Periprocedural Management of Anticoagulation in Atrial Fibrillation: When to Burn Your Bridges

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Learning Objectives:

1. Discuss the purpose of anticoagulant bridging in patients with atrial fibrillation undergoing a procedure.
2. Evaluate the evidence for the use of anticoagulant bridging in patients with atrial fibrillation.
3. Identify an appropriate atrial fibrillation candidate for bridging therapy.

Background

A) Atrial Fibrillation (AF)

a) Supraventricular tachycardia arising from disorganized atrial depolarization
b) Most common sustained cardiac arrhythmia [2]
c) Increasing prevalence in United States[3,4]
   i) >2 million in 2010 with an expected increase to 12.1 million by 2030
d) Increasing prevalence with age[5]
   i) 3.8% prevalence in patients <50 years old
   ii) 34.3% prevalence in patients ≥90 years old
e) AF-related mortality[6]
   i) Stroke remains a major contributor of death at 7% in the general AF population. However, the most common causes include:
      (1) ~35%: Non-cardiovascular-related death (trauma, infection, cancer, etc.)
      (2) ~22%: Sudden cardiac death
      (3) ~15%: Progressive heart failure (HF)

B) Assessment of Thrombotic Risk

a) AF-related strokes from 1992 to 2002[7]:
   i) Ischemic stroke rates have declined from 46.7 to 19.5 per 1000 patient years
   ii) Hemorrhagic stroke remains low, but steady with rates of 1.6 to 2.9 per 1000 patient years
b) Increasing use of oral anticoagulation (OAC) is major contributing factor to this decline
c) Risk stratification tools derived and validated in patients with AF:

Table 1. $CHADS_2$ Score for Assessment of Stroke Risk[8]

Characteristic	Correlating Point Value	$CHADS_2$ Score	Stroke Rate*[9]
Congestive heart failure	1	0	0.6
Hypertension	1	1	3.0
Age ≥75 years	1	2	4.2
Diabetes mellitus	1	3	7.1
Previous **S**troke or TIA**	2	4	11.1
Total	**6**	5	12.5
		6	13.0

*Unadjusted (aspirin treatment) rates of ischemic stroke per 100 patient years at risk
** TIA (transient ischemic attack)

Table 2. CHA_2DS_2-VASc Score for Assessment of Stroke Risk[10]

Characteristic	Correlating Point Value	CHA_2DS_2-VASc Score	Stroke Rate*[9]
CHF or LV dysfunction	1	0	0.2
Hypertension	1	1	0.6
Age ≥75 years	2	2	2.2
Diabetes mellitus	1	3	3.2
Previous **S**troke/TIA/TE**	2	4	4.8
Vascular disease+	1	5	7.2
Age 65-74 years	1	6	9.7
Sex **c**ategory (e.g. female)	1	7	11.2
Total	**9**	8	10.8
		9	12.2

*Unadjusted (aspirin treatment) rates of ischemic stroke per 100 patient years at risk
**Thromboembolism
+Vascular disease includes myocardial infarction, peripheral arterial disease, or aortic plaque

Table 3. Advantages and Disadvantages for the Use of $CHADS_2$ and CHA_2DS_2-VASc
Advantages
• Well-validated risk schemes
• Simple and easy to remember
• CHA_2DS_2-VASc may identify lower-risk patients vs. $CHADS_2$
Disadvantages
• Risk schemes obtained in warfarin-treated patients vs. aspirin-treated patients[2]
• Hypertension (HTN) not distinguished between poorly controlled vs. well controlled
• Most consistent independent risk factors for stroke include previous stroke/TIA, advanced age, HTN, diabetes mellitus (DM)[11,12]
○ Congestive heart failure (CHF) and female gender inconsistent and/or inconclusive risk factors
• Stroke prediction varies by analysis[8,9,10]
○ However, $CHADS_2$ and CHA_2DS_2-VASc have shown similar predictive value

C) Management of Stroke Prevention

a) Annual rates of AF-related stroke without antithrombotic therapy versus warfarin: 4.5% vs. 1.4%[11]
b) AF-related stroke results in higher 28-day mortality (19.1%) in comparison to non-AF-related stroke non-AF-related stroke (12.0%)[5]
c) Current recommendations for antithrombotic therapy:

Table 4. Recommendation for Antithrombotic Therapy in Patients with AF

CHEST Guidelines 9th ed. (2012)[2]				
Risk	$CHADS_2$	Preferred Regimen	Alternative Regimen	Grade
Low	0	No therapy	ASA	IIB
Moderate	1	OAC	ASA + clopidogrel	IIB
High	≥2	OAC	ASA + clopidogrel	IA
ACC/AHA/HRS Guidelines (2014)[13]				
Risk	CHA_2DS_2-VASc	Preferred Regimen	Alternative Regimen	Grade
Low	0	No therapy	(-)	IIA
Moderate	1	No therapy *or* OAC *or* ASA	(-)	IIB
High*	≥2	OAC	(-)	I

