

Appendix A: Procedural codes for both Distal Vascular (DV) and Cerebral Vascular (CV) groups including Current Procedural Terminology (CPT) codes and number for each descriptor.

Distal vascular group (DV, n=57840)

Most common CPT codes:

1. Endovascular repair infrarenal AAA w/ modular bifurcated 1 limb prosthesis (CPT:34802, n=4547, 8%)
2. Femoral-popliteal bypass w/ other than vein graft (CPT:35656, n=3150, 5%)
3. Femoral-popliteal bypass w/ vein graft (CPT:35556, n=3148, 5%)
4. Endovenous ablation of incompetent vein (CPT:37475, n=2900, 5%)
5. Amputation of leg through tibia and fibula (CPT:27880, n=2878, 4%)
6. Endovascular repair infrarenal AAA w/ modular bifurcated 2 limb prosthesis (CPT:34803, n=2375, 4%)
7. Femoral-anterior tibial bypass (CPT 35566, n=2369, 4%)
8. Thromboendarterectomy with patch graft (CPT:35371, n=1766, 3%)
9. Aortobifemoral bypass graft (CPT= 35646, n=1311, 2%)
10. Femoral-femoral bypass graft (CPT=35661, n=1265, 2%)

<u>CPT</u>	<u>n</u>	<u>CPT</u>	<u>n</u>	<u>CPT</u>	<u>n</u>	<u>CPT</u>	<u>n</u>
27880	2787	35103	116	35471	190	35638	141
27881	83	35111	16	35472	22	35646	1311
27882	531	35112	7	35500	4	35647	111
27884	114	35121	76	35511	1	35650	20
27886	249	35122	12	35512	8	35654	359
27888	50	35131	73	35516	2	35656	3150
27889	96	35132	22	35518	2	35661	1265
27892	29	35141	444	35521	47	35663	23
27893	19	35142	49	35522	22	35665	528
27894	24	35151	277	35523	26	35666	841
28800	59	35152	6	35525	34	35671	93
28805	796	35182	2	35531	53	35681	8
34800	681	35184	12	35533	43	35682	2
34802	4547	35189	6	35535	7	35683	1
34803	2375	35190	93	35537	11	35685	1
34804	818	35206	121	35538	22	35686	20
34805	400	35207	25	35539	40	35697	1
34808	15	35221	59	35540	153	35700	89
34812	314	35226	126	35556	3148	35721	53
34813	11	35236	51	35558	288	35741	27
34820	18	35251	8	35560	21	35761	101
34825	413	35256	47	35563	7	35820	18
34826	11	35261	14	35565	108	35840	55

34830	53	35266	21	35566	2369	35860	92
34831	49	35281	15	35570	52	35870	9
34832	24	35286	55	35571	691	35875	247
34833	12	35302	499	35572	10	25876	208
34834	9	35303	147	35583	558	35879	177
34900	217	35304	23	35585	660	35881	96
35011	135	35305	31	35587	65	35883	191
35013	12	35311	4	35612	7	35884	29
35021	6	35321	45	35616	6	35901	6
35022	2	35331	52	35621	246	35903	529
35045	59	35341	34	35623	25	35905	7
35081	1167	35351	120	35631	156	35907	72
35082	377	35355	599	35632	4	36475	2900
35091	482	35361	27	35633	63	36476	11
35092	127	35363	25	35634	8	36478	1091
35102	558	35371	1766	35636	4	36479	28
		35372	367	35637	52		

Cerebral vascular group (CV, n=22345)

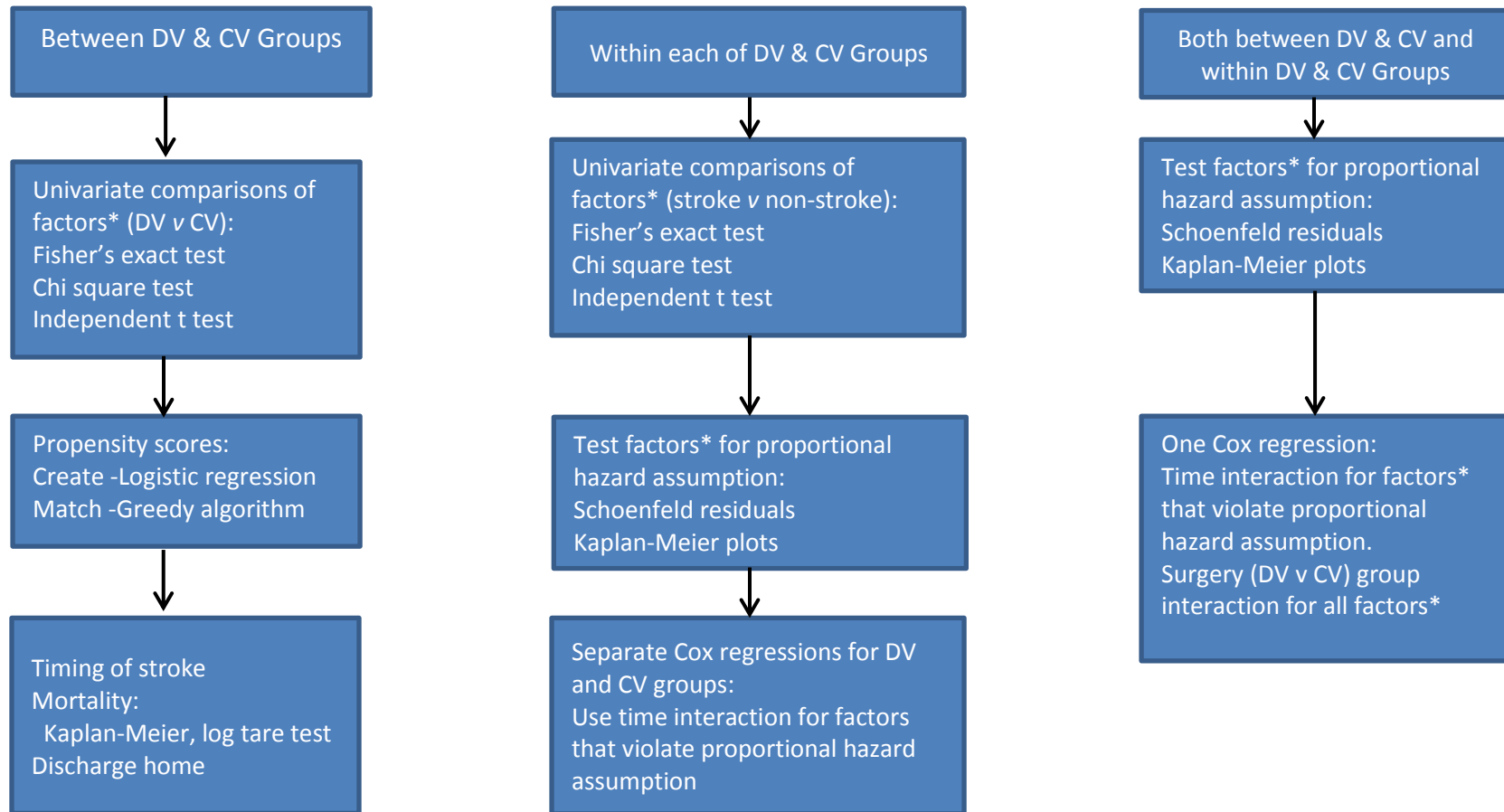
Most common CPT codes:

