Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018;378:708-18. DOI: 10.1056/NEJMoa1713973

Supplementary Material 1

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Interventionist Credentialing Requirements

Interventionist met the requirements outlined for training and experience below:

Training: Satisfactory completion of a 7-year ACGME approved neurosurgical residency OR Board certification (ABMS) Board in Neurology with subspecialty certification from an ACGME-accredited Vascular/Stroke Neurology Fellowship OR Board certification (ABMS) Board (Radiology) with subspecialty certification in Neuroradiology AND Interventionist has completed a minimum of 12 months of continuous training as a fellow in a dedicated Neuroendovascular fellowship

Experience: Interventionist has performed a minimum of 200 cerebral angiograms AND Interventionist has performed at least 20 stroke thrombectomy cases with stentrievers and/or suction thrombectomy devices as a primary operator. (When a prospective interventionist had extensive experience performing endovascular thrombectomies, but did not fully meet the training requirements, they could be approved by unanimous vote of the 4-member DEFUSE 3 Endovascular Committee)

Study Inclusion and Exclusion Criteria

Clinical Inclusion Criteria:

1. Signs and symptoms consistent with the diagnosis of an acute anterior circulation ischemic stroke
2. Age 18 - 90 years
3. Baseline NIHSSS is ≥ 6 and remains ≥6 immediately prior to randomization
4. Endovascular treatment can be initiated (femoral puncture) between 6 and 16 hours of stroke onset. Stroke onset is defined as the time the patient was last known to be at their neurologic baseline (wake - up strokes are eligible if they meet the above time limits).
5. modified Rankin Scale less than or equal to 2 prior to qualifying stroke (functionally independent for all ADLs)
6. Patient/Legally Authorized Representative has signed the Informed Consent form.

Clinical Exclusion Criteria:

1. Other serious, advanced, or terminal illness (investigator judgment) or life expectancy is less than 6 months.

2. Pre-existing medical, neurological or psychiatric disease that would confound the neurological or functional evaluations
3. Pregnant
4. Unable to undergo a contrast brain perfusion scan with either MRI or CT
5. Known allergy to iodine that precludes an endovascular procedure
6. Treated with tPA >4.5 hours after time last known well
7. Treated with tPA 3‐4.5 hours after last known well AND any of the following: age >80, current anticoagulant use, history of diabetes AND prior stroke, NIHSS >25
8. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency; recent oral anticoagulant therapy with INR > 3 (recent use of one of the new oral anticoagulants is not an exclusion if estimated GFR > 30 ml/min).
9. Seizures at stroke onset if it precludes obtaining an accurate baseline NIHSS
10. Baseline blood glucose of <50mg/dL (2.78 mmol) or >400mg/dL (22.20 mmol)
11. Baseline platelet count < 50,000/uL
12. Severe, sustained hypertension (Systolic Blood Pressure >185 mmHg or Diastolic Blood Pressure >110 mmHg)
13. Current participation in another investigational drug or device study
14. Presumed septic embolus; suspicion of bacterial endocarditis
15. Clot retrieval attempted using a neurothrombectomy device prior to 6 hours from symptom onset
16. Any other condition that, in the opinion of the investigator, precludes an endovascular procedure or poses a significant hazard to the subject if an endovascular procedure was performed.

Neuroimaging Inclusion Criteria:

1. ICA or MCA‐M1 occlusion (carotid occlusions can be cervical or intracranial; with or without tandem MCA lesions) by MRA or CTA

AND

2. Target Mismatch Profile on CT perfusion or MRI (ischemic core volume is < 70 ml, mismatch ratio is > 1.8 and mismatch volume* is > 15 ml)

Alternative neuroimaging inclusion criteria (if perfusion imaging or CTA/MRA is technically inadequate):

A) If CTA (or MRA) is technically inadequate: Tmax>6s perfusion deficit consistent with an ICA or MCA-M1 occlusion

AND

Target Mismatch Profile (ischemic core volume is < 70 ml, mismatch ratio is >1.8 and mismatch volume is >15 ml as determined by RAPID software)

B) If MRP is technically inadequate:
ICA or MCA‐M1 occlusion (carotid occlusions can be cervical or intracranial; with or without tandem MCA lesions) by MRA (or CTA, if MRA is technically inadequate and a CTA was performed within 60 minutes prior to the MRI)
AND
DWI lesion volume < 25 ml

C) If CTP is technically inadequate:
Patient can be screened with MRI and randomized if neuroimaging criteria are met.