*High-risk category also includes mechanical heart valve or previous stroke/TIA regardless of CHA_2DS_2-VASc score

D) Evaluation of Bleeding Risk

a) Warfarin is related to 10.2% of drug-related adverse events in Medicare outpatients[14]
   i) Prescribing, monitoring, and patient adherence all contributing factors
b) Quantifying risk of bleeding necessary for determining the benefit of antithrombotic therapy
   i) ACC/AHA preferred risk stratification tool derived and validated in AF patients[13]:

Table 5. HAS-BLED Score for Assessment of Bleeding Risk[16]

Characteristic	Correlating Point Value	Score	Bleeds/year*
Hypertension (uncontrolled)	1	0	(-)
Abnormal renal/liver function	1/1	1	0.7
Stroke	1	2	1.9
Bleeding history or predisposition	1	3	2.4
Labile INR	1	4	3.4
Elderly (>65 years)	1	5	5.7
Drugs (antiplatelet/NSAID *or* EtOH)	1/1	6	15.5
Total	**9**	7	(-)

*Major bleeds per year at risk in patients on OAC only

E) Periprocedural Management of Antithrombotic Therapy

a) ≥2 million currently on OAC in the United States[2]
b) Approximately 10% of the AF population will undergo an elective surgery or procedure each year requiring temporary discontinuation of OAC[17,18]
c) Discontinuation of vitamin K antagonist (VKA) (e.g. warfarin) is recommended 5 days prior to the procedure to decrease the risk of procedure-related bleeding[19]
   i) Warfarin $t_{1/2}$ 20-60 hours (mean ~40 hours)[20]
   ii) Vitamin K-dependent clotting factors[21,22]:

Procoagulant activity	$t_{1/2}$ (hours)	Anticoagulant activity	$t_{1/2}$ (hours)
Factor II	50-72	Protein C	8-14
Factor VII	8	Protein S	30-42
Factor IX	24		
Factor X	36		

d) Bridging therapy refers to the use of a short-acting anticoagulant periprocedurally to decrease risk of thrombosis while the international normalized ratio (INR) is outside therapeutic range
e) Current recommendations for bridging therapy:

Table 6. Recommendation for Bridging Therapy in Patients with AF
CHEST Guidelines 9th ed. (2012)[19]

Risk	$CHADS_2$	Recommendation	Grade	Continue OAC without interruption
Low	0-2	Forgo bridging therapy	IIC	Dental procedure
Moderate	3-4	Individualized decision	---	Dermatologic procedure
High	5-6	Initiate bridging therapy	IIC	Cataract surgery

Figure 1. General Approach to Bridging Therapy[19]

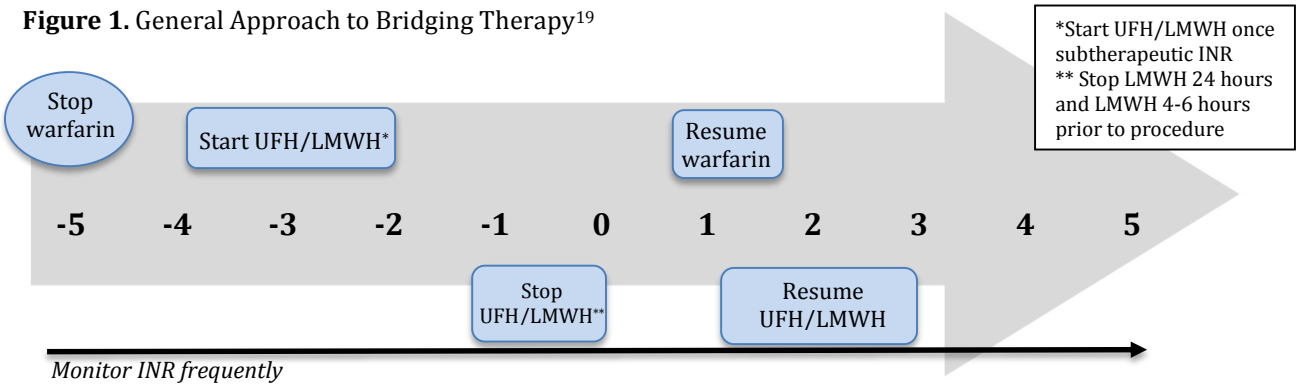


Table 7. Siegal, et al. - 2012[23]
Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists: Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Events