1. Thromboendarterectomy carotid (vertebral, subclavian) artery neck incision w/ patch graft (CPT=35301, n=20998, 94%)
2. Carotid artery stent with embolic protector (CPT=37215, n=543, 2%)
3. Carotid-subclavian bypass graft (CPT=35606, n=272, 1%)
4. Direct repair of aneurysm or excision and graft insertion for aneurysm carotid/subclavian (CPT=35001, 89, <1%)
5. Carotid-subclavian bypass with vein graft (CPT=35506, n=82, <1%)
6. Common carotid bypass graft (CPT=35601, n=57, <1%)
7. Carotid artery stent without embolic protector (CPT=37216, n=52, <1%)
8. Reoperative thromboendarterectomy carotid artery > 1 mo (CPT=35390, n=34, <1%)
9. Transpose/reimplant carotid/subclavian arteries (CPT=35694, n=28, <1%)
10. Direct repair of blood vessel neck (CPT=35201, n=26, <1%)

<u>CPT</u>	<u>n</u>	<u>CPT</u>	<u>n</u>	<u>CPT</u>	<u>n</u>
35001	89	35501	25	35642	3
35002	7	35506	82	35645	4
35005	8	35508	6	35691	15
35180	2	35509	4	35693	1
35188	3	35510	14	35694	28

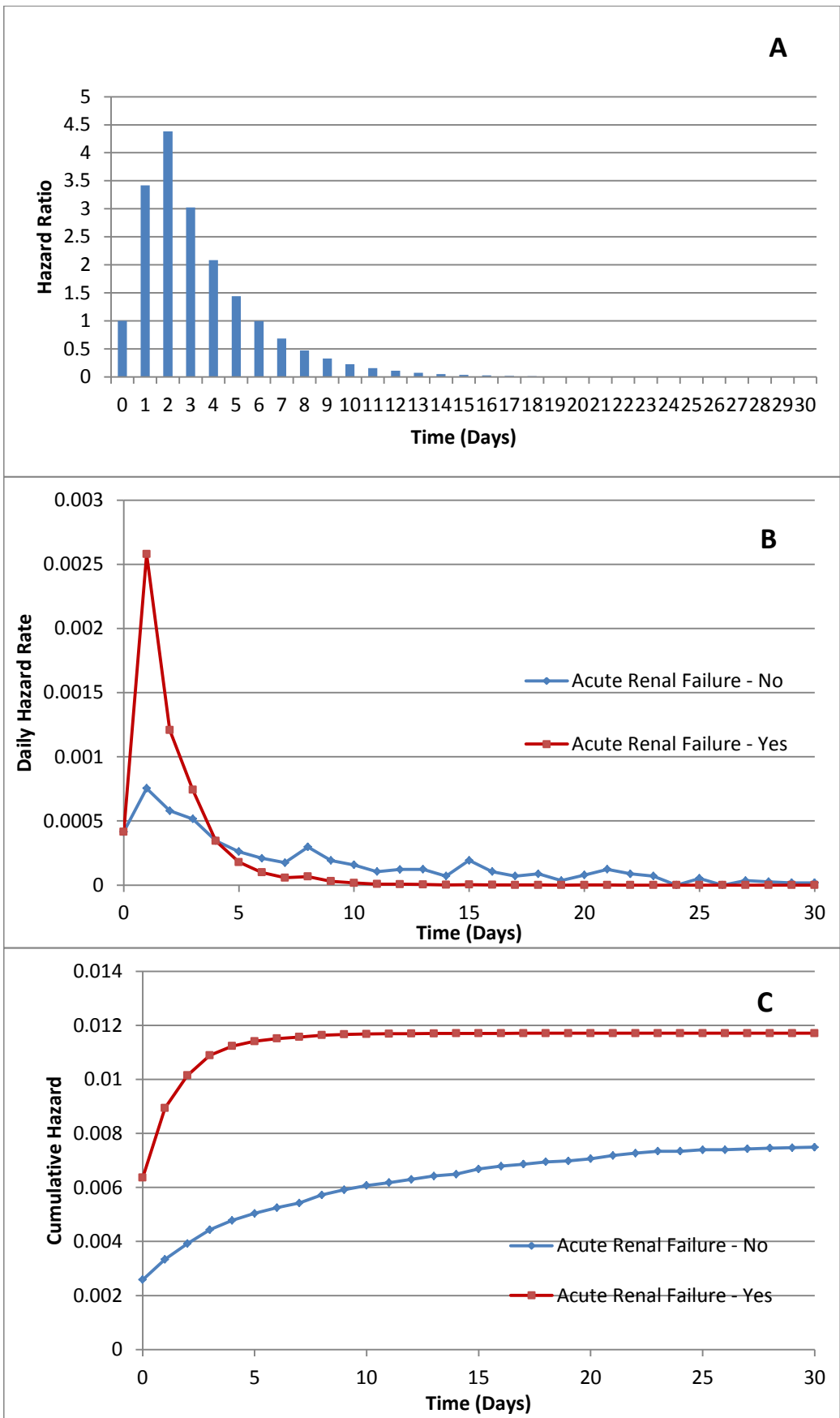
35201	26	35515	3	35695	8
35231	8	35526	5	35701	21
35301	20998	35601	57	35800	12
35390	34	35606	272	37215	543
		35626	15	37216	52

Appendix B: Flowchart of the statistical analyses. Distal vascular (DV) and cerebral vascular (CV) groups.

