Anticoagulation for Hypercoagulable Patients Associated with Complications after Large Cranioplasty Reconstruction

Eric W. Sankey, B.S.
Joseph Lopez, M.D., M.B.A.
Shuting (Susan) Zhong, B.S.
Harlyn Susarla, D.M.D., M.P.H.
Ignacio Jusué-Torres, M.D.
Jason Liauw, M.D.
Judy Huang, M.D.
Michael Streiff, M.D.
Henry Brem, M.D.
Chad R. Gordon, D.O., F.A.C.S.

Baltimore, Md.; and Rockford, Ill.

Background: Despite advancements in materials and techniques used for cranial reconstruction, complication rates following reconstructive cranioplasty remain significant.
Methods: In this study, the authors assessed the association of perioperative anticoagulation use and/or a hypercoagulable state with minor (i.e., not requiring surgical intervention) and major (i.e., surgical intervention required) complications after reconstructive cranioplasty for large skull defects. A retrospective cohort review of 108 consecutive cranioplasties performed between 2011 and 2014 was conducted. A multiple logistic regression analysis was performed to identify the adjusted association between the predictor variables and complications.
Results: Twenty-three primary (21.3 percent) and 85 secondary (78.7 percent) cranioplasties were performed on 94 patients with a median age of 50 years (interquartile range, 38 to 63 years). Median full-thickness calvarial defect size was 154 cm^2 (interquartile range, 104 to 230 cm^2). Eleven minor (10.2 percent) and 18 major postoperative complications (16.7 percent) occurred in 26 cases (24.1 percent). Multiple logistic regression analysis revealed that coagulation status (i.e., perioperative use of anticoagulation therapy or hypercoagulable state) was statistically significant in predicting minor complications (OR, 7.8; 95 percent CI, 2.4 to 25.2; $p = 0.001$). Of note, the odds of a minor complication were an order of magnitude higher when both perioperative anticoagulation and a hypercoagulable state were present.
Conclusion: To the authors' knowledge, this is the first study to document that the use of perioperative anticoagulant therapy for patients with thromboembolic conditions is a positive predictor of complications following cranioplasty reconstruction. (*Plast. Reconstr. Surg.* 137: 595, 2016.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

Cranial reconstruction, commonly referred to as cranioplasty, aims to restore cerebral protection, correct visual disfigurement from an acquired/congenital craniofacial deformity, and reverse "syndrome of the trephined."[1–5] Since its inception, reconstructive cranioplasty has traditionally been challenged with a high rate of complications, including wound infection, seizures, exposure of nonautologous material, wound dehiscence, cranial implant infection requiring removal, cerebrospinal fluid leak, intracranial hemorrhage, and death.[6–16] In an effort to improve outcomes, several alloplastic materials and cranioplasty techniques have been implemented.[3–5,17,18] Despite these advances, overall complication rates remain significant, ranging from approximately 15 to 43 percent.[6–16]

Understanding the patient-specific risk factors associated with postoperative complications is

From the Departments of Plastic and Reconstructive Surgery, Neurosurgery, and Hematology, The Johns Hopkins University School of Medicine; and the University of Illinois College of Medicine.
Received for publication March 20, 2015; accepted September 28, 2015.
Presented at the 60th Annual Meeting of the Plastic Surgery Research Council, in Seattle, Washington, May 14 through 16, 2015.

DOI: 10.1097/01.prs.0000475773.99148.ba

Disclosure: *Dr. Gordon is a consultant for Stryker CMF. All other authors have no conflicts of interest to report. No external funding sources were used for this study.*

essential for using optimal strategies for risk reduction. Although several studies have focused on the risk and predictors of infection and bleeding after cranioplasty,[12–15] research is sparse regarding the predictive factors associated with other types of postoperative complications.[7] Cited positive predictors of complications after cranioplasty include a history of irradiation, preoperative infection,[9] pneumocephalus,[16] nicotine abuse, age older than 60 years, lower Glasgow Outcome Scale,[19] and bifrontal cranioplasty.[20,21] However, despite a large body of research on perioperative anticoagulation, and the growing number of patients diagnosed with thromboembolic disease each year,[22–36] no study to date has investigated the impact of perioperative anticoagulant therapy on complications following cranioplasty reconstruction. In this study, we explore the association of perioperative anticoagulant use and/or a hypercoagulable state with minor/major complications in patients undergoing reconstructive cranioplasty for large skull defects.

PATIENTS AND METHODS

Patient Characteristics

Under an active institutional review board–approved protocol (NA_00087598), we reviewed the records of all patients who underwent large (>25 cm^2) reconstructive cranioplasty performed by a single multidisciplinary team between 2011 and 2014. Several perioperative variables were collected to assess their association with outcomes.

Demographic factors included age, sex, race, comorbidities, smoking history, preoperative and postoperative hematologic variables, history of cranial chemoradiotherapy, indications for craniectomy and cranioplasty, calvarial defect size and location, history of previous scalp reconstruction with free tissue transfer, history of previous bone flap osteomyelitis or implant infection, time from previous bone flap/implant infection and/or extruding hardware, and evidence of an open scalp wound at the time of surgery. Patients were considered to be in a hypercoagulable state if they had a history of multiple venous thromboembolisms and/or a known coagulopathy. Because of the high degree of overlap between perioperative anticoagulant and patients with a hypercoagulable state (e.g., antiphospholipid syndrome), a hybrid variable of "coagulation status" was created (not anticoagulated, no hypercoagulable state versus anticoagulated or hypercoagulable state versus anticoagulated and hypercoagulable state). The sizes for all cranial defects were calculated using computed tomographic images and/or fasciocutaneous scalp flap size. Additional perioperative information was collected, which included cranioplasty material used for reconstruction, operative time, length of hospitalization, and intraoperative and postoperative complications (Table 1). Postoperative computed tomographic imaging was performed to monitor for extraaxial fluid collections in all patients. Subcutaneous drains were placed within the extracranial space after each use. Based on the hematologist's recommendations, patients were transitioned off of Coumadin (Bristol-Myers-Squibb, New York, N.Y.) 5 days in advance with presurgical hospital admission and therapeutic heparin drip maintenance, which was then stopped 4 to 6 hours before planned cranioplasty surgery. Postoperatively, all patients were transitioned back to systemic heparin at approximately 48 to 72 hours, followed by Coumadin administration, also according to the hematologist's recommendation. Prophylactic dosing (i.e., 5000 units every 12 hours) of subcutaneous low-molecular-weight heparin was also used beginning no earlier than 24 hours after surgery. All postoperative complications were classified as either "minor" (i.e., not requiring surgical intervention) or "major" (i.e., surgical intervention required).