Objective	Evaluate the safety and efficacy of periprocedural bridging anticoagulation
Design	Systematic review and meta-analysis of 34 studies
Inclusion	• ≥18 years with long-term use of VKA pre-procedurally • Elective surgery or procedure • Per-procedural bridging with LMWH in at least some patients • Reporting of thromboembolic and bleeding events
Exclusion	• Unclear reporting of thromboembolic and bleeding events • Exclusive patient population with CrCl <30 mL/min
Outcomes	• Primary outcomes: o Rate of thromboembolic events o Rate of major bleeding events[a]
Methods	• Medline, EMBASE, Cochrane database search (01/2001 - 07/2010) • Bridging group classified by the use of any perioperative bridging strategy o Non standardized bridging regimens: ▪ 82% of trials stopped OAC ≥3 days prior to the procedure ▪ 100% of trials used LMWH, while 36% of trials used UFH as their bridging agent ▪ Of the trials with LMWH, 57% used LMWH at a therapeutic-dose[b] • Data compiled using the Mantel-Haenszel method for bridged and non-bridged groups • Primary outcomes analyzed with the Laird and Mosteller statistical method • Odds ratios (OR) generated through random-effects model • I^2 test to assess for heterogeneity in studies

Baseline Characteristics

Author	Study Design	Intervention/ Comparator	Participants	Follow-Up (days)
Varkarakis, et al (2005)	Cohort, retrospective	I: LMWH, UFH C: non-VKA	I: 25 C: 762	N/A
Marquie, et al (2006)	Cohort, retrospective	I: LMWH, UFH	I: 114	30
Garcia, et al (2008)	Cohort, prospective	I: LMWH C: no bridging	I: 108 C: 1185	30
Wysokinski, et al (2008)	Cohort, prospective	I: LMWH, UFH C: no bridging	I: 204 C: 182	90
Daniels, et al (2009)	Cohort, retrospective	I: LMWH, UFH C: no bridging	I: 342 C: 213	90
Jaffer, et al (2010)	Cohort, prospective	I: LMWH, UFH	I: 229	30
McBane et al (2010)	Cohort, prospective	I: LMWH C: no bridging	I: 514 C: 261	90
Tompkins, et al (2010)	Cohort, retrospective	I: LMWH, UFH C: no bridging/VKA cont./non-VKA	I: 155 C: 258/45/255	42

Results

Pooled Incidence Rates		
	Thromboembolic Events % [95% CI]	Major Bleeding % [95% CI]
Total Bridged Cohort	0.9 [0.0-3.4]	4.2 [0.0-11.3]
LMWH full dose	0.4 [0.0-0.9]	3.2 [1.3-5.2]

LMWH intermediate dose	0.2 [0.0-0.6]			3.4 [0.0-8.7]
Total Nonbridged Cohort	0.6 [0.0-1.2]			0.9 [0.2-1.6]

Thromboembolic Events[c]

	No Bridging	Bridging	Weight (%)	OR [95% CI]
Varkarakis (2005)	3/762	0/25	4.7	4.25 [0.21-84.56]
Marquie (2006)	2/114	0/114	4.6	0.20 [0.01-4.14]
Garcia (2008)	7/1185	0/108	5.2	0.72 [0.04-12.76]
Wyskokinski (2008)	4/182	3/204	18.6	0.66 [0.15-3.01]
Daniels (2009)	1/213	4/342	8.8	2.51 [0.28-22.60]
Jaffer (2010)	3/263	1/229	8.2	0.38 [0.04-3.68]
McBane (2010)	6/261	10/514	40.5	0.84 [0.30-2.35]
Tompkins (2010)	6/513	1/155	9.4	0.55 [0.07-4.59]
Total (95% CI)	**32/3493**	**19/1691**	**100.0**	**0.80 [0.42-1.54]**

Major Bleeding Events[c]

	No Bridging	Bridging	Weight (%)	OR [95% CI]
Garcia (2008)	2/1185	4/108	15.3	22.75 [4.12-125.68]
Wysokinski (2008)	4/182	6/204	20.8	1.35 [0.37-4.86]
Daniels (2009)	5/213	15/342	24.9	1.91 [0.68-5.33]
Jaffer (2010)	3/263	13/229	21.0	5.22 [1.47-18.54]
McBane (2010)	2/261	14/514	17.9	3.63 [0.82-16.08]
Total (95% CI)	**16/2104**	**52/1397**	**100.0**	**3.60 [1.52-8.50]**