Neuroimaging Exclusion Criteria:
1. ASPECT score <6 on non‐contrast CT (if patient is enrolled based on CT perfusion criteria)
2. Evidence of intracranial tumor (except small meningioma) acute intracranial hemorrhage, neoplasm, or arteriovenous malformation
3. Significant mass effect with midline shift
4. Evidence of internal carotid artery dissection that is flow limiting or aortic dissection
5. Intracranial stent implanted in the same vascular territory that precludes the safe deployment/removal of the neurothrombectomy device
6. Acute symptomatic arterial occlusions in more than one vascular territory confirmed on CTA/MRA (e.g., bilateral MCA occlusions, or an MCA and a basilar artery occlusion).

Table S1. Stratification Factors used for the web-based dynamic randomization system

Stratification Factor	Thresholds
Ischemic Core Lesion Volume (ml)	<10, 10-25, 26-50, >50.
Baseline NIHSS score	6-12, 13-18, >18
Age (years)	<55, 55-69, 70-79, >79
Time from symptom onset to treatment (hours)	<9, 9-12, >12

Table S2. Serious Adverse Events by Body System

	# Events			# Subjects					
	Endo-vascular	Medical	All Groups	Endo-vascular		Medical		All Groups	
	N	N	N	N	COL%	N	COL%	N	COL%
All Randomized	.	.	.	92	.	90	.	182	.
All Events*	62	68	130	40	43.5 %	48	53.3 %	88	48.4 %
Cardiac disorders	5	5	10	5	5.4%	4	4.4%	9	4.9%
Gastrointestinal disorders	7	3	10	6	6.5%	3	3.3%	9	4.9%
General disorders and administration site conditions	3	1	4	3	3.3%	1	1.1%	4	2.2%
Infections and infestations	4	8	12	4	4.3%	7	7.8%	11	6.0%
Injury, poisoning and procedural complications	0	2	2	0	0.0%	2	2.2%	2	1.1%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0	1	1	1.1%	0	0.0%	1	0.5%
Nervous system disorders	28	30	58	23	25.0 %	28	31.1 %	51	28.0 %
Product issues	0	1	1	0	0.0%	1	1.1%	1	0.5%
Psychiatric disorders	1	0	1	1	1.1%	0	0.0%	1	0.5%
Renal and urinary disorders	2	0	2	2	2.2%	0	0.0%	2	1.1%

Respiratory, thoracic and mediastinal disorders	7	15	22	7	7.6%	13	14.4 %	20	11.0 %
Vascular disorders	4	3	7	4	4.3%	3	3.3%	7	3.8%

***Number of subjects represents those with ANY serious adverse event.**

Table S3: Endovascular devices and other therapies (core lab adjudicated)

Intervention*	N
Stentriever	74
Aspiration alone (without stentriever)	25
Cervical angioplasty and/or stent placement[#]	13
None	2
Intra-arterial thrombolytic[+]	2
Intracranial angioplasty or stent placement[+]	3

*Indicates patients where this therapy was used alone or in combination (multiple interventions may be utilized within the same subject). In 2 patients, no intervention was attempted because the operator felt that device deployment was not possible or not safe.

12 patents had stents placed and 10 of these also had angioplasty before or after stent placement. One patient had angioplasty alone. One patient with presumed dissection had stenting alone. In one additional patient, the artery had spontaneously recanalized but the interventionist placed a series of self-expanding stents to treat a presumed dissection.