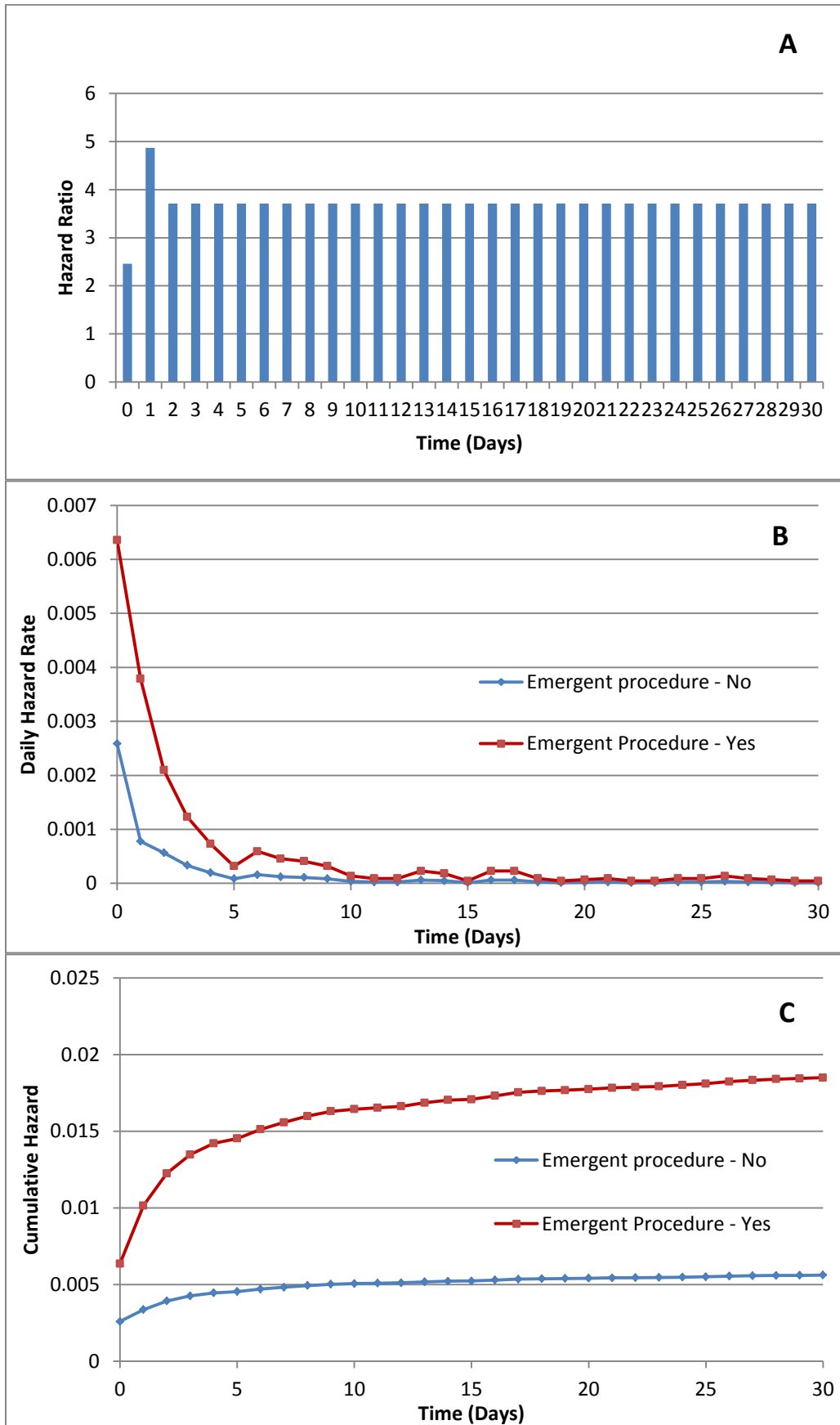


***FACTORS**
 Sex, Race, Comorbidities (Diabetes mellitus, Tobacco use, Dyspnea, Functional status, COPD, Heart failure, Hypertension, Dialysis, Acute renal failure, Mechanical ventilation, Wound infection, Sepsis, Weight loss, Disseminated cancer, steroid therapy, Bleeding disorders), Transfusion, Height, Weight, Laboratory values (Sodium, Urea nitrogen, Creatinine, Albumin, Bilirubin, SGOT, Alkaline phosphatase, White cell count, Hematocrit, Platelets, PTT, INR), Emergent procedure, ASA classification, Type of anesthetic, Operation time.

Appendix C: Hazard ratio (A), daily hazard rate (B), and cumulative hazard (C) for presence of acute renal failure and developing stroke in the Distal Vascular group (DV). The hazard ratio for stroke associated with acute renal failure violates the proportional hazard assumption and based on its time interaction first increases from Day 0 to Day 2 and then decreases. By Day 6, the hazard of stroke is not different between patients with and without acute renal failure, and subsequently, the hazard is lower in patients with acute renal failure (A). The daily hazard rate is the rate – as a proportion of patients – who develop stroke on a given day (B). The cumulative hazard is the proportion of patients who have developed stroke on or by that day (C).