Statistical Analysis

Deidentified data were entered into a statistical database (IBM SPSS Version 23.0; IBM Corp., Armonk, N.Y.) for analysis. Descriptive statistics were computed for the study population, including frequency (percentage) data for categorical measures and mean (interquartile range) for continuous measures. For intergroup comparison, the Wilcoxon rank sum test was used for continuous data and Fisher's exact test was used for categorical data. Variables with a value of $p < 0.15$ in the bivariate analyses were included as candidate variables in a multiple logistic regression model, with forward selection used to identify the most parsimonious model and adjusted associations between the predictors and major or minor complications. A value of $p < 0.05$ was considered statistically significant. Odds ratios were reported with 95 percent CIs.

RESULTS

Over 3 years, 108 large reconstructive cranioplasties were performed on 94 patients with a median age of 50 years (interquartile range, 38 to 63 years). Average length of follow-up for all patients was 3 months (interquartile range, 1 to 7 months). The majority of cranioplasties were performed in

Table 1. Summary of Patient Demographics

Characteristics	All Cases (%)	Non-AC/HC Cases (%)	AC/HC Cases (%)	*p**
No.	108	94	14	
Baseline				
Age, yr				†
Mean	50	51	44	
IQR	38–63	40–63	32–63	
Male sex	55 (51)	48 (51)	7 (50)	†
Race				†
Caucasian	79 (73)	69 (73)	10 (71)	
African American	15 (14)	13 (14)	2 (14)	
Other	14 (13)	12 (13)	2 (14)	
Comorbidities				0.019
Tumor	49 (45)	46 (49)	3 (21)	
HTN	27 (25)	22 (23)	5 (36)	
HLD	16 (15)	11 (12)	5 (36)	
DM	13 (12)	10 (11)	3 (21)	
CVD	12 (11)	7 (7)	5 (36)	
Obesity	6 (6)	4 (4)	2 (14)	
CKD/ESRD	2 (2)	2 (2)	0 (0)	
Hypothyroidism	9 (8)	9 (10)	0 (0)	
Autoimmune disease	8 (7)	6 (6)	2 (14)	
Chronic infection (e.g., HIV, hepatitis)	3 (3)	3 (3)	0 (0)	
History of cranial radiation	19 (18)	18 (19)	1 (7)	†
History of chemotherapy	13 (12)	12 (13)	1 (7)	†
Smoking history	45 (42)	40 (43)	5 (36)	†
Current smoker at surgery	25 (23)	24 (26)	1 (7)	
Hematologic parameters,				
INR				0.025
Median	1.4	1.0	1.1	
IQR	1.1–1.9	1.0–1.1	1.0–1.6	
aPTT, sec				0.017
Median	31.9	25.9	31.6	
IQR	29–44.6	24.0–27.6	26.0–36.9	
Hb, g/dl				†
Median	12.4	12.9	12.0	
IQR	11.1–13.9	11.2–13.9	11.2–13.0	
Hct, %				†
Median	37.9	38.9	37.0	
IQR	35.1–41.5	35.2–41.4	34.8–38.7	
History of scalp reconstruction with free tissue transfer	4 (4)	3 (3)	1 (7)	†
History of flap infection	54 (50)	46 (49)	8 (57)	†
Bone flap infection only	43 (40)	38 (40)	5 (36)	
Synthetic implant infection only	8 (7)	5 (5)	3 (21)	
Both bone and implant infection	3 (3)	3 (3)	0 (0)	
Open scalp wound	22 (20)	20 (21)	2 (14)	†
>3 mo from previous flap infection and/or extruding hardware	97 (90)	85 (90)	12 (86)	†
Indication for primary craniectomy				0.018
Tumor	49 (45)	46 (49)	3 (21)	
Trauma	29 (27)	27 (29)	2 (14)	
Vascular	27 (25)	18 (19)	9 (64)	
Infection	1(1)	1 (1)	0 (0)	
Other	2(2)	2 (2)	0 (0)	
Indication for cranioplasty				†
Acquired/persistent defect	59 (55)	53 (56)	6 (43)	
Flap infection	45 (42)	37 (39)	8 (57)	
Other	4 (4)	4 (4)	0 (0)	
Primary vs. secondary cranioplasty				0.038
Primary	23 (21)	23 (24)	0 (0)	
Secondary	85 (79)	71 (76)	14 (100)	
Calvarial defect size, cm^2				0.071
Median	158	154	216	
IQR	104–230	101–226	120–336	

(*Continued*)

Table 1. (*Continued*)

Characteristics	All Cases (%)	Non-AC/HC Cases (%)	AC/HC Cases (%)	*p**
Anatomical location of defect				†
Pterional	49 (45)	39 (41)	10 (71)	
Frontal	20 (19)	20 (21)	0 (0)	
Temporal	8 (7)	8 (9)	0 (0)	
Frontoparietal	8 (7)	8 (9)	0 (0)	
Hemicranium	7 (6)	4 (4)	3 (21)	
Frontotemporal	5 (5)	5 (5)	0 (0)	
Temporoparietal	3 (3)	2 (2)	1 (7)	
Midline vertex	2 (2)	2 (2)	0 (0)	
Skull base	2 (2)	2 (2)	0 (0)	
Multiple locations	2 (2)	2 (2)	0 (0)	
Other	2 (2)	2 (2)	0 (0)	
Bilateral defect	17 (16)	17 (18)	0 (0)	†
Cranioplasty material				0.005
PMMA	55 (51)	45 (48)	10 (71)	
Autologous bone	23 (21)	21 (22)	2 (14)	
Titanium mesh	21 (19)	19 (20)	2 (14)	
PEEK	8 (7)	8 (9)	0 (0)	
Medpor	1 (1)	1 (1)	0 (0)	
Perioperative				
Operative time, min				†
Median	184	183	171	
IQR	151–224	152–223	121–234	
EBL, cc				†
Median	100	100	125	
IQR	50–200	50–200	56–200	
Blood transfusion required	15 (14)	13 (14)	2 (14)	†
Postoperative Hb, g/dl				†
Median	11.1	11.0	11.3	
IQR	10.1–12.2	10.1–12.1	10.6–12.4	
Postoperative Hct, %				†
Median	33.1	33.0	34.9	
IQR	30.7–36.1	30.7–36.0	32.8–37.5	
Total inpatient wound drainage, cc				†
Median	278	275	281	
IQR	179–403	179–398	218–611	
Duration of wound drain(s), days				†
Median	5	5	5	
IQR	3–7	3–8	3–8	
Length of hospitalization, days				0.024
Median	4	3	5	
IQR	2–7	2–6	5–11	
Duration of follow-up, mo				†
Median	3	3	5	
IQR	1–7	1–7	1–12	

AC, anticoagulated; HC, hypercoagulable; IQR, interquartile range; HTN, hypertension; CVD, cardiovascular disease; HLD, hyperlipidemia; DM, diabetes mellitus; CKD, chronic kidney disease; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; INR, international normalized ratio; aPTT, activated partial thromboplastin time; Hb, hemoglobin; Hct, hematocrit; PMMA, poly(methylmethacrylate); PEEK, poly(etheretherketone); EBL, estimated blood loss;

*The *p* values denote differences among characteristics between anticoagulated/hypercoagulable patients and non–anticoagulated/hypercoagulable patients.