+ There were 5 protocol violations (5.4%) in the endovascular treatment group- 2 patients received IA-tPA, 2 patients had intracranial stents placed (in M1) and 1 patient had intracranial angioplasty (in M1).

Table S4. Additional Baseline Characteristics and Process Measures

	Endovascular (N=92)	Medical (N=90)
Race – no. (%)		
Black	10 (10.9)	5 (5.6)
White	78 (84.8)	80 (88.9)
Asian	3 (3.3)	3 (3.3)
Other	1 (1.1)	2 (2.2)
Ethnicity — no. (%)		
Hispanic	14 (15.2)	10 (11.1)
Non-Hispanic	77 (83.7)	80 (88.9)
Unknown	1 (1.1)	0 (0.0)

Medical history — no. (%)		
Hypertension	71 (77.2)	72 (80)
Diabetes mellitus	28 (30.4)	27 (30)
Atrial fibrillation	34 (37.0)	28 (31.1)
Prior Stroke	13 (14.1)	12 (13.3)
Premorbid modified Rankin scale score		
0— no. (%)	80 (87.0)	70 (77.8)
1— no. (%)	9 (9.8)	10 (11.1)
2— no. (%)	3 (3.3)	10 (11.1)
SBP at hospital arrival, mm Hg — median (IQR)	141 (131-161)	147 (130-159)
Serum glucose, mg/dl	123.5 (107.5-155.5)	124.0 (109.0-152.0)
Baseline Imaging		
Stroke lesion characteristics — median, IQR*		
Mismatch volume, ml	95.1 (63.7-130.9)	93.9 (59.7-136.4)
Mismatch ratio	11.8 (4.5-41.5)	10.2 (5.2-56.4)
Process measures		
Time from Stroke to — median (IQR)		
Femoral Puncture, HH:MM	11:27 (9:12-12:50)	NA
First Clot Removal Attempt, HH:MM	11:57 (9:30-13:14)	NA