Appendix D: Hazard ratio (A), daily hazard rate (B), and cumulative hazard (C) for having an emergent procedure and developing stroke in the Cerebral Vascular group (CV). While the hazard ratio changes from Day 0 to Day 1 and to Day 2, it is then constant from Day 2 to 30 (A). The daily hazard rate is the rate – as a proportion of patients – who develop stroke on a given day (B). The cumulative hazard is the proportion of patients who have developed stroke on or by that day (C).

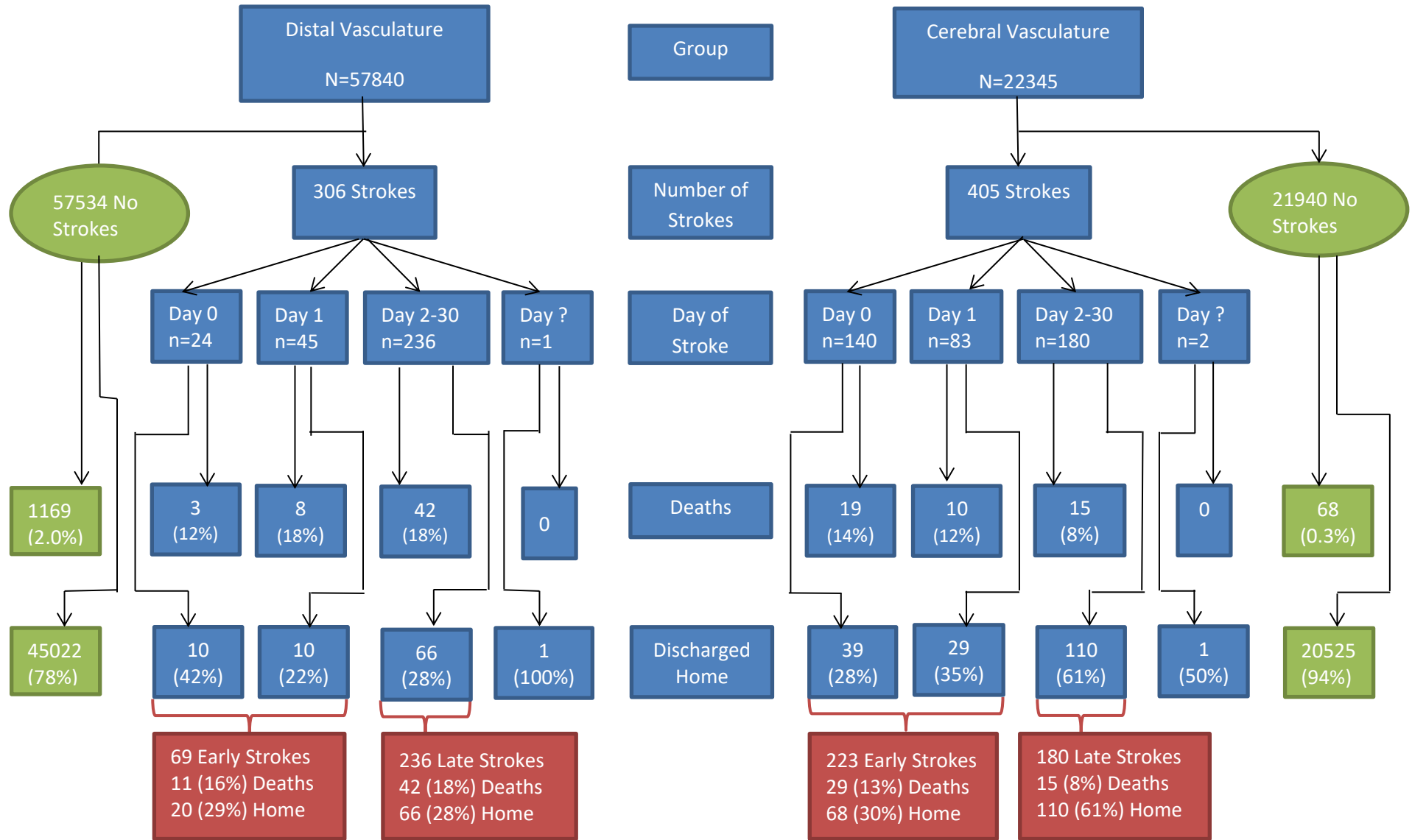


Appendix E: Interpretation of Time-interactions in Cox models.

The intent of time-varying Cox analyses is to analyze how clinical associations vary over time, rather than assuming the hazard ratios remain temporally constant. This is clinically relevant when assessing a complex outcome such as postoperative stroke. When the results of a Cox model include a statistically significant interaction term, such as the hazard ratio (HR) for having a stroke on POD 2-30 for female*time = 0.96, (**Table 3**) this shows that the HR to have a stroke decreases with time from POD 2 to POD 30: for day n counting from 1 on POD 2 to 29 on POD 30, it's 0.96^n ; for POD 2, it's $0.96^1 = 0.96$; for POD 3, it's $0.96^2 = 0.92$; for day 10, it's $0.96^9 = 0.69$. However, in this example, female is also a statistically significant factor with a HR = 2.12. To get the HR for having a stroke in a female compared to a male on any given POD 2-30, the HR to have a stroke associated with being female is multiplied by the HR of the female*time interaction term on that day. For day 2, it's $2.12*0.96^1 = 2.04$; for day 3, it's $2.12*0.96^2 = 1.95$; for day 10, it's $2.12*0.96^9 = 1.46$. So, the hazard for a female to have a stroke is initially greater than a male to have a stroke, but the HR decreases with time and eventually becomes less than that of a male. The HR is 2.12 on POD 2 and decreases to 0.65 on POD 30. For clarity we present the HR without the confidence intervals and p-values.