Author's Conclusion	Bridging with therapeutic-dose regimens should be avoided in the periprocedural setting in patients with low thromboembolic risk.
Strengths	• Large systematic-review and meta-analysis • No heterogeneity found for thromboembolic outcomes
Weaknesses	• Observational data in 33 of 34 studies • Broad inclusion criteria limits applicability to AF patients • Non-standardized TE risk stratification, bridging regimens, or reporting of adverse events • Baseline bleed risk not reported • Heterogeneity in intervention groups • Time in warfarin therapeutic range unknown • Only able to include portion of studies for primary outcomes • Bleeding outcomes analysis of LMWH regimens, but no note of heparin regimen • Significant heterogeneity for major and overall bleeding outcomes[d] • Uneven distribution of thromboembolic events
Take Away	Bridging therapy is associated with higher bleeding rates and similar thromboembolic risk when compared to patients who forgo bridging therapy.
Footnotes	a. Major bleeding as defined by primary studies included need for transfusion, bleeding at a critical site, decreased Hgb >2 g/L, requirement for surgical hemostasis, need for re-hospitalization, and fatal bleeding. b. LMWH treatment-dose defined as: dalteparin 200 units/kg/day or 100-120 units/kg BID, enoxaparin 1.5 mg/kg/day or 1 mg/kg BID, ardeparin 100-130 units/kg BID, tinzaparin 175 units/kg/day. c. Forest-plots representing the primary outcomes can be found in the Appendix, Figure 3. d. Overall bleeding outcomes can be found in the Appendix, Table 13.

Table 8. Steinberg, et al. - 2015[24]

Use and Outcomes Associated With Bridging During Anticoagulation Interruptions in Patients With Atrial Fibrillation: Findings From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)

Objective

Evaluate the patterns of bridging use relative to underlying risk and outcomes between bridging and non-bridging regimens.

Design

Prospective, observational, multicenter cohort study

Inclusion

- Patients enrolled in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
- ≥18 years on oral anticoagulation (unspecified) with ≥1 follow-up visit

ORBIT-AF Criteria[25]

Inclusion	Exclusion
• Age ≥18 years • AF with ECG documentation • Anticipated ability to adhere to scheduled follow-up visits	• Anticipated life expectancy <6 months • Transient AF secondary to a reversible condition

Exclusion

- Patients not meeting inclusion criteria

Outcomes

- Analysis of patients who received bridging therapy versus no bridging:
  - Adverse events occurring during interruption of long-term anticoagulation
  - Adverse events occurring within 30 days post procedure date

Statistics

- Bridging therapy defined as temporary anticoagulant used in place of long-term therapy
- Patients with multiple interruptions included unless occurring within one 30-day period
- Univariate analysis and X^2 test to assess categorical values and their differences
- Wilcoxon rank-sum test for differences in groups for continuous variables
- Multivariable analysis to assess 30-day outcomes[a]

Baseline Characteristics

	No Bridging (n = 1608)	Bridging (n = 592)	P Value
Age, years	75 (68-81)	74 (67-80)	0.009
Male, %	59	58	0.7
Caucasian, %	92	91	---
Warfarin, %	93	96	---
$CHADS_2$, mean±SD	2.34±1.21	2.53±1.31	0.004
CHA_2DS_2-VASc, mean±SD	4.03±1.62	4.25±1.74	0.01
Cerebrovascular event, %	15	22	0.0003
CHF, %	34	44	<0.0001
Percentage time within goal INR range[b], %	67	62	0.0002
ATRIA score, mean±SD	2.74±1.94	2.72±1.95	0.9

Bridging Agent, no. (%)	
LMWH	487/665 (73)
UFH	97/665 (14)

Results

Periprocedural Outcomes

Event, no. (%)	No Bridging (n = 1766)	Bridging (n = 514)	P Value
Bleeding event	31 (1.8)	19 (3.7)	0.02
Thrombotic event	9 (0.5)	4 (0.8)	0.5