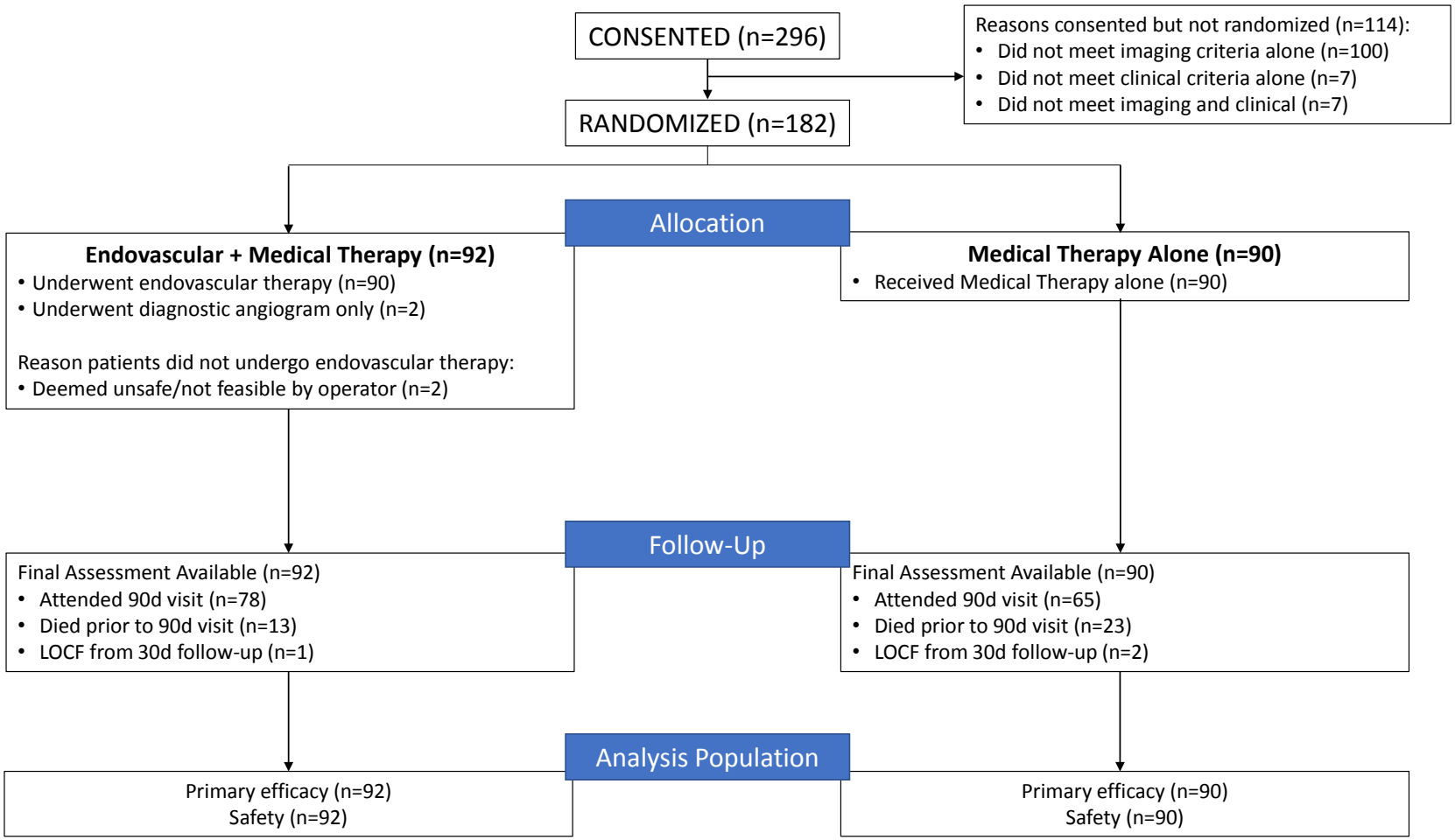
Reperfusion, HH:MM	12:08 (9:44-13:37)	NA
Time to Femoral Puncture — median (IQR)		
Arrival at Study Site to Femoral Puncture, HH:MM	1:52 (1:20- 2:30)	NA
Randomization to Femoral Puncture, HH:MM	0:29 (0:21- 0:36)	NA
Time from stroke to randomization stratified by patient subgroup — median (IQR)		
Stroke onset witnessed, HH:MM	9:34 (7:50-12:51)	9:31 (8:00-12:42)
Stroke onset not witnessed / wake-up, HH:MM	11:39 (10:30-12:22)	11:12 (10:12-13:38)
Stroke onset not witnessed / non-wake-up, HH:MM	9:37 (7:32-11:45)	9:29 (8:14-11:52)

*Central Imaging Laboratory values are reported.

Due to 2 technically inadequate perfusion studies, the Ns for mismatch volume and mismatch ratio are: 92 for the endovascular group and 88 for the medical group.