†Not significant ($p > 0.05$).

males [$n = 55$, (50.9 percent)] and Caucasians [$n = 79$, (73.1 percent)] (Table 1). Nine patients (9.6 percent) were on long-term therapeutic anticoagulant therapy, with either low-molecular-weight heparin ($n = 1$) or Coumadin ($n = 8$), for a history of venous thromboembolism ($n = 5$), atrial fibrillation ($n = 2$), mechanical heart valve ($n = 1$), or cardiac stent ($n = 1$). The median time from the last anticoagulant dose before surgery was 5 days (interquartile range, 3 to 7 days). Two patients on a perioperative anticoagulant were also taking aspirin before surgery, and stopped 7 and 14 days before surgery. Eight patients ($n = 10$ cases) were defined as hypercoagulable because of a history of multiple venous thromboembolism ($n = 8$ cases), antiphospholipid syndrome ($n = 1$ case), or Moyamoya disease ($n = 1$ case). Patients with a hypercoagulable state received a perioperative anticoagulant in six of the 10 cases—following consultation with the hematologist and individual risk stratification. All other baseline characteristics are listed in Table 1.

No intraoperative complications were encountered. However, 11 minor (10.2 percent) and 18 major postoperative complications (16.7 percent) occurred in 26 cases (24.1 percent). Three cases (2.8 percent) had both minor and major postoperative complications during follow-up. The majority of minor complications consisted of nine cases (8.3 percent) of extraaxial fluid collection/hematoma, which gradually self-resorbed, seven (6.5 percent) of which were subcutaneous (i.e., above the cranial implant) and two of which were epidural (1.9 percent) (i.e., below the implant). The two remaining minor complications included one postoperative seizure (0.9 percent), which improved with antiepileptic medication; and one case of transient, acute hydrocephalus (0.9 percent), which improved without intervention. Major complications consisted of seven epidural hematomas (6.4 percent) requiring acute surgical evacuation, six cases (5.6 percent) of wound dehiscence, four postoperative wound infections (3.7 percent) necessitating washout and cranioplasty revision, and one postoperative deep vein thrombosis (0.9 percent) requiring inferior vena cava filter placement with delayed therapeutic anticoagulant (Table 2). The median time to minor and major postoperative complications was 3 days (interquartile range, 1 to 12 days) and 21 days (interquartile range, 8 to 82), respectively.

On bivariate analysis, several factors were associated with minor complications after cranioplasty, such as the use of perioperative anticoagulation ($p < 0.001$), hypercoagulable state ($p = 0.003$), calvarial defect size ($p = 0.02$), and the amount ($p = 0.04$) and duration ($p = 0.008$) of wound drainage (Table 3). However, on multiple logistic regression, only coagulation status (OR, 7.8; 95 percent CI, 2.4 to 25.2; $p = 0.001$) and duration of wound drainage (OR, 1.2; 95 percent CI, 1.1 to 1.3; $p = 0.045$) were statistically significant in predicting minor postoperative complications (Table 4). Of note, the odds of a minor complication were an order of magnitude higher when both perioperative anticoagulation and a hypercoagulable state were present. Factors associated with major postoperative complications following cranioplasty included history of previous bone flap infection (OR, 6.5; 95 percent CI, 2.4 to 17.6; $p < 0.0001$) and length of hospitalization (OR, 1.2; 95 percent CI, 1.1 to 1.3; $p < 0.0001$) on multiple logistic regression analysis (Table 4). The effect of antiplatelet therapy, including aspirin, was not assessed.

A subset analysis of the nine patients who developed complications while on anticoagulation therapy showed that eight patients (89 percent) were on a long-term regimen of Coumadin therapy and one patient (11 percent) was taking therapeutic doses of low-molecular-weight heparin before surgery. All patients were transitioned to prophylactic dosing (i.e., 5000 units every 12 hours) of subcutaneous low-molecular-weight heparin, before surgery. Six minor and four major complications occurred after cranioplasty in these patients. Minor complications were most commonly because of extraaxial fluid collection/hematoma [$n = 4$ (44 percent)]; other minor complications included one (11 percent) postoperative seizure and one (11 percent) case of acute, transient hydrocephalus. The four major complications in anticoagulated patients included one case (11 percent) of extraaxial fluid collection/hematoma requiring surgical evacuation, one wound infection (11 percent), one wound dehiscence (11 percent), and one postoperative deep venous thrombosis (11 percent) requiring therapeutic anticoagulant and inferior vena cava filter placement (Table 2). The patients who were on a perioperative anticoagulant resumed therapy at a median of 3 days (interquartile range, 1 to 4 days) postoperatively;

Table 2. Summary of Postoperative Complications*

	Minor Complications			Major Complications		
Type of Complication	**Non-AC/HC (%)**	**AC/HC (%)**	***p***	**Non-AC/HC (%)**	**AC/HC (%)**	***p***
No.	5	6		14	4	
Type of complication						
Extraaxial fluid collection/ hematoma	5 (5)	4 (29)	0.016	6 (10)	1 (7)	†
Wound infection	0 (0)	0 (0)	†	3 (3)	1 (7)	†
Wound dehiscence	0 (0)	0 (0)	†	5 (5)	1 (7)	†
Seizure	0 (0)	1 (7)	†	0 (0)	0 (0)	†
DVT	0 (0)	0 (0)	†	0 (0)	1 (7)	†
Acute hydrocephalus	0 (0)	1 (7)	†	0 (0)	0 (0)	†

AC, anticoagulated; HC, hypercoagulable; DVT, deep venous thrombosis.
*Percentages for non-AC/HC cases were based on a total of 94 cases, and percentages for AC/HC cases were based on a total of 14 cases.
†Not significant ($p > 0.05$).

Table 3. Bivariate Analyses of Major and Minor Complications Identified within 108 Consecutive Reconstructive Cranioplasties

