analysis of the effect of clopidogrel on the post pipeline complication rate is associated with an increased post pipeline complication rate (OR, 0.24; CI95%, 0.08 to 0.70; p=0.01). In a multivariable mixed-effects logistic regression, clopidogrel is also associated with an increased post pipeline complication rate (OR, 0.28; CI95%, 0.08 to 1.01; p=0.05). This was consistent with the propensity score adjusted model where p-value was slightly superior to 0.05 (OR, 0.27; CI95%, 0.07 to 1.03; p=0.055).

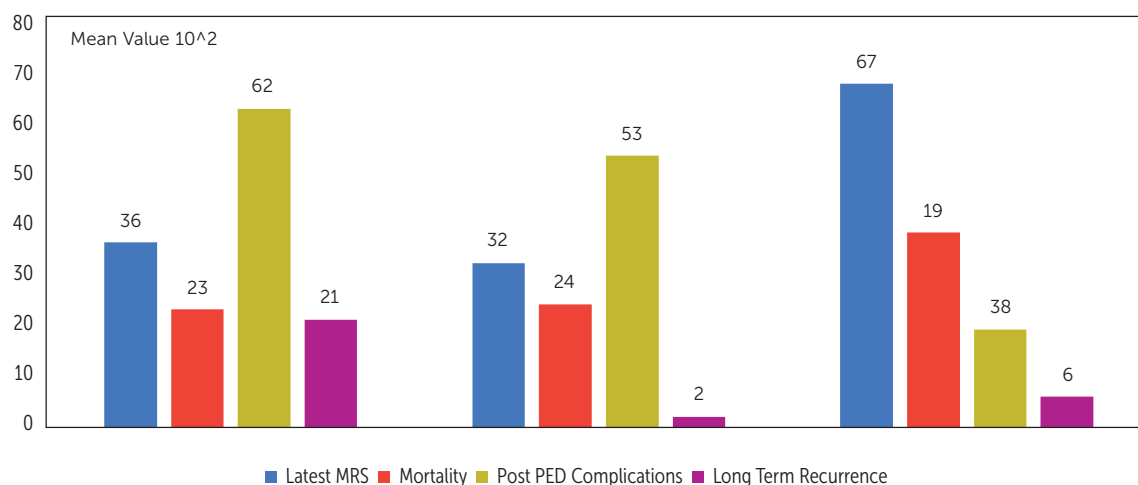


Figure 1. Graph showing the mean values of the clinical outcomes according to the prescribed antiplatelet drug

d. Thromboembolic complications

Of 374 patients prescribed clopidogrel, the mean of thromboembolic events was 0.72(SD=0.26). While 28 (7.4%) patients receiving clopidogrel had thromboembolic complications, only 1 patient dispensed prasugrel suffered from word finding difficulty. A univariate analysis of the effect of clopidogrel on the thromboembolic complication rate does not show any correlation between the two variables (OR, 0.43; CI95%, 0.14 to 1.32; $p=0.14$). We found similar results in a multivariable mixed-effects logistic regression (OR, 0.46; CI95%, 0.12 to 1.67; $p=0.36$) and a propensity score adjusted model (OR, 0.39; CI95%, 0.11 to 1.41; $p=0.82$).

e. Hemorrhagic complications

None of the patients receiving prasugrel or ticagrelor suffered from hemorrhagic complication. Of 374 patients receiving clopidogrel the mean of the hemorrhagic complications was 0.45(5.6%; SD=0.21). A univariate analysis of the effect of clopidogrel on the hemorrhagic complication rate does not show any correlation between the two variables (OR, 0.36; CI95%, 0.10

to 1.33; $p=0.13$). In a multivariable mixed effect logistic regression, clopidogrel was not associated with an increased hemorrhagic event rate (OR, 0.39; CI95%, 0.91 to 1.64; $p=0.20$). We found similar results with the propensity score adjusted model (OR, 0.33; CI95%, 0.08 to 1.37; $p=0.13$).