For an interaction term, such as transfusion*time, with an HR > 1.0, in this case 1.05, the HR increases with time: for day n counting from 1 on POD 2 to 29 on POD 30, it's 1.05^n ; for POD 2, it's $1.05^1 = 1.05$; for POD 3, it's $1.05^2 = 1.10$; for day 10, it's $1.05^9 = 1.55$. Although not statistically significant, the main effect of transfusion also has a HR = 1.05, so the HR of having a stroke associated with a transfusion on any day between POD 2 and POD 30 is the product of the 2 terms: $1.05*1.05^1 = 1.10$ for POD 2, $1.05*1.05^2 = 1.16$ for POD 3, and $1.05*1.05^9 = 1.63$ for POD 10. The HR of having a stroke will exponentially increase with time between POD 2 and POD 30. However, the baseline risk of having a stroke (~20/10000 on day 2 and ~1.3/10,000 on day 10) decreases faster than the HR increases, hence, the absolute risk of a stroke related to the transfusion is lower on day 10 than on day 2.

Appendix F: Flowchart of all patients undergoing distal vascular (DV) and cerebral vascular (CV) surgery. This shows the number and timing of early (days 0 and 1) and late (days 2-30) strokes, mortality, and discharge to home. Day ? is for patients for whom the timing of stroke is unknown.



Appendix G Univariate associations with stroke for distal vascular group (DV, n=57,859)

Variable	Description	No stroke	n=57553	Stroke	n=306	p-value
		n	%	n	%	
Female		21237	37	136	44	0.007
Race	White	43481	76	230	75	0.018
	Black	7272	13	45	15	
	Asian	1275	2	6	2	
	American Indian	259	0	0	0	
	Pacific Islander	305	1	0	0	
	Not reported	1233	6	26	6	
Anesthesia	General	45133	78	273	89	0.002
	MAC/IV sedation	9345	16	25	8	
	Other	3075	5	8	3	
Diabetes mellitus	No	38100	66	195	64	0.616
	Non-insulin	8387	15	46	15	
	Insulin	11066	19	65	21	
Tobacco		20553	36	130	42	0.016
Dyspnea		7564	13	57	19	0.129
Functional status	Independent	52672	92	271	89	0.149
	Partially dependent	3916	7	29	10	
	564	1	4	1		
	Totally dependent					
Mechanical ventilation		368	1	12	4	<0.001
COPD		7930	14	50	16	0.210
Congestive heart failure		1611	3	11	4	0.382
Hypertension		44393	77	265	87	<0.001
Dialysis		40403	7	27	9	0.216
Disseminated cancer		321	1	0	0	0.423
Open wound/infection		12060	21	72	24	0.261
Steroid therapy		2637	5	7	2	0.054
10% body weight loss		745	1	6	2	0.301
Bleeding disorders		12132	21	79	26	0.047
Preoperative transfusion		1797	3	25	8	<0.001
Sepsis	No	53909	94	252	82	<0.001
	Sepsis	1311	2	13	4	
	Septic shock	258	0	6	2	
	SIRS	2075	4	35	11	
ASA classification	1	909	2	0	0	<0.001
	2	6354	11	5	2	
	3	35250	61	160	52	
	4	13540	24	127	42	

	5	524	1	9	3	
Emergency		5305	9	80	26	<0.001
		n	Mean±SD	n	Mean±SD	
Work RVUs		57553	20±9	306	23±9	<0.001
Height (inches)		56183	67±4	294	66±4	<0.001
Weight (lbs)		56762	179±47	302	172±49	0.007
Sodium (meq/L)		53949	138±4	300	138±4	0.008
BUN (mg/dL)		53062	21±13	294	22±12	0.304
Creatinine (mg/dL)		54375	1.46±1.57	300	1.66±1.79	0.049
Albumin (g/dL)		27537	3.6±0.7	167	3.3±0.8	<0.001
Bilirubin (mg/dL)		26181	0.6±0.6	161	0.7±0.5	0.044
SGOT (U/L)		26228	28±37	163	25±18	0.141
Alk phos (U/L)		26252	94±58	163	97±92	0.559
WBC (10 ⁹ /L)		53621	8.5±3.7	301	10.1±4.9	<0.001
Hematocrit (%)		54291	37.6±6.3	301	36.8±6.5	0.027
Platelets (10 ⁹ /L)		53566	238±92	301	240±105	0.675
PTT (sec)		35114	34.3±13.2	212	36.7±16.1	0.029
INR		42002	1.1±0.4	245	1.2±0.4	0.162
Operation time (min)		57534	155±108	303	203±123	<0.001

MAC - monitored anesthesia care; COPD – chronic obstructive pulmonary disease; transfusion - transfusion of 1 or more units packed or whole red blood cells in 72 hours prior to surgery; SIRS – systemic inflammatory response syndrome; ASA – American Society of Anesthesiologists patient classification; RVU – relative value unit; Alk phos – alkaline phosphatase; WBC – white blood cell count; SD - Standard deviation.