	Major Complications ($n = 18$)		Minor Complications ($n = 11$)	
Variables	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Preoperative				
Age	1.0 (0.97–1.02)	0.77	1.0 (0.96–1.04)	1
Smoking history	0.65 (0.23–1.9)	0.43	0.78 (0.20–2.8)	0.71
Obesity	2.7 (0.45–15.9)	0.28	1.8 (0.20–17.4)	0.59
Diabetes mellitus	0.0 (0.00–0.00)	1	0.71 (0.08–6.0)	0.75
Coagulopathy	1.5 (0.28–7.8)	0.64	10.5 (2.3–48.2)	0.003*
Cancer history	0.62 (0.30–1.3)	0.19	1.3 (0.60–2.7)	0.54
History of radiation therapy	0.54 (0.11–2.6)	0.44	1.05 (0.21–5.3)	0.96
Preoperative therapeutic anticoagulation	2.3 (0.54–10.1)	0.25	15.2 (3.4–67.3)	<0.001*
History of free flap transfer	17.8 (1.7–182.6)	0.02*	3.1 (0.30–33.0)	0.34
History of previous bone flap infection	0.2 (0.05–0.70)	0.01*	0.46 (0.09–2.5)	0.37
Open wound at the time of surgery	1.7 (0.52–5.3)	0.4	1.5 (0.37–6.4)	0.55
Indication for primary craniectomy	0.59 (0.30–1.2)	0.13	1.4 (0.69–2.7)	0.37
Cranioplasty material	1.1 (0.66–1.8)	0.72	1.4 (0.76–2.4)	0.31
Primary vs. secondary cranioplasty	4.30E + 07	1	0.69 (0.17–2.9)	0.61
Preoperative hemoglobin	0.9 (0.65–1.2)	0.5	1.2 (0.77–1.9)	0.41
Anatomical location of defect	0.94 (0.84–1.05)	0.26	0.94 (0.82–1.08)	0.36
Calvarial defect size	1.0 (0.99–1.01)	0.18	1.01 (1.00–1.02)	0.02*
Postoperative				
Amount of wound drainage	1.0 (0.99–1.0)	0.07*	1.0 (1.0-1.0)	0.04*
Duration of wound drainage	1.1 (1.02–1.2)	0.02*	1.2 (1.04–1.3)	0.008*
Drains present at discharge	0.58 (0.19–1.8)	0.33	1.4 (0.4–4.9)	0.59
Length of hospitalization	1.1 (1.03–1.2)	0.002*	1.01 (0.96–1.06)	0.7
Duration of follow-up	1.1 (1.04–1.2)	0.005*	1.05 (0.5–1.2)	0.32

*Statistically significant ($p < 0.05$).

the postoperative anticoagulant dose was therapeutic after eight cases and prophylactic after two cases. One patient on a perioperative anticoagulant became supratherapeutic (international normalized ratio of 3.8 and 3.9) postoperatively on two occasions because of drug interactions between Coumadin, ketorolac, ciprofloxacin, and sertraline. The patient's Coumadin was held for 3 days until her international normalized ratio normalized.

DISCUSSION

Given the significant morbidity commonly reported after secondary cranial reconstruction and the critical need for patients with large cranial defects to undergo secondary cranioplasty reconstruction, a thorough understanding of the risk factors associated with postoperative complications is crucial for the effective management of this challenging patient population. In our study, several factors previously shown to be associated with an increased risk of infection, bleeding, and/or impaired wound healing were assessed. However, after correcting for confounding variables under multivariate logistic regression, only the use of perioperative anticoagulant and/or a hypercoagulable state and the duration of wound drainage were found to be predictive of minor complications, with the odds of a minor complication being an order of magnitude higher when both perioperative anticoagulant and a hypercoagulable state are present.

Several other factors have been found to be predictive of complications following cranioplasty. For example, Lee et al. found that an indication of trauma for the primary craniectomy was

Table 4. Summary of Results Using Multiple Logistic Regression Analysis

	Major Complications ($n = 18$)		Minor Complications ($n = 11$)	
Variables	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Preoperative				
Coagulation status*	—	—	7.8 (2.4–25.2)	0.001
History of previous bone flap infection	6.5 (2.4–17.6)	<0.0001	—	—
Postoperative				
Duration of wound drainage	—	—	1.2 (1.1–1.3)	0.045
Length of hospitalization	1.2 (1.1–1.3)	<0.0001	—	—

*Coagulation status includes use of perioperative anticoagulation or hypercoagulable state.

associated with a higher risk of postoperative seizure ($p = 0.03$).[7] In addition, Reddy et al. discovered that a history of irradiation was the strongest positive predictor of postoperative complications of any type after cranioplasty (OR, 6.91; $p < 0.005$) and that preoperative infection increased the risk of alloplastic hardware exposure (OR, 3.13; $p < 0.05$).[9] Likewise, a history of previous osteomyelitic bone flap infection was found to be predictive of major complications in our study (OR, 6.5; $p < 0.0001$). Interestingly, all cases of wound dehiscence ($n = 6$) and wound infection ($n = 4$) in our study occurred in patients with a history of osteomyelitic bone flap and/or implant infection; however, this finding was not significant ($p > 0.05$). In contrast, recent studies have not found that previously cited risk factors such as timing of operation, defect size, cranioplasty material, and method of flap preservation are significantly associated with complications after cranioplasty.[15,37,38]

Our study is unique in that we assessed a modifiable risk factor, perioperative anticoagulation, and found that its use may also increase patients' short-term risk for minor postcranioplasty complications. A potential explanation for this finding stems from the fact that the use of perioperative anticoagulant can lead to prolonged venous oozing within the surgical site and/or surrounding the dissection field. Such oozing can lead to a subclinical extraaxial fluid collection/hematoma, which was seen after approximately half of the cases performed in anticoagulated patients in our study. Theoretically, infections may be more common in the setting of an anticoagulant, as oxidative damage and bacterial growth are more likely in the presence of a high iron content contained in the hemoglobin within the hematoma.[39–41] In the context of increased oxidative stress, wound dehiscence is also more likely to occur because of impaired wound healing.[42] Given the association between perioperative anticoagulant and postoperative complications, management strategies to mitigate this risk are needed—especially because any degree of scalp dehiscence may lead to irreversible bacterial contamination of the underlying alloplastic cranial implant and ultimate removal.

Not surprisingly, length of hospitalization was significantly associated with major postoperative complications in our study (OR, 1.2; 95 percent CI, 1.1 to 1.3; $p < 0.0001$). Patients who had a major postoperative complication had a mean hospital stay of 16.4 ± 19.7 days, compared with 5.4 ± 5.7 days for those without a major postoperative complication ($p < 0.001$). One possible explanation for this finding is a prolonged hospital course secondary to a major postoperative complication. However, the mean time to a major postoperative complication was 57.7 ± 86.4 days (range, 0 to 356 days; median, 21 days; interquartile range, 6.3 to 87.5 days), suggesting that the majority of major complications occurred after discharge. Another reason for prolonged hospital admissions in this subset could be related to additional time needed to manage their anticoagulation bridging (preoperative and postoperative) with heparin drip administration—both on the front end (to wean off systemic anticoagulation preoperatively) and on the back end (to wean onto therapeutic levels postoperatively). However, aside from a history of osteomyelitic bone flap infection, none of the other variables assessed in our study were significantly associated with major complications. Therefore, additional research is needed to assess which factors are associated with delayed, major complications after large cranial reconstruction. The rate of postoperative complications after neurosurgical procedures ranges from approximately 20 to 60 percent, with approximately 25 percent experiencing more than one complication.[43,44] For example, in their prospective study of 162 patients, Magni et al. observed early postoperative complications after intracranial surgery in 57 percent of patients.[43] Unfortunately, studies regarding perioperative anticoagulant administration among neurosurgical patients in general remain sparse.[45] Currently, there is no consensus on the most appropriate perioperative anticoagulant regimen in elective and emergent cranial reconstructive surgery. As a result, many surgeons base their therapy regimen on anecdotal observations and personal professional experiences—and in some instances, surgeons may avoid surgery altogether because of the lack of literature. This type of unfortunate avoidance commits neurosurgical patients to wearing lifelong helmet protection and the unavoidable social stigmata that accompany this decision.[46] To complicate matters further, neurosurgical procedures in general are placed within the high-risk category for perioperative bleeding and coagulation because of the confined intracranial space.[28,35]