f. Mortality

Patients receiving clopidogrel had a mean mortality rate 0.02(2.67%; SD=0.15). (Figure.1) 9 patients were lost: 6 patients dying from various non PED related events such as severe sepsis (1), malignant hypertension with large middle cerebral artery infarct (1), severe gastro-intestinal complication (1), non reported cause of death (3). Only 3 patients from this group were announced dead from acute SAH (2) and intra-parenchymal hemorrhage (1). None of the patients receiving prasugrel and ticagrelor were lost. A univariate analysis of the effect of clopidogrel on the mortality rate does not show any correlation between the two variables, (OR, 0.61; CI95%, 0.75 to 5.03; $p=0.65$). In a multivariable mixed effect logistic regression, clopidogrel was

not associated with an increased mortality rate (OR, 2.18; CI95%, 0.11 to 43.27; $p=0.61$). This persisted in a propensity score adjusted model (OR, 0.73; CI95%, 0.75 to 7.17; $p=0.79$). (Table.2)

g. Latest clinical status

Of 22 patients receiving prasugrel or ticagrelor, All the patients had a mRS ≤ 2 on their latest follow-up visit with a mean of 0.67(SD= 1.15). 98.4% of 374 patients receiving clopidogrel had a mRS ≤ 2 on their latest follow-up visit with a mean of 0.32(SD= 0.75). (Figure.1) in a multivariate analysis were the latest mRS is a dependent variable, clopidogrel did not affect the mRS score on last follow-up, $p=0.14$. (Figure.1)

h. Post interventional hospital stay

Of 22 patients receiving prasugrel or ticagrelor, the mean of their post interventional length of stay was 3 days (SD= 6.20). (Figure.1) Of 374 patients receiving clopidogrel the mean of the post procedural stay was 1.81 days (SD= 2.67). In a multivariate analysis clopidogrel did not affect the patients' post operational length of stay, $p=0.94$.

DISCUSSION

Using a retrospective cohort of candidates with cerebrovascular aneurysm(s), we did not identify any association between clopidogrel administration with mortality, thromboembolic accidents, long term recurrence, intra-pipeline stenosis, hemorrhagic events, mRS on latest follow-up and post operational hospital length of stay. We found that clopidogrel is associated with post-procedural complications. Prasugrel and ticagrelor are increasingly adopted in clopidogrel resistant individuals treated for their cerebral aneurysm(s). Compared to clopidogrel, both prasugrel and ticagrelor inhibit platelets aggregation more rapidly and consistently with lower rates of inter-subjects variability.¹⁶

In the present study, the efficacy of prasugrel, depicted by intra-pipeline stenosis and long-term recurrence, was roughly similar to clopidogrel (6.1% vs. 5% and 1.6% vs. no recurrence respectively). These results are consistent with the more favorable pharmacokinetic and pharmacodynamic profiles of prasugrel, which affords a more potent and rapid inhibition of platelet aggregation.¹ They are also in line with the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) where clopidogrel-naïve patients with acute coronary syndrome scheduled for percutaneous coronary intervention on prasugrel therapy showed significantly reduced rates of ischemic events, including patients with cardiac stent thrombosis.¹⁷ A recent meta-analysis done by Patti et al found that switching from clopidogrel to prasugrel, in patients undergoing percutaneous coronary intervention, tended to decrease the incidence of major adverse cardiac events during follow-up.⁹ Despite the lack of clear evidence supporting its use in cerebrovascular procedures, Leslie-Mazwi et al were the first to report the successful use of prasugrel for acute in-stent thrombosis in a patient with reduced clopidogrel response undergoing elective stent-assisted aneurysm coiling.⁷

In our series, patients on aspirin and prasugrel did not have any hemorrhagic complications. The small number of

patients who were on both aspirin and prasugrel could explain these results, as the use of DAPT with aspirin and prasugrel would be expected to increase the relative risk of bleeding by 30% compared to aspirin and clopidogrel.^{8,17} Interestingly, the greatest benefit with prasugrel vs. clopidogrel in the TRITON-TIMI 38 study was seen in high-risk patients especially diabetics or those who suffered an ST-segment elevation myocardial infarction, where the major adverse cardiac events' reduction with prasugrel was not paralleled by an increased risk of bleeding.⁹ This may infer that there are certain subgroups of patients who are at a decreased risk of the hemorrhagic adverse events from prasugrel use. The incidence of thromboembolic complications was approximately akin in the aspirin/clopidogrel group (7.4%) and in the aspirin/prasugrel group (5%). This was not similar to the extrapolated results of many studies present in the cardiac literature that demonstrated superior reduction of ischemic events using prasugrel as part of DAPT compared to clopidogrel.^{10,17}

Ticagrelor/aspirin combination was used only on two patients who either did not achieve the desired P2Y₁₂ platelet inhibition with prasugrel or were allergic to it. One patient had an intra-pipeline stenosis and another suffered from a post-procedural hemorrhagic complication manifesting as mild aphasia. Conclusions about efficacy and safety of ticagrelor in patients with PED cannot be drawn from our series because of our limited number of patients. In their series of 18 patients, Hanel et al presented their successful experience with patients using ticagrelor for different neuroendovascular procedures as an alternative to clopidogrel in nonresponders.⁵ Further investigations in patients undergoing treatment with PED and other neuroendovascular procedures are needed to assess the efficacy and safety profile of ticagrelor in hypo-responders and non-responders to clopidogrel.