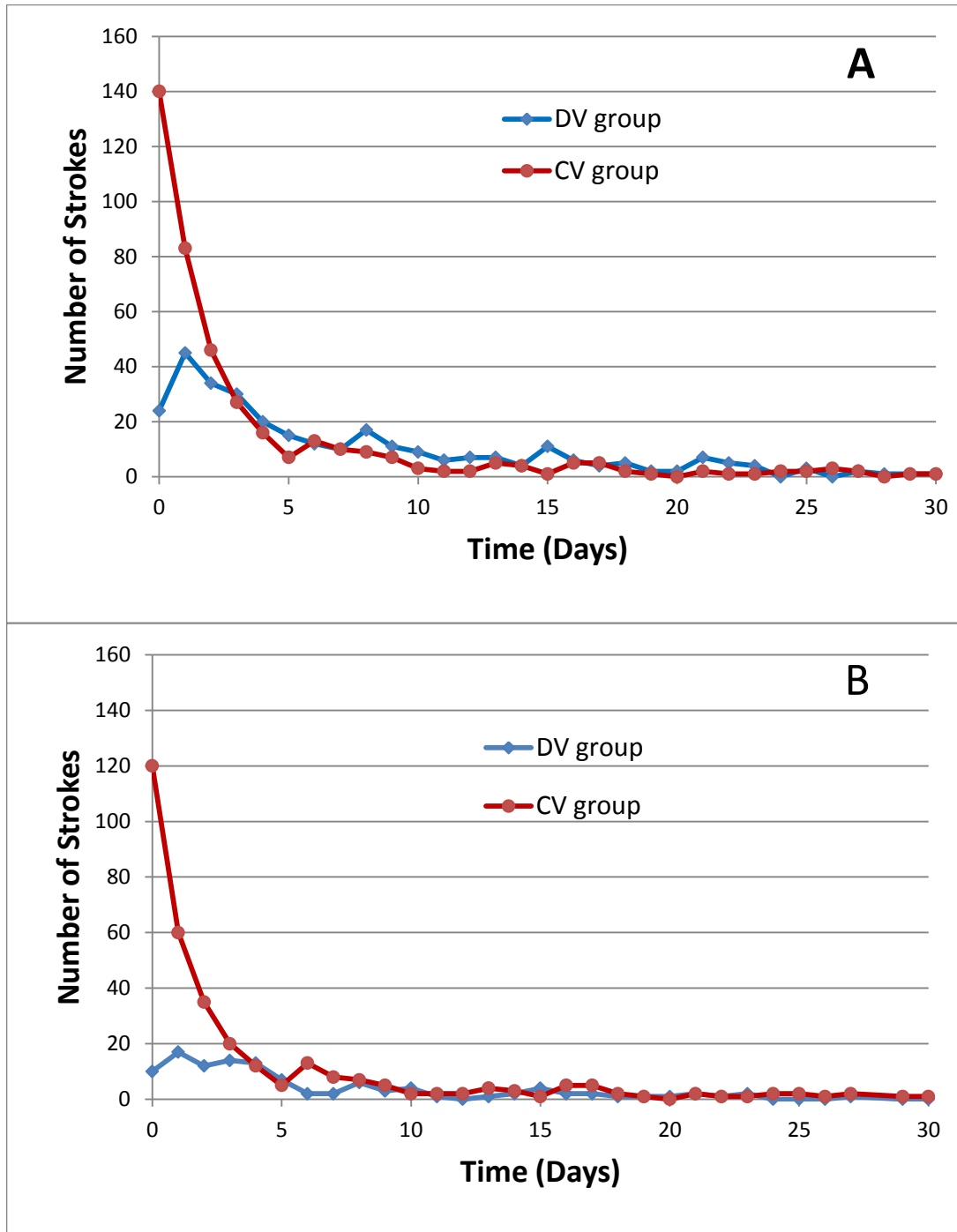
Appendix H Univariate associations with stroke for cerebral vascular group (CV, n=22,345)

Variable	Description	No stroke	n=21940	Stroke	n=405	p-value
		n	%	n	%	
Female		8818	40	169	42	0.540
Race	White	19087	87	336	83	0.018
	Black	1110	5	26	6	
	Asian	402	2	13	3	
	American Indian	65	0	4	1	
	Pacific Islander	42	0	0	0	
	Not reported	1233	6	26	6	
Anesthesia	General	18926	86	340	84	0.507
	MAC/IV sedation	1300	6	29	7	
	Other	1714	8	36	9	
Diabetes mellitus	No	15439	70	256	63	0.008
	Non-insulin	4043	18	92	23	
	Insulin	2458	11	57	14	
Tobacco		6305	29	124	31	0.407
Dyspnea		3162	14	62	15	0.662
Functional Status	Independent	21092	96	377	93	0.002
	Partially dependent	703	3	25	6	
	Totally dependent	57	0	0	0	
Mechanical ventilation		16	0	4	1	<0.001
COPD		2508	11	50	12	0.586
Congestive heart failure		311	1	8	2	0.293
Hypertension		18497	84	350	86	0.484
Dialysis		257	1	6	1	0.216
Disseminated cancer		64	0	1	0	0.999
Open wound/infection		274	1	9	2	0.108
Steroid therapy		695	3	14	3	0.668
10% body weight loss		99	0	2	0	0.706
Bleeding disorders		4999	23	99	24	0.439
Preoperative transfusion		94	0	6	1	0.010
Sepsis	No	21770	99	397	98	0.056
	Sepsis	18	0	1	0	
	Septic shock	2	0	0	0	
	SIRS	150	1	7	2	
ASA Classification	1	34	0	0	0	<0.001
	2	1325	6	25	6	
	3	16663	76	261	64	