For example, Hamilton et al. found that postoperative deep venous thromboses are encountered after greater than 25 percent of craniotomies performed in patients who do not receive anticoagulant therapy.[47] In a recent study by Scheller et al. assessing the management of patients who experienced postoperative deep venous thrombosis or pulmonary embolism, the authors concluded that more aggressive use of anticoagulant therapy

after craniotomies may be justified given the ability of drugs such as low-molecular-weight heparin to reduce the risk of deep venous thrombosis and pulmonary embolism by 8.9 percent and 40.2 percent, respectively.[45,48] In addition, temporary perioperative interruption of long-term anticoagulant therapy exposes patients to an increased risk of thromboembolism and stroke.[28,49,50] Fortunately, we experienced only one case of a postoperative deep venous thrombosis in a patient with Ehlers-Danlos syndrome (type IV) on a long-term regimen of Coumadin, which was stopped 6 days before surgery. In contrast, our analysis reveals that continuation or early postoperative use of therapeutic anticoagulant not only is associated with an increased short-term risk of bleeding[22,28,46,50–52] but may also be associated with overall complications, including infection and wound dehiscence. Therefore, a successful balance between these two opposing considerations is essential for safe and effective management of patients who undergo reconstructive cranioplasty—especially in the setting of nonautologous custom cranial implants.[53]

Given the dearth of literature regarding perioperative anticoagulation in patients undergoing reconstructive cranioplasty, and our findings regarding the risk of complications in these patients, we propose a standard strategy for anticoagulant management in this challenging and high-risk patient population (Fig. 1). Based on our experience and the high risk of bleeding associated with intracranial procedures,[28,35,54,55] our multidisciplinary team's algorithm includes mandatory perioperative consultation with a hematologist for all patients who are on chronic anticoagulant therapy—both before and after surgery. A similar approach to elective cases can be taken after emergent surgery. Our approach should be considered only as a proposed guideline for patients on Coumadin and heparin therapy, and is not a substitute for clinician judgment regarding perioperative anticoagulant management. Likewise, newer anticoagulant and antiplatelet therapies may require different perioperative management.

As a result of the findings in this study, our team, in conjunction with anticoagulation management services at our institution, has implemented this algorithm for clinical management of anticoagulation in patients undergoing cranioplasty procedures. Although the retrospective nature of this study does pose limitations in the context of generalizability and possible selection bias, we are proceeding with a prospective analysis of outcomes among this group of patients, with emphasis on the effectiveness of an algorithmic approach to management and the importance of interdisciplinary collaboration.

One strength of this study is our team-oriented approach to the management of anticoagulated patients undergoing large reconstructive cranioplasty, which combines the skill and precision of neurosurgery, craniofacial plastic surgery, and hematology—by way of a well-established multidisciplinary adult cranioplasty center. In addition, our large experience, together with the consistency of a single craniofacial surgeon, helps to minimize the variability in management among the cases included in our study. Furthermore, we explored a large number of potential variables that have been shown to be associated with complications after cranioplasty, and accounted for potential confounders discovered in our initial bivariate analysis. Lastly, we enlisted the knowledge and expertise of our hematology department to provide recommendations for the complex management of patients who require perioperative anticoagulation (Figs. 2 through 6), which we found to be the strongest predictor of complications in our study.

Several limitations of our study merit consideration. These include retrospective data collection, restricted sample size, and inconsistent use of preoperative hematologic testing and bridging therapy because of varying risk stratification per patient (individual decisions made after comparing "estimated postoperative bleed risk" to "estimated thromboembolic risk"). Another limitation is the average duration of follow-up (approximately 3 months) based on our last clinical examination. As such, we will continue to monitor our cranioplasty cohort for latent infections because alloplastic materials are at continued risk even years postoperatively, which can be further complicated by our high-risk patient cohort.[56–58] For example, in our heterogeneous cohort, we experienced an implant infection rate of 4 percent (four of 108). Again, long-term follow-up will be crucial to evaluate the heightened risk of late implant-related complications in this patient cohort. Although we are aware that each alloplastic material has its own unique complication profile, we cannot accurately comment on the efficacy of each specific material because of the relatively low incidence of infections in our 4-year experience.[4,53,59]

However, despite these limitations, this is the first study to date that has assessed the impact of perioperative anticoagulant therapy on reconstructive cranioplasty outcomes. Our results, in a deficient area of study within neurosurgery and craniofacial surgery, suggest that caution regarding