It is noteworthy to state that our series followed during a mean of 15.8 months (SD=12.4 months) have showed no regression but an increasingly improvement of the patients' clinical wellbeing. All our patients had a mRS score ≤ 2 and their mean length of stay in the hospital was approximately 3 days with

65% discharged within two days. This goes in line with the series of Stetler who also was able to discharge his patients on prasugrel on day 1 postoperatively.¹⁴ We may reckon that prasugrel would not only be efficacious, it could be safe whilst dispensed in this context. This patient-safety model is definitely multifactorial and it might not be plainly related to the use of prasugrel. Although, we might imply that prasugrel would not be adversely interfering with the patient's clinical wellbeing.

There is still no clear indication for the use of prasugrel as an alternative treatment for patients' resistance to clopidogrel during the placement of PED. The main concern of clinicians is the increased bleeding risks associated with its use as shown in several cardiovascular studies.^{9,17} However, the difference in end organ result response (brain vs. cardiac muscle), tortuosity of intracranial vasculature, and amount of metal implanted make it ineffective to simply apply cardiac literature to intracranial procedures.⁵ Akbari et al¹ presented their experience with prasugrel and aspirin in a cohort of 25 patients undergoing different neuro-endovascular procedures, nine of which undergoing PED placement. They observed a significant increase in hemorrhagic complications (19.4% vs. 3.6%; $p=0.02$) in the prasugrel/aspirin group as compared to patients treated with clopidogrel/aspirin. Jones et al tried using low dose prasugrel in two cases following PED implantation in patients who showed hypo-responsiveness to clopidogrel. Both patients did well with no thromboembolic or hemorrhagic complications.⁶ Our series of patients treated with PED placement who were started on prasugrel due to hypo-responsiveness to clopidogrel is the largest so far. We did not observe any ischemic events related to thromboembolism or in-stent thrombosis. We also did not find an increased risk of bleeding in those patients. Whether our patients fall into a subgroup of patients, which has a lower propensity to have bleeding complications with prasugrel, or these results are due to serendipity alone is not clear. Conclusions cannot be drawn at this level, and more investigations should be warranted to study the efficacy and safety of prasugrel in patients treated endovascularly with PED placement who

are hypo-responders to clopidogrel. The higher cost of prasugrel compared to clopidogrel should be also taken into consideration when prescribing the drug.⁴

LIMITATIONS

While our series is one of the largest to date documenting the safety and efficacy of prasugrel in the endovascular pipeline setting, our study design is limited by the small sample size and by the retrospective nature of data collection. None of the patients receiving prasugrel manifested major adverse events. This does not definitively show that prasugrel is as effective as clopidogrel in the pipeline patient population and our results could not be extrapolated to all the neuro-intervention specialized centers. Further randomized clinical trials are indispensable to display the promising outcome of these drugs in what they could replace clopidogrel in patients receiving PED flow diversion treatment.

CONCLUSION

The key in assuring clopidogrel resistant patients long term clinical wellbeing is by applying the right anti-aggregation protocol. Approximately 30% of the patients receiving clopidogrel are heterozygote for the CYP2C19 gene and showing a hypo-responsiveness or resistance (<30% platelet inhibition). Prasugrel is to be considered in clopidogrel resistant and allergic patients undergoing flow diversion treatment for their intracranial aneurysms.

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Functional Recovery and Risk of Readmission in Low-Grade aSAH Patients

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ABSTRACT

Introduction: Patients with aneurysmal subarachnoid hemorrhage (aSAH) are traditionally hospitalized for 14-21 days due to the high risk of cerebral vasospasm. The guidelines for low-grade SAH are less concrete and such patients are often discharged sooner given their lower risk of neurological complications. There is however a paucity of evidence regarding their risk of complications after discharge and their risk of readmission.