30-Day Outcomes

	Unadjusted, no. (%)	Adjusted

		No Bridging (n = 1724)	Bridging (n = 503)	P Value	P Value[a]
	Cardiovascular events[c]	43 (2.5)	23 (4.6)	0.02	0.07
	Bleeding events[d]	22 (1.3)	25 (5.0)	<0.0001	<0.0001
	Composite[e]	108 (6.3)	64 (13)	<0.0001	0.0001
Author's Conclusion	The use of bridging therapy should not be routinely used in patients with atrial fibrillation.				
Strengths	• Baseline characteristics include thromboembolic and bleed risk (CHADS, CHADS-VASc, ATRIA) • Pre-procedural percentage of time within therapeutic INR reported (62-67%) • Standardized definition of major bleeding as defined by the International Society of Thrombosis and Haemostasis[f] o Definition used indicated in non-surgical patients • Bleeding rates correlate with procedure's bleeding-risk[g]				
Weaknesses	• Observational data • Analysis of any oral anticoagulant (warfarin therapy 93-96%)) • Non-standardized bridging regimens • Thirty day follow-up • ATRIA for bleeding risk stratification not preferred tool via ACC/AHA guidelines[13,27] • Lack data correlating type of surgery with bridging agent • Time in therapeutic INR range not reported				
Take Away	Use of bridging anticoagulation is associated with an increased risk of bleeding and cardiovascular adverse events after interruption				
Footnotes	a. Covariates include age, estimated glomerular filtration rate (eGFR), sex, prior cerebrovascular events, significant valvular disease, mechanical valve replacement, prior GI bleed, CHF, type of AF (new onset, paroxysmal, persistent, long-standing persistent), $CHADS_2$, left atrial diameter size, patient level of education, procedure, oral anticoagulant (warfarin, dabigatran). b. Percentage of time within INR range (2-3) prior to procedure calculated using the Rosendaal et al. method. c. CV events include stroke, systemic embolism, or cardiovascular hospitalization. d. Bleeding events include major bleeding or bleeding hospitalization. e. Overall composite includes stroke, MI, major bleeding, hospitalization, and death. f. ISTH definition of major bleeding in non-surgical patients[26]: o Fatal bleeding o Symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome) o Decrease in Hgb ≥2mg/L or leading to transfusion of ≥2 PRBCs or whole blood g. Primary outcomes by surgery type can be found in Appendix, Table 14.				

Table 9. Douketis, et al. - 2015[28]
Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

Objective	Assess the need for anticoagulant bridging in patients with atrial fibrillation during warfarin interruption for a procedure.
Design	Multicenter, randomized, double-blind, placebo-controlled trial
Inclusion	• ≥18 years with AF receiving warfarin therapy for ≥3 months • Have ≥1 major risk factor for stroke: ○ CHF or LV dysfunction ○ HTN ○ Age >75 years ○ Diabetes mellitus ○ Previous ischemic stroke, systemic embolism, or TIA
Exclusion	• Mechanical heart valve • Any of the following within the past 12 weeks: ○ Stroke, systemic embolism, TIA, VTE • Major bleeding within the past 6 weeks • Severe renal insufficiency (CrCl <30 mL/min) • Any one of the following high bleed risk procedures: ○ Cardiac surgery ○ Intracranial or intraspinal neurosurgery ○ High-risk non-surgical procedure (e.g., brain biopsy) ○ Any other procedure requiring use of anticoagulant at the discretion of the physician
Outcomes	• Primary Efficacy Endpoint ○ Rate of ATE (ischemic stroke, systemic embolism, TIA) at 30 days • Primary Safety Endpoint ○ Rate of major bleed at 30 days defined as: i. Symptomatic and clinically overt[a] ii. Intra-operative bleeding that is not expected from procedure
Intervention	A. Dalteparin 100 units/kg subcut BID B. Placebo subcut BID

Stop warfarin	Start study drug	Procedure	Restart study drug	Stop study drug when goal INR
Day -5	-3 to -1	0	+0.5/1/2/3[b]	+5 →

Restart warfarin

Statistics	• Primary efficacy endpoint analyzed for non-inferiority with a one-sided test at 0.025 level • Noninferiority margin set at 1.0%, where noninferiority determined if difference in outcomes reached <1.0 percentage point • Primary safety endpoint analyzed for superiority with a two-sided test at 0.05 level • Per-protocol population included in primary efficacy and safety outcome analysis • 95% CI using Barnard's test • P-value calculated via Fisher's mid-P test • Revised sample size of 1882 patients to provide 90% power for primary outcomes

Baseline Characteristics

	No Bridging (n = 950)	Bridging (n = 934)
Age - years	71.8±8.74	71.6±8.88
Male - no. (%)	696 (73.3)	686 (73.4)
Caucasian - no. (%)	860 (90.5)	849 (90.9)
$CHADS_2$ - mean	2.3±1.03	2.4±1.07
0	1 (0.1)	1 (0.1)
1	216 (22.7)	212 (22.7)
2	382 (40.2)	351 (37.6)

	3	229 (24.1)	232 (24.8)
	4	96 (10.1)	106 (11.3)
	5	23 (2.4)	27 (2.9)
	6	3 (0.3)	5 (0.5)
	Hypertension - no. (%)	833 (87.7)	806 (86.3)
	Diabetes mellitus - no. (%)	390 (41.1)	382 (40.9)
	Stroke/TIA - no. (%)	158 (16.6)	176 (18.8)

Results

	No Bridging (n = 918)	Bridging (n = 895)	P Value
Primary Outcome - no. (%)			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73**
Stroke	2 (0.2)	3 (0.3)	---
Transient ischemic attack	2 (0.2)	0	---
Systemic embolism	0	0	---
Major bleeding	12 (1.3)	29 (3.2)	0.005

*P value for non-inferiority
**P value for superiority

Author's Conclusion

In patients requiring warfarin interruption for a procedure, forgoing bridging therapy was noninferior to the use of bridging therapy for the prevention of thromboembolism.