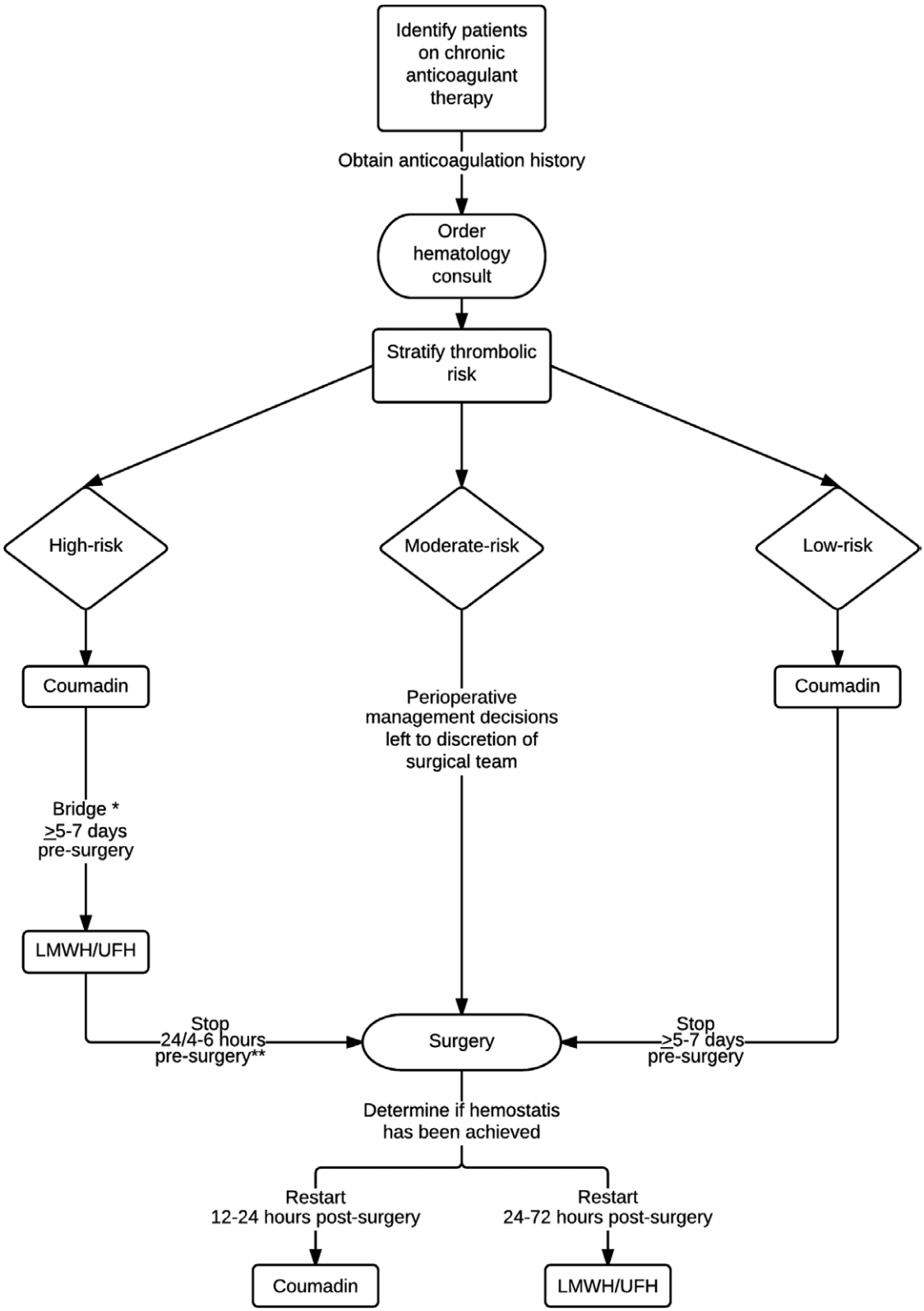

Fig. 1. Proposed algorithm for perioperative anticoagulation management for reconstructive cranioplasty patients. *Bridging therapy refers to stopping Coumadin and transitioning to intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin. **Anticoagulation is stopped at least 24 hours before surgery in patients receiving low-molecular-weight heparin, or 4 to 6 hours if unfractionated heparin is used. *LMWH*, low-molecular-weight heparin; *UFH*, unfractionated heparin.

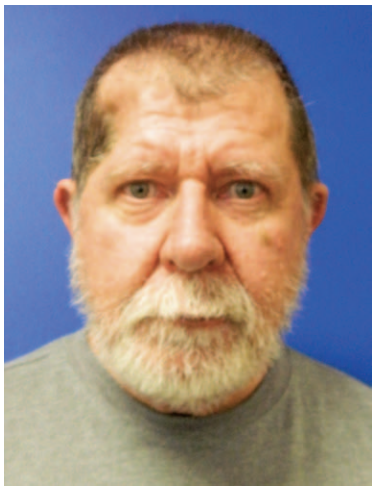

Fig. 2. A neurosurgical patient referred to the Johns Hopkins Multidisciplinary Adult Cranioplasty Center for complex reconstructive cranioplasty using a customized craniofacial implant. In addition, this patient required long-term anticoagulation for a mechanical heart valve. No complications were encountered using the algorithm provided in Figure 1.

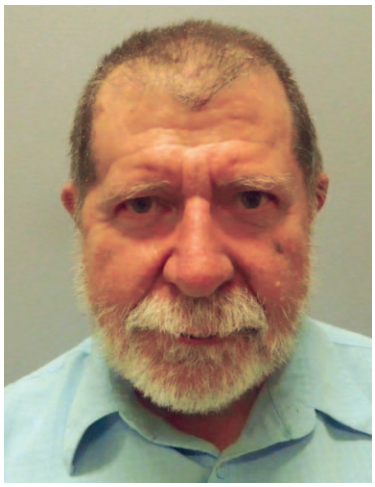

Fig. 4. Postoperative photograph (frontal view) at 1 year demonstrates optimal craniofacial symmetry.

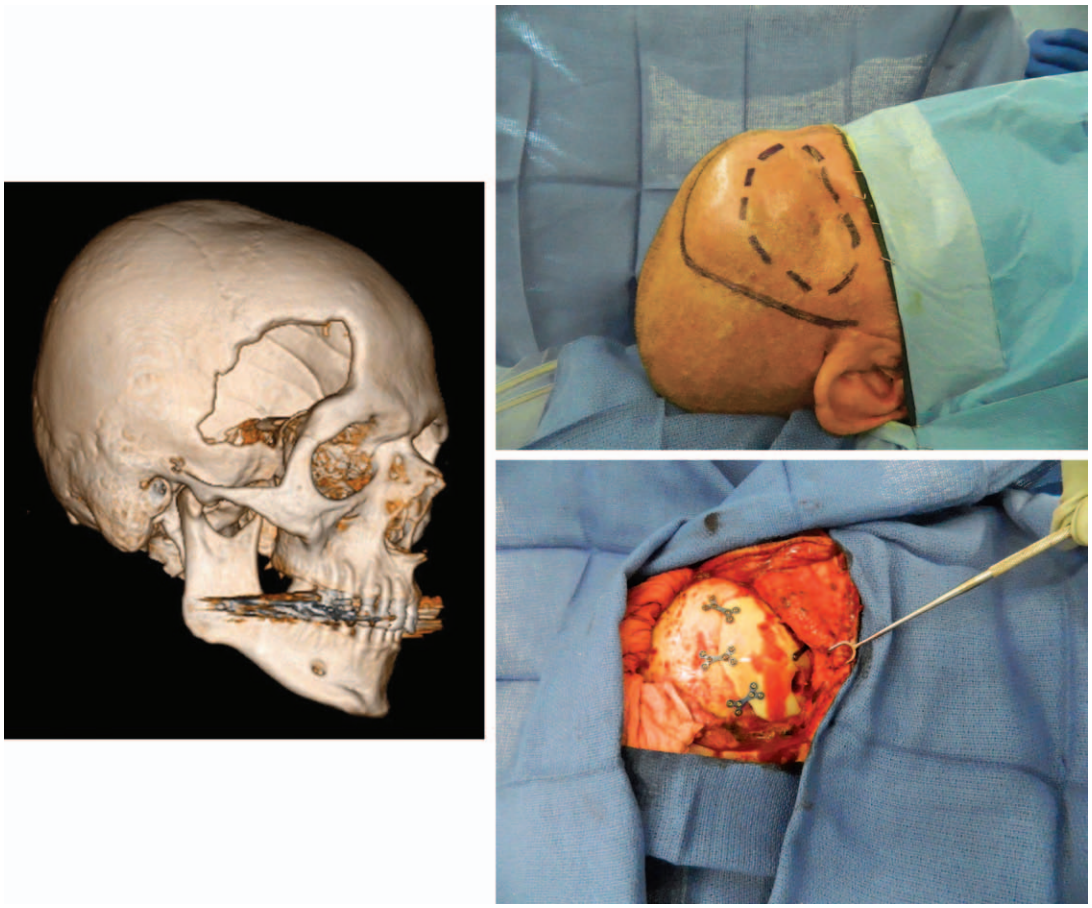

Fig. 3. Preoperative three-dimensional computed tomography scan on right oblique view shows large, right-sided, frontotemporoparietal skull defect (*left*). Intraoperative photograph demonstrates well-healed neurosurgical incision (*solid marked line*) and underlying skull defect requiring cranioplasty (*dotted marker line*) (*above, right*). Intraoperative photograph showing customized cranial implant in place with rigid fixation and pericranial-onlay cranioplasty technique (*below, right*).