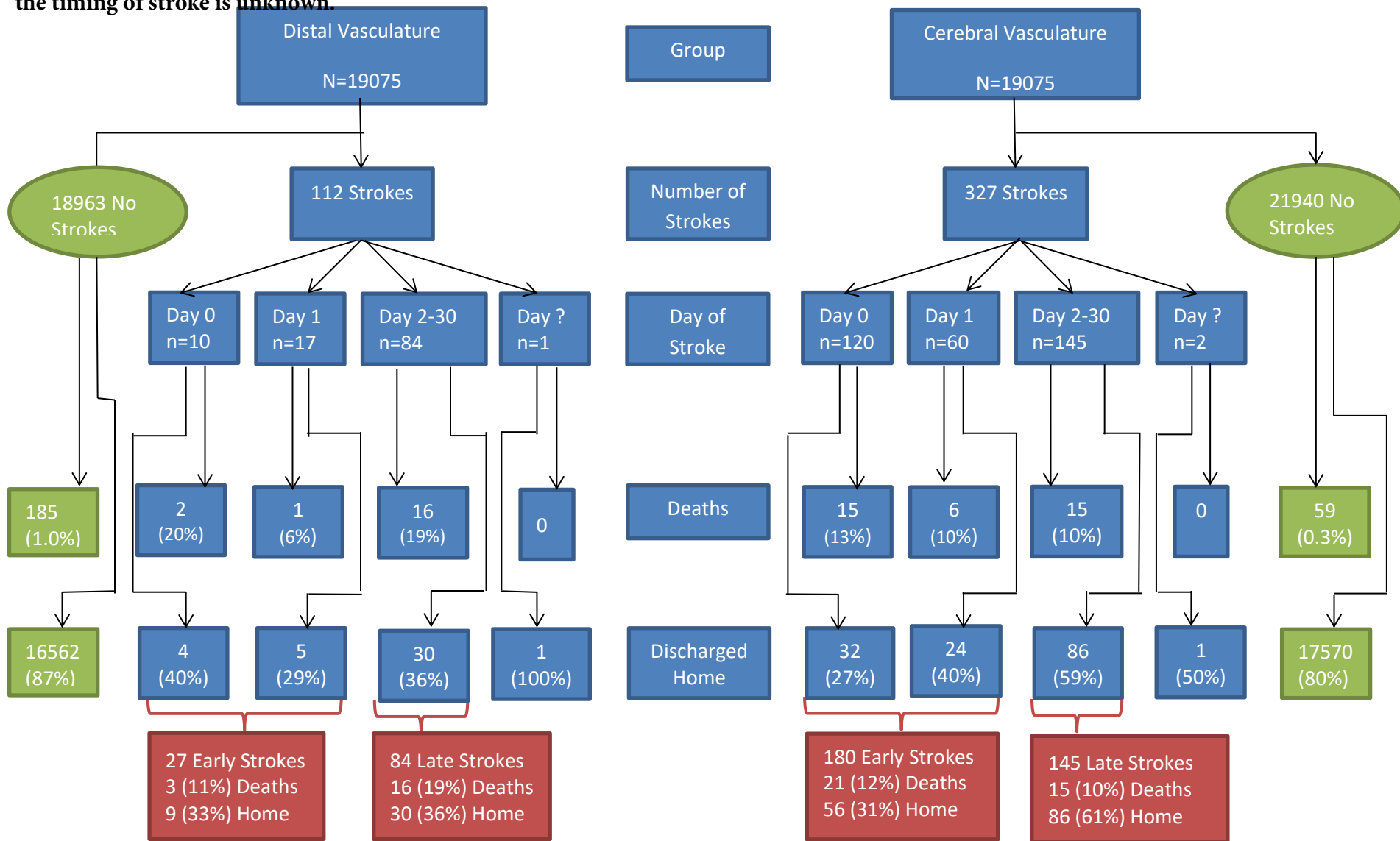
	4	3863	18	117	29	
	5	13	0	0	0	
Emergency		515	2	34	8	<0.001
		n	Mean±SD	n	Mean±SD	
Work RVU's		21940	20±1	405	20±1	0.172
Height (inches)		21723	66±4	395	66±4	0.009
Weight (lbs)		21238	179±41	400	175±40	0.066
Sodium (meq/L)		21122	139±3	392	139±3	0.564
BUN (mg/dL)		20848	20±10	385	20±9	0.884
Creatinine (mg/dL)		21252	1.13±0.72	395	1.16±0.79	0.410
Albumin (g/dL)		10739	3.9±0.5	204	3.9±0.6	0.459
Bilirubin (mg/dL)		10246	0.6±0.4	195	0.6±0.3	0.880
SGOT (U/L)		10545	25±18	195	25±20	0.857
Alk phos (U/L)		10318	81±36	196	75±21	<0.001
WBC (10 ⁹ /L)		20994	7.6±2.4	387	8.0±2.9	0.001
Hematocrit (%)		21238	39.4±4.9	396	39.0±5.3	0.169
Platelets (10 ⁹ /L)		20985	226±70	386	236±86	0.005
PTT (sec)		12996	32.7±12.0	257	34.5±13.1	0.032
INR		15457	1.06±0.29	293	1.06±0.19	0.994
Operation time (min)		21936	116±52	405	132±61	<0.001

MAC - monitored anesthesia care; COPD – chronic obstructive pulmonary disease; transfusion – transfusion of 1 or more units packed or whole red blood cells in 72 hours prior to surgery; SIRS – systemic inflammatory response syndrome; ASA – American Society of Anesthesiologists patient classification; RVU – relative value unit; Alk phos – alkaline phosphatase; WBC – white blood cell count; SD - Standard deviation.

Appendix I: Temporal distribution of postoperative strokes for surgical groups from postoperative days 0-30. Charts show the number of strokes occurring on each postoperative day for the distal vascular (DV) and cerebral vascular (CV) groups for the entire cohort (Figure A) and for the propensity-matched cohort (Figure B). One patient in the DV group and two patients in the CV group were missing data on the postoperative day of stroke.



Appendix J: Flowchart of propensity score matched patients undergoing distal vascular (DV) and cerebral vascular (CV) surgery. This shows the number and timing of early (days 0 and 1) and late (days 2-30) strokes, mortality, and discharge to home. Day ? is for patients for whom the timing of stroke is unknown.



Appendix K: Results of the time-varying Coefficients Cox analysis with distal vasculature/cerebral vascular surgery (DV/CV) group interaction.