Methods: This is retrospective study of 424 patients with low-grade aSAH admitted to Thomas Jefferson University Hospital from 2008-2015. We collected data of patient comorbidities, Hunt-Hess (H-H) grade, length of stay (LOS), and complications and performed a logistic regression to determine the cause

Results: Out of 424 patients, 50 (11.8%) developed neurological complications after the first week that warranted prolonged ICU admission (mean 16.3 ± 6.5 days). Of the remaining 374 (88.2%) patients without neurological complications, 83 (22.2%) developed late medical complications with mean LOS of 15.1 ± 7.6 days, while those without medical complications stayed 11.8 ± 6.2 days ($p=0.001$). Among the patients with late medical complications, 55 (66.3%) did not have any hospital-associated complications in the first week. Smoking ($p=0.062$), history of cardiac disease ($p=0.043$), H-H grade 3 ($p=0.012$), IVH ($p=0.012$), external ventricular drain (EVD) placement ($p=0.002$) and DVT/UTI/pneumonia in the first week ($p=0.001$) were individually associated with late medical complications. Multinomial logistic regression showed early DVT/UTI/pneumonia ($p=0.026$) and increasing H-H grade ($p=0.057$) to be the most important risk factors for late medical complications.

Conclusion: While an extended ICU admission offers the benefit of closer monitoring, many patients develop hospital-associated complications, despite being low risk for neurological complications. We report in detail the characteristics of low-grade aSAH patients who would benefit from early discharge in an effort to prevent hospital-associated complications.

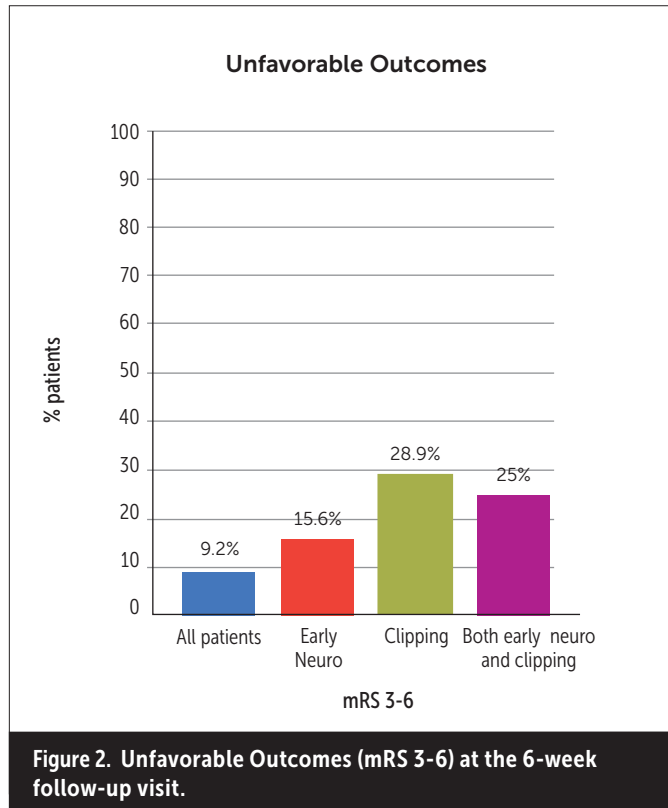
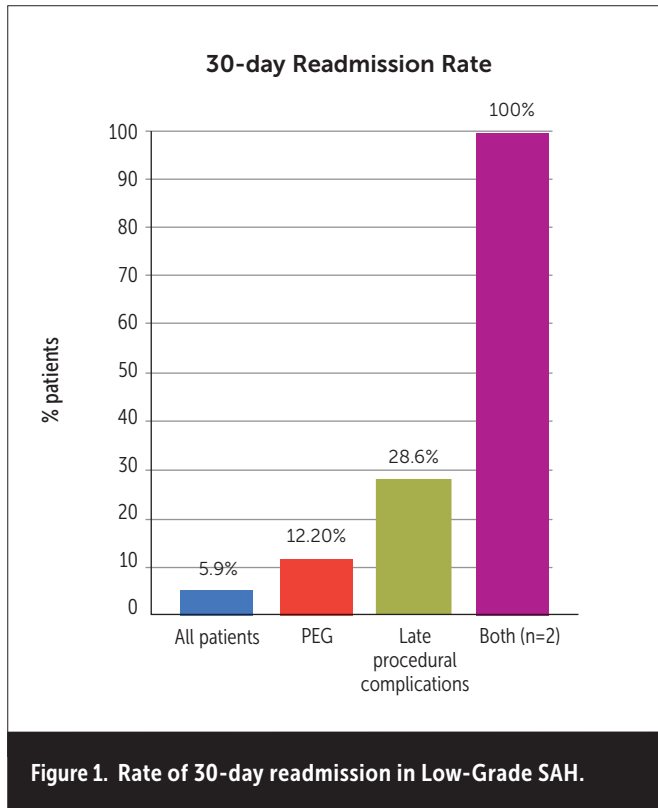
INTRODUCTION