Strengths

- Randomized, double-blind, placebo controlled trial
- Standardized bridging regimen (timing, drug, dose)
- Large sample size with most common procedures well represented

Weaknesses

- Populations unrepresented include:
  - Recent thromboembolic event
  - $CHADS_2 \geq 4$ and high-risk of bleeding
  - Procedures with high bleeding risk (89.4% minor procedure)
  - Mechanical heart valves
- Primary efficacy outcome tested for non-inferiority
- Recalculated sample size (x3 total) due to lower than expected primary efficacy outcome
- Time in therapeutic INR range not reported

Take Away

Patients with mild to moderate risk for TE requiring warfarin interruption for a minor bleeding-risk procedure have similar rates of ATE and lower rates of major bleeding with forgoing bridging therapy.

Footnotes

a. Clinically overt bleeding associated with either

1. Transfusion ≥2 units PRBCs or whole blood
2. Decreased Hgb >2 g/dL (not related to hemodilution from intra-operative fluid administration)
3. Need for invasive intervention

b. Reinitiation of LMWH or placebo based on procedure-related bleeding risk (Appendix, Table 16.) and physician's discretion, where:

- Low-bleeding-risk: Resumed 12-24 hours post-procedure
- High-bleeding-risk: Resumed 48-72 hours post-procedure

Ongoing Studies

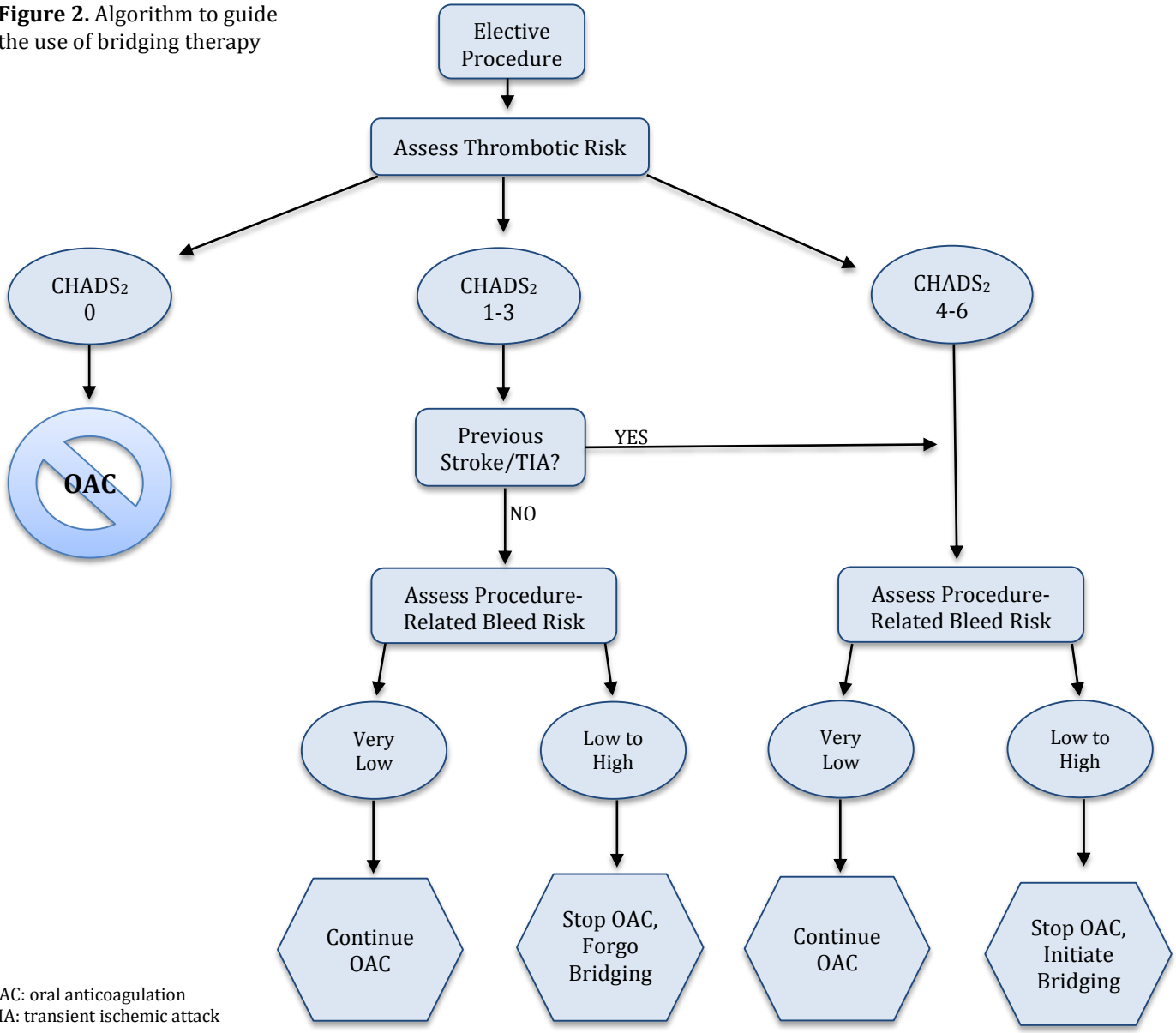
Table 10. Kovacs et al.[31] A Double Blind Randomized Control Trial of Post-Operative Low Molecular Weight Heparin Bridging Therapy Versus Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism (PERIOP 2) (NCT00432796)	
Design	Multicenter, randomized, double-blind, placebo-controlled trial
Population	• Mechanical heart valves *or* • Atrial fibrillation with high risk for stroke
Intervention	• Dalteparin 5000 units or 200 units/kg subcutaneously once daily (dose determined on type of surgery) • Placebo subcutaneously once daily
Primary Outcome	• Major thromboembolism 90 days from randomization
Estimated Completion Date	• March 2017