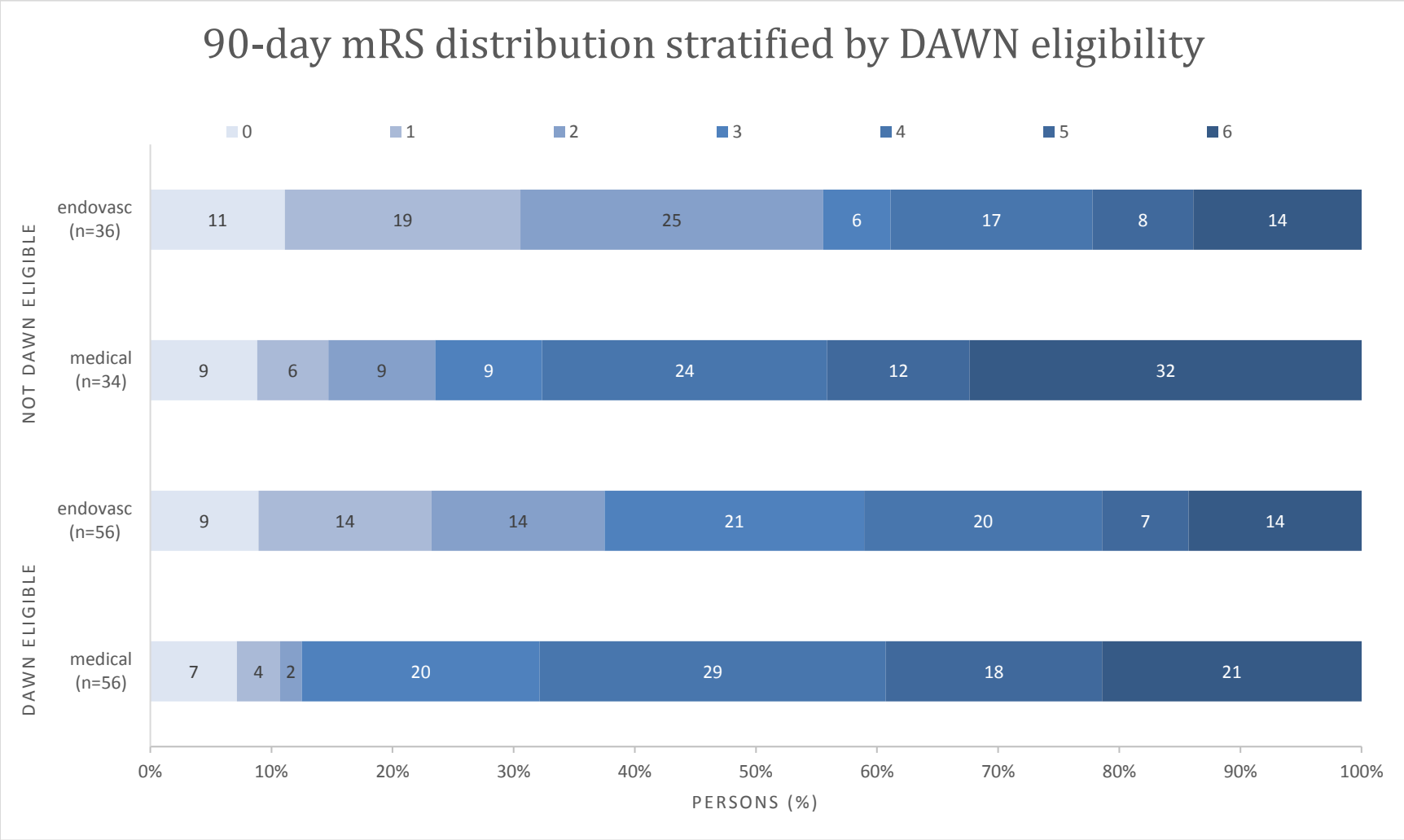
There are no significant differences between the treatment groups for any baseline characteristic