Patients with aSAH are traditionally hospitalized for 14-21 days due to the high risk of vasospasm, cerebral edema and hydrocephalus. The risk of each of these complications varies significantly based on the clinical presentation and hemorrhage characteristics. Low-grade SAH patients are at a lower risk of complications and are often discharged sooner. However, the guidelines for this patient population are less concrete. There is a paucity of evidence regarding the appropriate time for discharge and their risk of readmission.

Most of the literature focuses on high-grade SAH patients despite the fact that the majority of patients experience low-grade SAH (Mocco, 2006). As the rate of readmission is a prevalent metric of quality of care, it needs to be taken into consideration when assessing the extent of monitoring and hospitalization of our SAH patients. The literature shows that one in ten SAH patients is readmitted within 30 days, most commonly with hydrocephalus, infections, UTIs, pneumonia, or thromboembolism (Greenberg, 2016; Singh, 2013; Low, 2016). Having a more complicated initial admission has been shown to be a risk factor for readmission, such as increased ICU length of stay and having an EVD (Singh, 2013). The majority of the readmissions are due to late complications of the neurological injury that the patients suffered and only one-fourth of the chief complaints at readmission could have been prevented with different management (Greenberg, 2016). In this study, we aim to identify the causes and predictors of readmission at our institution in the low-grade SAH patient.

METHODS

This is a retrospective study where electronic medical records were reviewed to identify a total of 424 patients with low-grade aSAH admitted to Thomas Jefferson University Hospital from 2008-2015. The study protocol was approved by the University Institutional Review Board. We collected data on patient comorbidities, SAH characteristics including H-H and modified Fischer scale grading, ICU length of stay (LOS), medical, neurological and procedure-related complications, and readmission within 30 days. Neurological complications include vasospasm confirmed by angiography, hydrocephalus, elevated intracranial pressure, transient ischemic attack, stroke, or hemorrhage. Medical complications included



hospital-acquired pneumonia, UTI, DVT, or bacteremia. Procedure-related complications included any issues involving placement, adjustment or removal of drains/catheters. Data analysis was carried out using unpaired t-test, Chi-square, Fisher's exact tests, and Mantel Haenszel test for linear association as appropriate. Univariable analysis was used to test covariates predictive of the following dependent variables: ICU LOS, unfavorable functional outcome defined as modified Rankin Scale 3-6, discharge destination (home or rehabilitation facility), and readmission. Interaction and confounding was assessed through stratification and relevant expansion covariates. Factors predictive in univariable analysis ($p < 0.20$) were entered into a multivariable logistic regression analysis. P-values of ≤ 0.05 were considered statistically significant. Statistical analysis was carried out with Stata 10.0 (College Station, TX).

RESULTS

A total of 424 patients were included in our retrospective study, of whom 74.1% were women and 25.9% were men. The mean age of our patients was 55.0 ± 13.4 years. Nearly half (47.6%) were smokers, 9.0% had history of cardiovascular disease, and 7.5% had family history of ruptured or unruptured aneurysms. On presentation, 22.2% of patients were H-H grade 1, 18.6% were H-H grade 2, and 59.2% of them were H-H grade 3. On CT imaging, their subarachnoid hemorrhage was Modified Fischer scale grade 1 in 15.6% of patients, grade 2 in 17.5%, grade 3 in 25.2% and grade 4 in 41.7% of the patients. Intraventricular hemorrhage and intraparenchymal hemorrhage were present in 65.1% and 11.8% of patients respectively. An external ventricular drain was placed in 65.8% of patients. Of the 424, 81.8% of patients underwent endovascular coiling, 17% underwent surgical clipping, 0.7% underwent coiling followed by surgical clipping and 0.5% were not treated.

Upon discharge, 29 (6.8%) of our total 424 patients were re-admitted within the 30-day period with a mean time to readmission of 13.6 ± 9.8 days. Multivariate analysis showed that requiring a gastrostomy tube (OR 2.89, 95% CI 1.19-6.99, $p = 0.019$) or developing a procedural complication late in their initial hospitalization (OR 4.93, 95% CI 0.87-27.88, $p = 0.071$) were the two factors that placed patients at a higher risk for readmission (Figure 1). Higher HH or modified Fisher grade, EVD placement, longer ICU stay were not independently correlated with increased risk of readmission.