Summary

Table 11. Overview of Trials Presented[23,24,28]

Trial	Primary Outcomes	Bridging Regimen	Results
Siegal, et al. (2010)	• TE rates • Bleeding rates	Any (Non-standard timing, drug, dose)	↑ Bleeding risk = TE risk
Steinberg, et al. (2015)	• TE rates • Bleeding rates • CV events	Any (Unknown timing, dose)	↑ Bleeding risk = TE risk
Douketis, et al. (2015)	• TE rates • Bleeding rates	Standardized	↑ Bleeding risk = TE risk

Figure 2. Algorithm to guide the use of bridging therapy



OAC: oral anticoagulation
TIA: transient ischemic attack

G) Conclusion and Recommendation

a) The decision to bridge anticoagulation is a growing challenge for clinicians as our AF population increases
b) Data is limited to observational studies and one randomized control trial
c) Risk factors associated with bridging include increased bleeding risk, while risk factors associated with forgoing bridging include increased TE risk
d) Decisions to initiate or forgo bridging therapy should be based on:
   i) TE risk and bleeding risk of the patient
   ii) Procedure-related bleeding risk
e) Candidates for bridging therapy include:
   i) Patients with a $CHADS_2$ score of 0-3 without a previous stroke or TIA
   ii) Patients undergoing a low-risk bleeding procedure
   iii) Forgoing bridging therapy in these patients decreases the risk of bleeding without increasing the risk of TE

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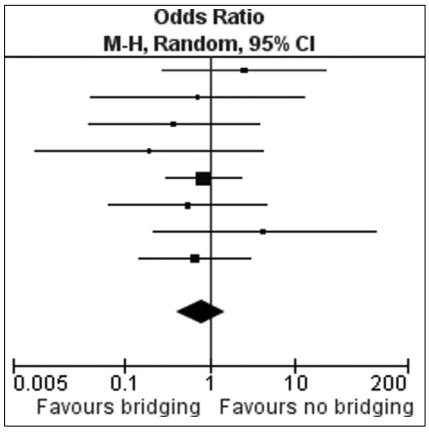
Appendices

Table 12. List of Abbreviations Used			
AF	Atrial fibrillation	INR	International normalized ratio
ASA	Aspirin	LMWH	Low-molecular-weight-heparin
ATE	Ateriothromboembolism	LV dysfunction	Left-ventricular dysfunction
CHF	Congestive heart failure	NSAIDs	Non-steroidal anti-inflammatory drugs
CV	Cardiovascular	OAC	Oral anticoagulants
DM	Diabetes mellitus	PRBCs	Packed red blood cells
eGFR	Estimated glomerular filtration rate	TE	Thromboembolism
EtOH	Ethyl alcohol	TIA	Transient ischemic attack
GI	Gastrointestinal	UFH	Unfractionated heparin
Hgb	Hemoglobin	VTE	Venous thromboembolism
HTN	Hypertension		