Fig. 5. Right-sided lateral postoperative photograph at 1 year demonstrates well-healed incision and acceptable craniofacial contour.

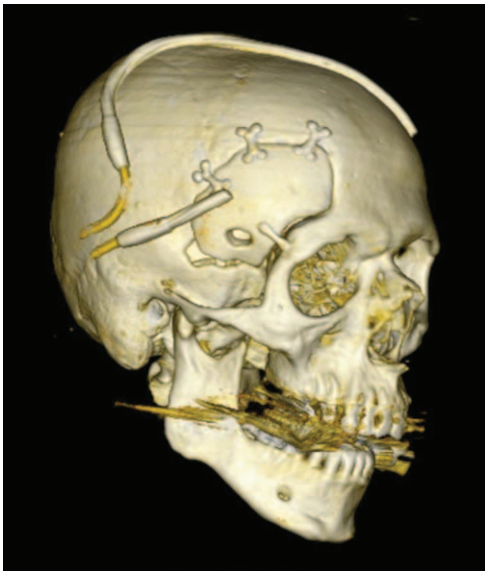

Fig. 6. Postoperative three-dimensional computed tomography scan on right oblique view shows large cranioplasty reconstruction with customized cranial implant and temporary placement of closed suction drains.

perioperative anticoagulant management *must* be exercised when making clinical decisions regarding definitive reconstruction. Ultimately, data from large, prospective, randomized, controlled trials are needed to further guide management in this complex, high-risk patient population.

CONCLUSIONS

To our knowledge, this is the first study to document that the use of perioperative anticoagulant therapy for patients with thromboembolic conditions is a positive predictor of complications following large reconstructive cranioplasty. Patient-specific strategies and multidisciplinary efforts should be used to reduce this risk.

Chad R. Gordon, D.O., F.A.C.S.
The Johns Hopkins Hospital
JHOC, 8th Floor
601 North Caroline Street
Baltimore, Md. 21287
cgordon@jhmi.edu

PATIENT CONSENT

The patient provided written consent for the use of his images.

REFERENCES

1. Dujovny M, Aviles A, Agner C, Fernandez P, Charbel FT. Cranioplasty: Cosmetic or therapeutic? *Surg Neurol.* 1997;47:238–241.
2. Aciduman A, Belen D. The earliest document regarding the history of cranioplasty from the Ottoman era. *Surg Neurol.* 2007;68:349–352; discussion 352–353.
3. Aydin S, Kucukyuruk B, Abuzayed B, Sanus GZ. Cranioplasty: Review of materials and techniques. *J Neurosci Rural Pract.* 2011;2:162–167.
4. Gordon CR, Fisher M, Liauw J, et al. Multidisciplinary approach for improved outcomes in secondary cranial reconstruction: Introducing the pericranial-onlay cranioplasty technique. *Neurosurgery* 2014;10(Suppl 2):179–189; discussion 189–190.
5. Goldstein JA, Paliga JT, Bartlett SP. Cranioplasty: Indications and advances. *Curr Opin Otolaryngol Head Neck Surg.* 2013;21:400–409.
6. Lee JC, Kleiber GM, Pelletier AT, Reid RR, Gottlieb LJ. Autologous immediate cranioplasty with vascularized bone in high-risk composite cranial defects. *Plast Reconstr Surg.* 2013;132:967–975.
7. Lee L, Ker J, Quah BL, Chou N, Choy D, Yeo TT. A retrospective analysis and review of an institution's experience with the complications of cranioplasty. *Br J Neurosurg.* 2013;27:629–635.
8. Moreira-Gonzalez A, Jackson IT, Miyawaki T, Barakat K, DiNick V. Clinical outcome in cranioplasty: Critical review in long-term follow-up. *J Craniofac Surg.* 2003;14:144–153.
9. Reddy S, Khalifian S, Flores JM, et al. Clinical outcomes in cranioplasty: Risk factors and choice of reconstructive material. *Plast Reconstr Surg.* 2014;133:864–873.
10. Lee EI, Chao AH, Skoracki RJ, Yu P, DeMonte F, Hanasono MM. Outcomes of calvarial reconstruction in cancer patients. *Plast Reconstr Surg.* 2014;133:675–682.
11. Walcott BP, Kwon CS, Sheth SA, et al. Predictors of cranioplasty complications in stroke and trauma patients. *J Neurosurg.* 2013;118:757–762.
12. Tokoro K, Chiba Y, Tsubone K. Late infection after cranioplasty: Review of 14 cases. *Neurol Med Chir (Tokyo)* 1989;29:196–201.
13. Matsuno A, Tanaka H, Iwamuro H, et al. Analyses of the factors influencing bone graft infection after delayed cranioplasty. *Acta Neurochir (Wien)* 2006;148:535–540; discussion 540.