All patients are scheduled for a 6-week follow up appointment in clinic upon discharge. Of the 424 patients in our study, 327 patients were able to attend the appointment. Of them, 90.8% had a favorable outcome (mRS 0-2) and 30 patients (9.2%) had a mRS score of 3-6. The multivariate regression analysis showed that undergoing clipping (OR 3.32, 95% CI 1.01-10.95, $p = 0.048$) and having neurological complications during the hospitalization (OR 3.85, 95%

CI 1.28-11.50, $p=0.016$) were significant predictors of unfavorable outcome at 6 weeks. The rate of unfavorable outcome increased from 9.2% of all patients to 15.6% among those with neurological complications, and increased to 28.9% of those that underwent aneurysm clipping. Additionally, one in four (25%) of those who had their aneurysm clipped and experienced an early neurological complication had an unfavorable outcome at 6 weeks (Figure 2).

DISCUSSION

Patients with subarachnoid hemorrhage are well known to have a high risk of delayed neurological complications. This risk is significantly lower in patients with low-grade SAH patients and the length of close monitoring in the ICU is up to debate for this population. While there is often the concern that early discharge can lead to increased 30-day readmission and worse 6-week outcomes, our findings showed that patients with a gastrostomy tube were more likely to be readmitted (12.2% vs. 5.9% in general patient population) as well as those

with procedure-related complications during their initial stay (28.6% vs. 5.9%) when controlling for severity of the SAH, clinical exam on presentation, length of stay, or hospital-acquired complications. These findings suggest that emphasis on follow-up care, home nursing, and better patient education are likely to be more effective than more extensive hospitalization. Similarly, undergoing clipping and developing early neurological complications were the sole predictors of unfavorable outcome (mRS 3-6) at follow-up. The SAH patients that undergo coiling can be safely discharged in the absence of vasospasm and should expect favorable outcome at 6 weeks.

CONCLUSION

Among patients with low-grade SAH (HH 1-3), the risk of delayed neurological complications is low and early discharge is deemed safe in those with an uncomplicated hospitalization. In this study, we identified the predictors that increase the risk of readmission and unfavorable functional outcome in order to assist with decision-making for such patients.

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Support Groups

Brain Aneurysm and AVM Support Group at Jefferson

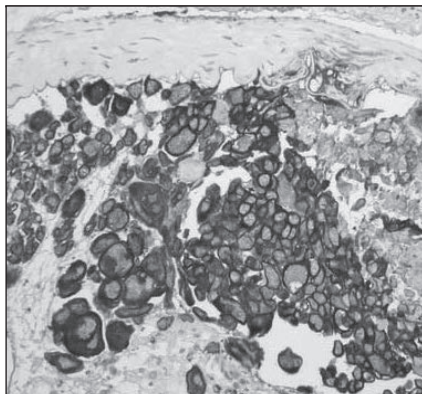
The Brain Aneurysm and AVM (arteriovenous malformation) Support Group provides support for individuals, family members and friends who have been affected by cerebral aneurysms, subarachnoid hemorrhage and AVMs. The purpose of the group is to gain and share knowledge and understanding of these vascular anomalies and the consequences of these disease processes. The group provides mutual support to its members by creating an atmosphere that engenders active listening and sincere and thoughtful speech within a caring environment.

When	Third Wednesday of every month (September through June)
Time	6:30-8:30 p.m.
Place	900 Walnut Street, 3rd Floor, Conference Room Philadelphia, PA 19107
Moderator/ Secretary	Jill Galvao
Parking	Complimentary parking is provided in the parking garage located in the JHN Building (Jefferson Hospital for Neuroscience) on 9th Street (between Locust & Walnut)
Information	For additional information please call: 215-503-1714

The Brain Tumor Support Group at Jefferson

The Delaware Valley Brain Tumor Support Group at Jefferson provides an opportunity for patients and their families to gain support in obtaining their optimum level of well-being while coping with, and adjusting to the diagnosis of brain tumor. Members are encouraged to share their support strategies so members can confront the challenges that this disease process has imposed on their lives. The strength gained from group can be a source of comfort and hope for whatever lies ahead.