Fig S1. Consort Diagram

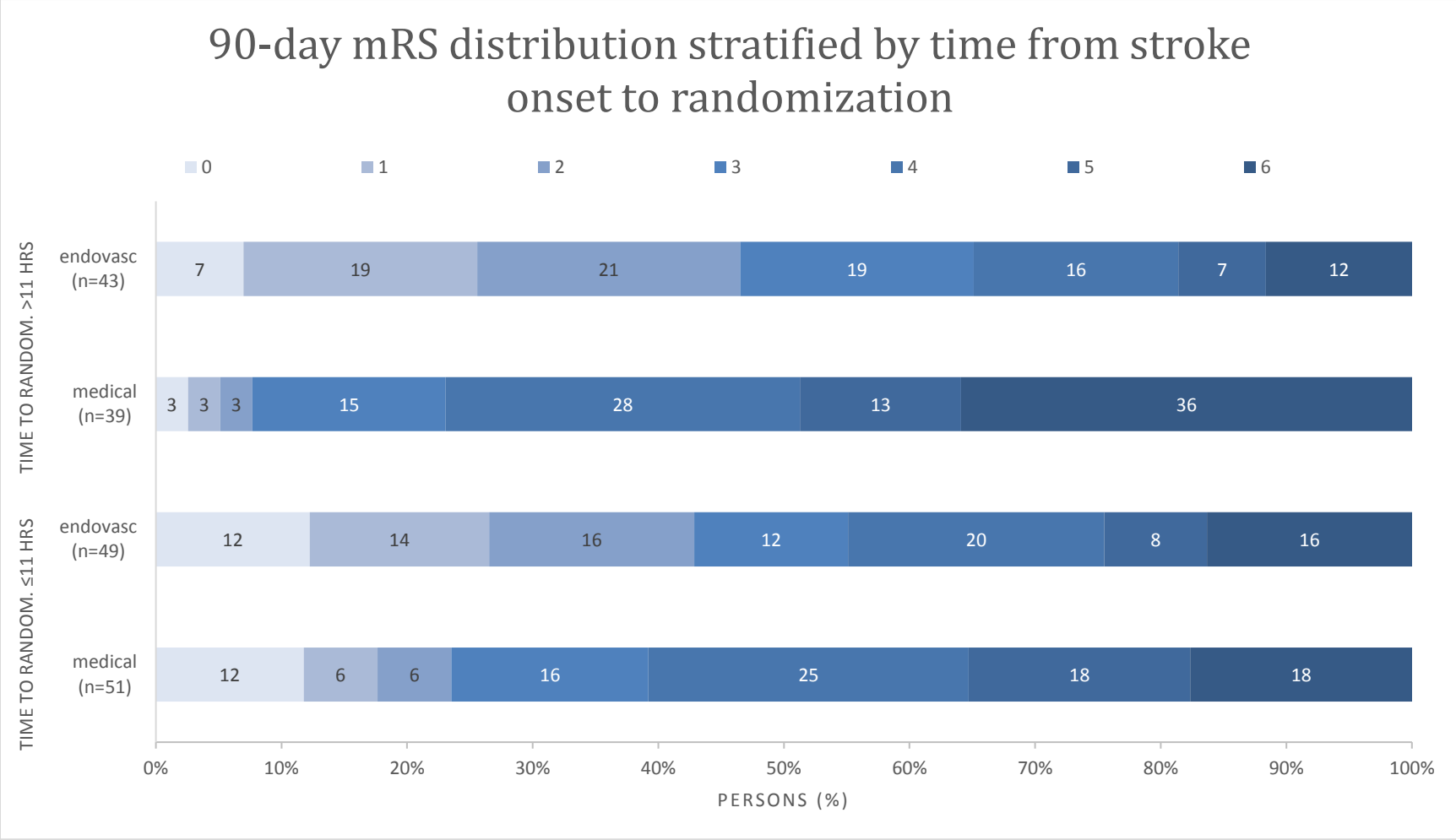


Among the 107 patients who did not meet baseline imaging criteria, 45 (42%) did not have a target vessel (ICA or M1) occlusion and/or no perfusion lesion, 45 (42%) had a large ischemic core (core >70 mL and/or ASPECTS <6), 8 (7%) had a matched lesion (mismatch ratio <1.8 and/or mismatch volume <15mL), and 9 (8%) met other imaging exclusion criteria. Among the 7 patients who did not meet clinical criteria alone, 2 were outside the 6-16 hour time-window, 2 had mild symptoms (NIHSS <6), and 3 met other clinical exclusion criteria.