14. Inamasu J, Kuramae T, Nakatsukasa M. Does difference in the storage method of bone flaps after decompressive craniectomy affect the incidence of surgical site infection after cranioplasty? Comparison between subcutaneous pocket and cryopreservation. *J Trauma* 2010;68:183–187; discussion 187.
15. Yadla S, Campbell PG, Chitale R, Maltenfort MG, Jabbour P, Sharan AD. Effect of early surgery, material, and method of flap preservation on cranioplasty infections: A systematic review. *Neurosurgery* 2011;68:1124–1129; discussion 1130.
16. Lee JW, Kim JH, Kang HI, Moon BG, Lee SJ, Kim JS. Epidural fluid collection after cranioplasty: Fate and predictive factors. *J Korean Neurosurg Soc.* 2011;50:231–234.
17. Harris DA, Fong AJ, Buchanan EP, Monson L, Khechoyan D, Lam S. History of synthetic materials in alloplastic cranioplasty. *Neurosurg Focus* 2014;36:E20.
18. Hammon WM, Kempe LG. Methyl methacrylate cranioplasty: 13 years experience with 417 patients. *Acta Neurochir (Wien)* 1971;25:69–77.
19. Wachter D, Reineke K, Behm T, Rohde V. Cranioplasty after decompressive hemicraniectomy: Underestimated surgery-associated complications? *Clin Neurol Neurosurg.* 2013;115:1293–1297.
20. De Bonis P, Frassanito P, Mangiola A, Nucci CG, Anile C, Pompucci A. Cranial repair: How complicated is filling a "hole"? *J Neurotrauma* 2012;29:1071–1076.
21. Gooch MR, Gin GE, Kenning TJ, German JW. Complications of cranioplasty following decompressive craniectomy: Analysis of 62 cases. *Neurosurg Focus* 2009;26:E9.
22. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. *N Engl J Med.* 1997;336:1506–1511.
23. Douketis JD. Perioperative anticoagulation management in patients who are receiving oral anticoagulant therapy: A practical guide for clinicians. *Thromb Res.* 2002;108:3–13.
24. Black JM. Anticoagulation in elective surgery. *Plast Surg Nurs.* 2004;24:8–11; quiz 12–13.
25. Jafri SM, Mehta TP. Periprocedural management of anticoagulation in patients on extended warfarin therapy. *Semin Thromb Hemost.* 2004;30:657–664.
26. Spyropoulos AC. Perioperative bridging therapy for the at-risk patient on chronic anticoagulation. *Dis Mon.* 2005;51:183–193.
27. Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med.* 2008;168:63–69.
28. Thachil J, Gatt A, Martlew V. Management of surgical patients receiving anticoagulation and antiplatelet agents. *Br J Surg.* 2008;95:1437–1448.
29. O'Donnell M, Kearon C. Perioperative management of oral anticoagulation. *Cardiol Clin.* 2008;26:299–309, viii.
30. Pederson WC. Clinical use of anticoagulants following free tissue transfer surgery. *J Hand Surg Am.* 2008;33:1435–1436.
31. Levin LS, Cooper EO. Clinical use of anticoagulants following replantation surgery. *J Hand Surg Am.* 2008;33:1437–1439.
32. Grant PJ, Brotman DJ, Jaffer AK. Perioperative anticoagulant management. *Anesthesiol Clin.* 2009;27:761–777.
33. Jokuszies A, Herold C, Niederbichler AD, Vogt PM. Anticoagulative strategies in reconstructive surgery: Clinical significance and applicability. *Ger Med Sci.* 2012;10:Doc01.
34. Kozek-Langenecker SA. Perioperative management issues of direct oral anticoagulants. *Semin Hematol.* 2014;51:112–120.
35. Zakaryan A. Perioperative management of neurosurgical patients receiving chronic anticoagulation therapy. *Front Pharmacol.* 2014;5:64.
36. Gleason LJ, Friedman SM. Preoperative management of anticoagulation and antiplatelet agents. *Clin Geriatr Med.* 2014;30:219–227.
37. Beauchamp KM, Kashuk J, Moore EE, et al. Cranioplasty after postinjury decompressive craniectomy: Is timing of the essence? *J Trauma* 2010;69:270–274.
38. Hill CS, Luoma AM, Wilson SR, Kitchen N. Titanium cranioplasty and the prediction of complications. *Br J Neurosurg.* 2012;26:832–837.
39. Wagner KR, Sharp FR, Ardizzone TD, Lu A, Clark JF. Heme and iron metabolism: Role in cerebral hemorrhage. *J Cereb Blood Flow Metab.* 2003;23:629–652.
40. Pieracci FM, Barie PS. Iron and the risk of infection. *Surg Infect (Larchmt.)* 2005;6(Suppl 1):S41–S46.
41. Keep RF, Zhou N, Xiang J, Andjelkovic AV, Hua Y, Xi G. Vascular disruption and blood-brain barrier dysfunction in intracerebral hemorrhage. *Fluids Barriers CNS* 2014;11:18.
42. Schäfer M, Werner S. Oxidative stress in normal and impaired wound repair. *Pharmacol Res.* 2008;58:165–171.
43. Magni G, La Rosa I, Gimignani S, Melillo G, Imperiale C, Rosa G. Early postoperative complications after intracranial surgery: Comparison between total intravenous and balanced anesthesia. *J Neurosurg Anesthesiol.* 2007;19:229–234.
44. Manninen PH, Raman SK, Boyle K, el-Beheiry H. Early postoperative complications following neurosurgical procedures. *Can J Anaesth.* 1999;46:7–14.
45. Scheller C, Rachinger J, Strauss C, Alfieri A, Prell J, Koman G. Therapeutic anticoagulation after craniotomies: Is the risk for secondary hemorrhage overestimated? *J Neurol Surg A Cent Eur Neurosurg.* 2014;75:2–6.
46. Rachinger JC, Koman G, Scheller C, Prell J, Rampp S, Strauss C. Practice in the perioperative prevention of deep vein thrombosis in German neurosurgical departments: Is there a trend towards homogenization? *Cent Eur Neurosurg.* 2011;72:115–119.
47. Hamilton MG, Hull RD, Pineo GF. Venous thromboembolism in neurosurgery and neurology patients: A review. *Neurosurgery* 1994;34:280–296; discussion 296.
48. Nurmohamed MT, van Riel AM, Henkens CM, et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. *Thromb Haemost.* 1996;75:233–238.
49. Schanbacher CF, Bennett RG. Postoperative stroke after stopping warfarin for cutaneous surgery. *Dermatol Surg.* 2000;26:785–789.
50. Lecompte TP. Antithrombotic agents and invasive procedures: Hematologist point of view. *Thromb Res.* 2012;130(Suppl 1):S61–S62.
51. Laohaprasit V, Mayberg MR. Risks of anticoagulation therapy after experimental corticectomy in the rat. *Neurosurgery* 1993;32:625–628; discussion 628–629.
52. Schaible KL, Smith LJ, Fessler RG, Rachlin JR, Brown FD, Mullan S. Evaluation of the risks of anticoagulation therapy following experimental craniotomy in the rat. *J Neurosurg.* 1985;63:959–962.
53. Huang GJ, Zhong S, Susarla SM, Swanson EW, Huang J, Gordon CR. Craniofacial reconstruction with poly(methyl methacrylate) customized cranial implants. *J Craniofac Surg.* 2015;26:64–70.
54. Lazio BE, Simard JM. Anticoagulation in neurosurgical patients. *Neurosurgery* 1999;45:838–847; discussion 847–848.
55. Douketis JD, Spyropoulos AC, Spencer FA, et al.; American College of Chest Physicians. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(Suppl):e326S–350S.

56. Gilardino SM, Cabiling SD, Bartlett PS. Long-term follow-up experience with carbonated calcium phosphate cement for cranioplasty in children and adults. *Plast Reconstr Surg.* 2009;125:983–994.
57. Zins EJ, Moreira-Gonzalez A, Papay FA. Use of calcium-based cements in the repair of large, full-thickness cranial defects: A caution. *Plast Reconstr Surg.* 2007;120:1332–1343.
58. Mason PN, Crawley WA, Hoopes JE. Frontal cranioplasty: Risk factors and choice of cranial vault reconstruction material. *Plast Reconstr Surg.* 1986;77:888–894.
59. Lopez J, Snakey EW, Zhong S, et al. Time interval reduction for delayed implant-based cranioplasty reconstruction in the setting of previous bone flap osteomyelitis. *Plast Reconstr Surg.* (in press).