When	Second Thursday of every month
Time	7-8:30 p.m.
Place	Jefferson Hospital for Neuroscience, 3rd Floor conference room 900 Walnut Street Philadelphia, PA 19107
Facilitator	Joseph McBride, BSN, RN and Katelyn Salvatore, BSN, RN. 215-955-4429 or katlyn.salvatore@jefferson.edu
Parking	Complimentary parking is available at the Jefferson Hospital for Neuroscience parking lot. Light refreshments and snacks will be served.



Neurosurgical Emergency Hotline

Jefferson Hospital for Neuroscience
Aneurysms • AVMs • Intracranial Bleeds
7 day • 24 hour coverage
1-866-200-4854

UPCOMING JEFFERSON NEUROSURGERY CME PROGRAMS

As a part of the Vickie and Jack Farber Institute for Neuroscience at Jefferson, the Department of Neurological Surgery is one of the busiest academic neurosurgical programs in the country, offering state-of-the-art treatment to patients with neurological diseases affecting the brain and spine, such as brain tumors, spinal disease, vascular brain diseases, epilepsy, pain, Parkinson's disease and many other neurological disorders (Jefferson.edu/Neurosurgery).

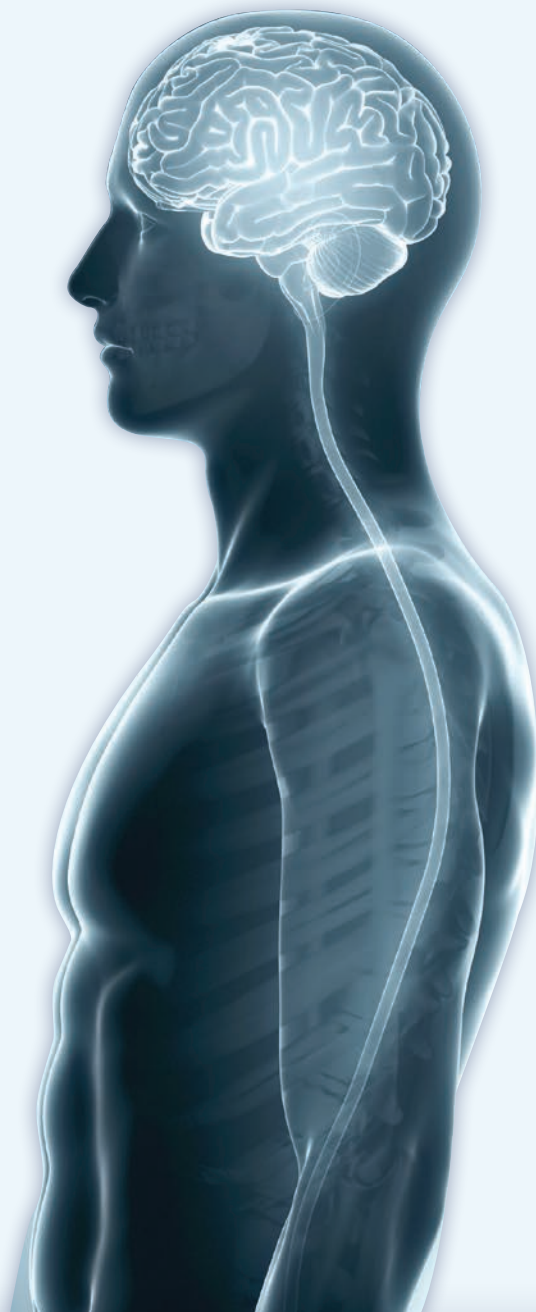
As part of a larger educational initiative from the Jefferson Department of Neurological Surgery, the Sidney Kimmel Medical College Office of Continuing Medical Education is offering the following continuing professional educational opportunities for 2018:

- **17th Annual Cerebrovascular Update**
March 15-16, 2018
Hyatt at The Bellevue, Philadelphia
- **Fundamental Critical Care Support Course**
April 12-13, 2018
Dorrance H. Hamilton Building, Center City Campus of Thomas Jefferson University
- **4th Annual Philadelphia Spine Summit**
May 11, 2018
Jefferson Alumni Hall, Center City Campus of Thomas Jefferson University
- **8th Annual Brain Tumor Symposium**
October 26, 2018
Philadelphia, PA
- **30th Annual Pan Philadelphia Neurosurgery Conference**
December 7, 2018
The Union League of Philadelphia