Figure 3. Siegal, et al. - 2012

A. Rate of thromboembolic events



B. Rate of major bleeding events

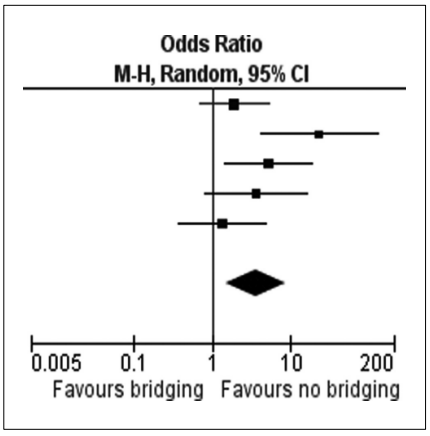


Table 13. Siegal, et al. - 2012
Overall Bleeding Events

	No Bridging	Bridging	Weight (%)	OR [95% CI]
Dotan (2002)	1/20	2/20	3.7	2.11 [0.18-25.35]
Varkarakis (2005)	7/762	2/25	5.9	9.38 [1.85-47.64]
Marquie (2006)	2/114	21/114	6.4	12.65 [2.89-55.34]
Garcia (2008)	9/1185	14/108	8.8	19.46 [8.21-46.14]
Wysokinski (2008)	6/182	15/204	8.4	2.33 [0.88-6.13]
Daniels (2009)	18/213	36/342	9.8	1.27 [0.70-2.31]
Robinson (2009)	3/35	20/113	7.2	2.29 [0.64-8.24]
Tischenko (2009)	5/117	9/38	7.6	6.95 [2.16-22.33]
Ercan (2010)	21/1421	11/44	9.0	22.22 [9.92-49.81]
Ghanbari (2010)	3/74	6/29	6.5	6.17 [1.43-26.68]
Jaffer (2010)	7/263	24/229	8.8	4.28 [1.81-10.14]
McBane (2010)	5/261	34/514	8.4	3.63 [1.40-9.39]
Tompkins (2010)	15/513	23/155	9.5	5.78 [2.94-11.40]
Total (95% CI)	**102/5160**	**217/1935**	**100.0**	**5.40 [3.00-9.74]**

Table 14. Steinberg, et al. - 2015
Primary Outcomes Based on Type of Procedure

	Cardiovascular Events - no. (%)		Bleeding Events - no. %	
	No Bridging (n = 1724)	Bridging (n = 503)	No Bridging (n = 1724)	Bridging (n = 503)
Non-CV Surgery	6/410 (1.5)	2/149 (1.3)	5/410 (1.2)	12/149 (8.1)
Cardiac Catheterization	9/139 (6.5)	3/65 (4.6)	2/139 (1.4)	1/65 (1.5)
Endoscopy	9/343 (2.6)	2/64 (3.1)	5/343 (1.5)	5/64 (7.8)
Cardiac Device	9/139 (6.5)	2/38 (5.3)	0/139 (0)	0/38 (0)
Catheter Ablation	1/66 (1.5)	5/41 (12.2)	1/66 (1.5)	0/41 (0)
Cardiac Surgery	3/48 (6.3)	2/28 (7.1)	2/48 (4.2)	2/28 (7.1)
Dental	1/166 (0.6)	0/16 (0)	0/166 (0)	0/16 (0)
Other	5/413 (1.2)	7/102 (6.9)	7/413 (1.7)	5/201 (4.9)

Table 15. Steinberg, et al. - 2015
Bridging Group by Type of Procedure - no. (%)

Non-CV Surgery	208/746 (28)
Cardiac Catheterization	95/282 (34)
Endoscopy	85/504 (17)
Cardiac Device	56/244 (23)
Catheter Ablation	54/150 (36)
Cardiac Surgery	45/109 (42)
Dental	19/239 (8)
Other	156/712 (22)

Table 16. Douketis, et al. - 2015
Classification of Surgery or Procedure-Related Bleeding Risk

Minor or Low-Bleeding-Risk	
• Gastrointestinal endoscopy	• Ophthalmologic procedure
• Cardiac catheterization	• Surgery or procedure lasting <1 hour
• Dental procedure	
Major or High-Bleeding-Risk	
• Intra-abdominal surgery	• Urologic surgery
• Intra-thoracic surgery	• Permanent pacemaker or defibrillator insertion
• Major orthopedic surgery	• Major procedure (e.g., colonic polyp resection)
• Peripheral arterial revascularization	• Surgery or procedure lasting >1 hour