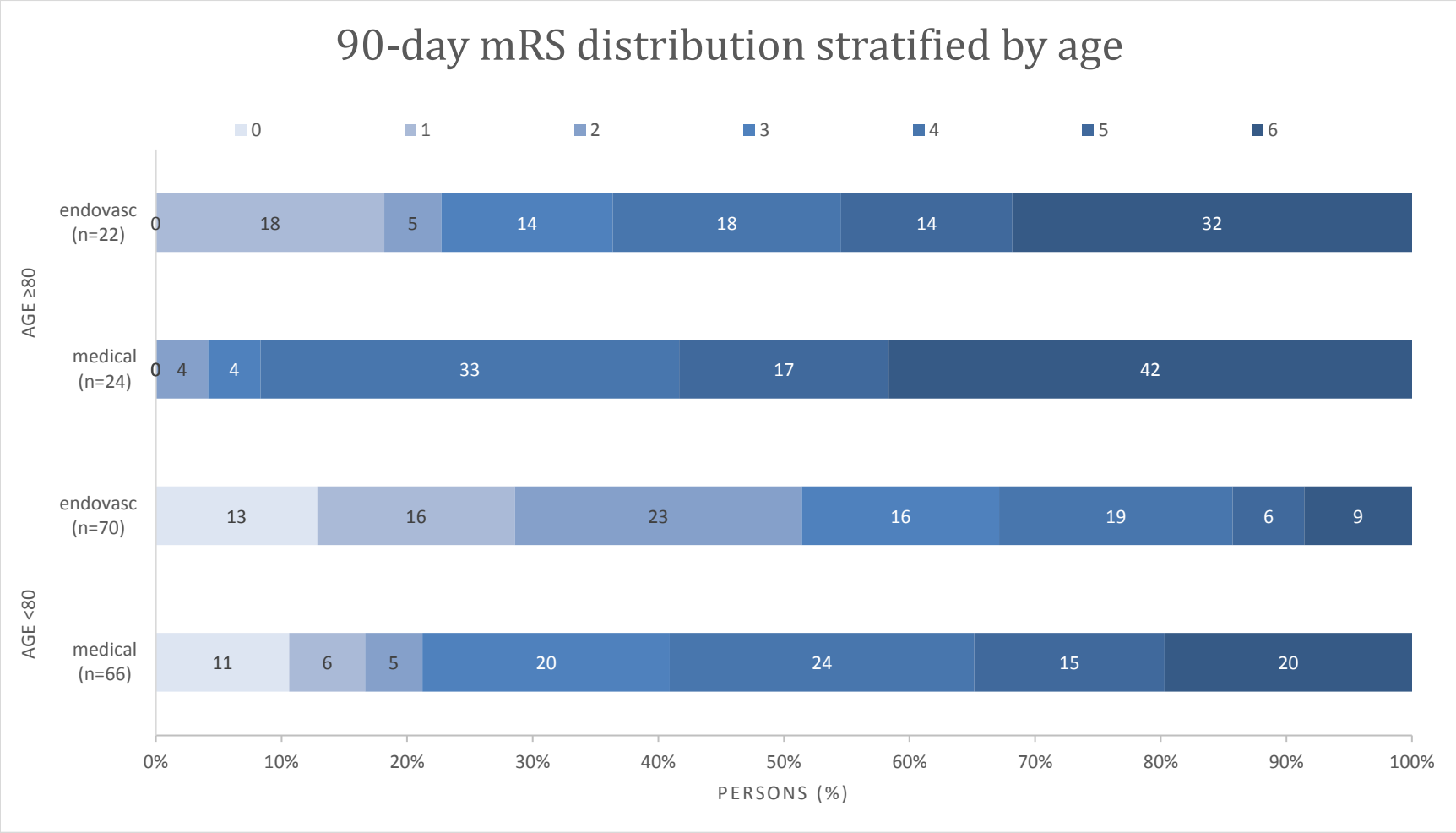
Figure S2: Primary endpoint in subgroups