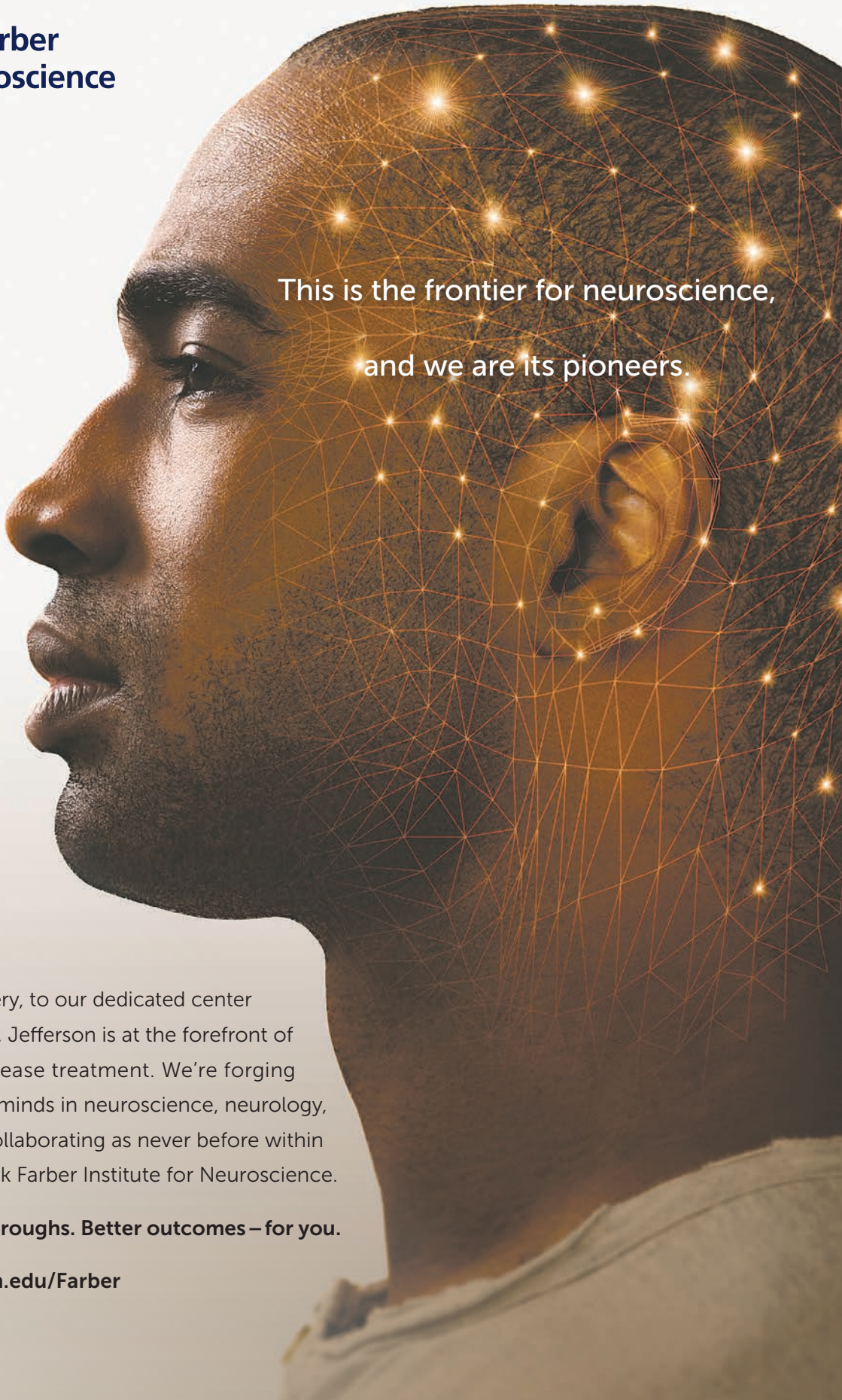
For additional information regarding these and other Jefferson CME programs, please visit our website at CME.Jefferson.edu or call the Office of CME at 888-JEFF-CME (888-533-3263).

Sidney Kimmel Medical College at Thomas Jefferson University is accredited by the ACCME to provide continuing medical education for physicians.

Many of the activities above offer additional CE accreditations.



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This is the frontier for neuroscience,
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From the nation's first brain surgery, to our dedicated center for ALS research and patient care, Jefferson is at the forefront of neuroscience discovery and disease treatment. We're forging ahead again – with the brightest minds in neuroscience, neurology, neurosurgery and psychiatry – collaborating as never before within one institute – the Vickie and Jack Farber Institute for Neuroscience.

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