This model evaluates the effect of preoperative risk factors on the interval to postoperative stroke onset for both DV and CV groups. Factors that have * DV group have an interaction between that factor and which surgery DV or CV that the patient has undergone. That is, there are different hazard ratios (HR) for the same factor depending on the type of surgery. The HR for these interaction terms are shown for the DV group. The HR for the CV group would be 1. Factors without a group interaction have the same HR for both groups. Factors that have * time (days) have time-varying coefficients – the proportional hazards assumption was violated for these variables. The two main effects HR = 1.46 for females vs. males and HR = 0.19 for DV vs. CV group show a higher stroke hazard for females and a lower stroke hazard for DV group surgery. The interaction term female*DV group HR = 0.83 shows that the HR of females vs. males for having a stroke on POD 0 differs between the DV group and the CV group. It is lower in the DV group (83% of the CV group HR for females vs. males to have a stroke on POD 0). HR for factors that have an interaction with surgery group (shown as *DV group) is calculated by multiplying the HR of the two main factors by the HR of the interaction term (see Appendix F), e.g. the HR for a female with DV surgery to have a stroke on POD 0 is (1.46 HR for female)*(0.83 HR for female*DV group)*(0.19 HR for DV group) = 0.23. The HR for having a stroke for a female with CV surgery on POD 0 is (1.46 HR for female)*(1 for female not in the DV group)*(1 for being in the CV group) = 1.46. The HR for having a stroke on POD 0 for a male in the DV group is (1 for male)*(1 for not being female in the DV group)*(0.19 HR for being in the DV group) = 0.19. The hazard ratio for having a stroke on POD 0 for a male in the CV group is (1 for male)*(1 for not being female in the DV group)*(1 for being in the CV group) = 1. When the interaction is time-based [shown as *time (days)], the HR varies with time, thus, the number of days is included in calculating the HR. If the HR of the time-based interaction term >1, then the HR increases with time; if the HR < 1, then the HR decreases with time. The HR for a given day is determined by multiplying the HR of the factor by the HR of the *time term raised to the number of days, starting with POD 2 as day 1. For example, the HR for having a stroke during POD 2 – 30 of the main effect of acute renal failure is 1.33. The HR of the acute renal failure * time interaction term is 0.88. Hence, the HR for having a stroke on POD 2 if the patient has acute renal failure is $1.33 \times 0.881 = 1.17$; on POD 3, it's $1.33 \times 0.882 = 1.03$; and on POD 5, it's $1.33 \times 0.884 = 0.80$. “Stroke onset” represents POD that stroke is recognized, HR = hazard ratio, CI = confidence interval, DV = distal vasculature group (n=57589, 24 strokes on POD 0, 45 on POD 1, and 236 on POD 2-30), CV = cerebral vascular group (n=22345, 140 strokes on POD 0, 83 on POD 1, and 180 on POD 2-30). The HR are a ratio of the hazards of Factor A to Factor B, for example of DV to CV. Instead, if one wants the HR of Factor B to Factor A, CV to DV instead of DV to CV, one divides the HR into 1. E.g., the HR for DV group compared to CV group for POD 0, 1, and 2-30 are 0.19, 0.051, and 0.16, respectively. For CV group compared to DV group, the HR would be 1/0.19, 1/0.051, and 1/0.16, which equal 5.15, 19.49, and 6.22, respectively. One patient in the DV group and 2 in the CV group are missing time of stroke. WBC = White Blood Cell. †represents reference level for subsequent variables in the same category. a represents the p-value for the whole category.

Appendix K – Time-Varying Coefficients Cox Analysis with Surgery Type (DV or CV) Interaction

Stroke Onset	Preoperative Variable	HR	95% CI	p-value
POD 0	Female	1.46	1.13 – 1.87	0.003
(n=166)	Female * DV group	0.83	0.71 – 0.96	0.014
	Dyspnea	1.99	1.05 – 3.76	0.034
	Platelets – not measured†	1		<0.001 ^a
	Platelet < 193 k/μL	3.47	1.86 – 6.47	<0.001
	Platelet 193-253 k/μL	2.64	1.43 – 4.87	0.002
	Platelet > 253 k/μL	1.60	0.87 – 2.97	0.134
	Platelets – not measured * DV group†	1		<0.001 ^a
	Platelet < 193 k/μL *DV group	0.47	0.33 – 0.67	<0.001
	Platelet 193-253 k/μL *DV group	0.61	0.43 – 0.86	0.005
	Platelet > 253 k/μL * DV group	0.88	0.62 – 1.24	0.455
	DV group	0.19	0.14-0.26	<0.001
POD 1	Female	1.40	1.09 – 1.79	0.007
(n=128)	Female * DV group	0.86	0.74 – 0.999	0.049
	Hypertension	2.80	1.36 – 5.74	0.005
	Emergency	2.65	1.40 -5.01	0.003
	WBC – not measured†	1		0.007 ^a
	WBC <7000/μL	14.3	1.78 – 115	0.012
	WBC 7000-8700/μL	24.2	3.07 – 190	0.002
	WBC >8700/μL	25.9	3.31 – 203	0.002

	WBC – not measured * DV group†	1		0.035 ^a
	WBC <7000/μL * DV group	0.23	0.08 – 0.71	0.011
	WBC 7000-8700/μL * DV group	0.20	0.06 – 0.60	0.004
	WBC >8700/μL * DV group	0.21	0.07 – 0.63	0.005
	DV group	0.051	0.016-0.16	<0.001
POD 2-30	Female	1.67	1.60 – 1.75	<0.001
(n=416)	Age (10 years)	1.08	1.06 – 1.09	<0.001
	Mechanical ventilation	1.46	1.28 – 1.67	<0.001
	Mechanical ventilation * time (days)	0.93	0.87 – 0.99	0.049
	Congestive heart failure	1.51	1.33 – 1.71	<0.001
	Acute Renal failure	1.33	1.17 – 1.51	<0.001
	Acute Renal failure * time (days)	0.88	0.83 – 0.93	<0.001
	Wound infection	1.06	1.00 – 1.12	0.036
	Wound infection * DV group	0.65	0.57 – 0.75	<0.001
	Steroid use	2.22	1.93 – 2.55	<0.001
	Steroid use * DV group	0.43	0.36 – 0.51	<0.001
	Sepsis - None†	1		<0.001 ^a
	Sepsis	1.52	1.34 - 1.71	<0.001
	Septic shock	1.94	1.63 - 2.30	<0.001
	SIRS	2.06	1.90 - 2.21	<0.001
	Emergency	2.36	2.23 – 2.50	<0.001
	Emergency * DV group	0.71	0.65 – 0.78	<0.001
	Smoked	1.44	1.38 – 1.51	<0.001
	Wound Class - Clean†	1		<0.001 ^a

	Wound Class – Clean/contaminated	1.31	1.14 - 1.49	<0.001
	Wound Class - Contaminated	1.26	1.08 - 1.46	0.003
	Wound Class - Dirty	1.88	1.66 - 2.11	<0.001
	Dyspnea	1.37	1.30 – 1.45	<0.001
	Dyspnea * DV group	0.77	0.71 – 0.83	<0.001
	Transfusion	1.75	1.43 – 2.16	<0.001
	Transfusion * DV group	2.05	1.56 – 2.70	<0.001
	Transfusion * time (days)	1.04	1.02 – 1.06	<0.001
	DV group	0.16	0.13-0.20	<0.001