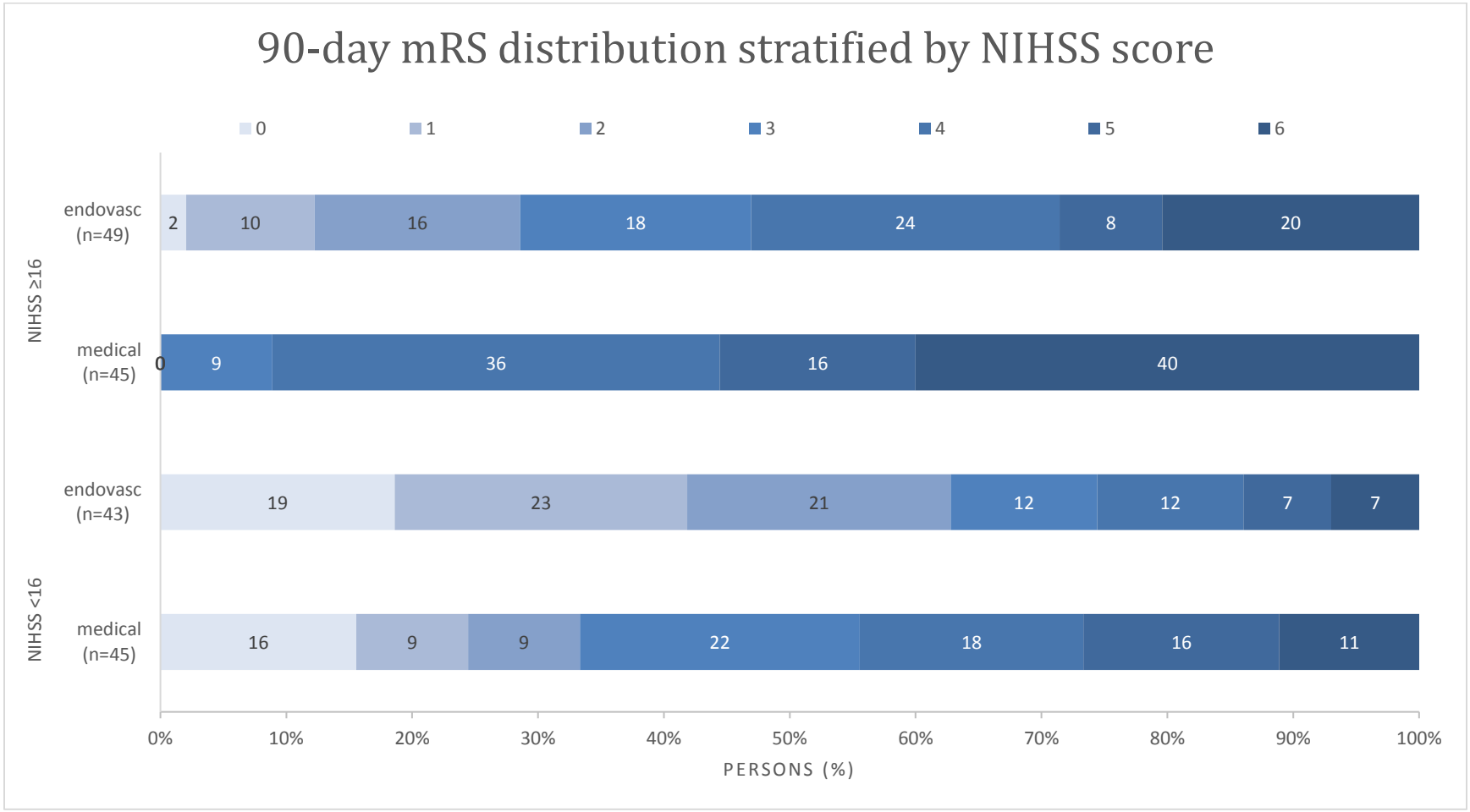
DAWN Ineligible, (OR 2.96, 95% CI 1.26-6.97); DAWN Eligible, (OR 2.66, 95% CI 1.36-5.23) P value for interaction = 0.47



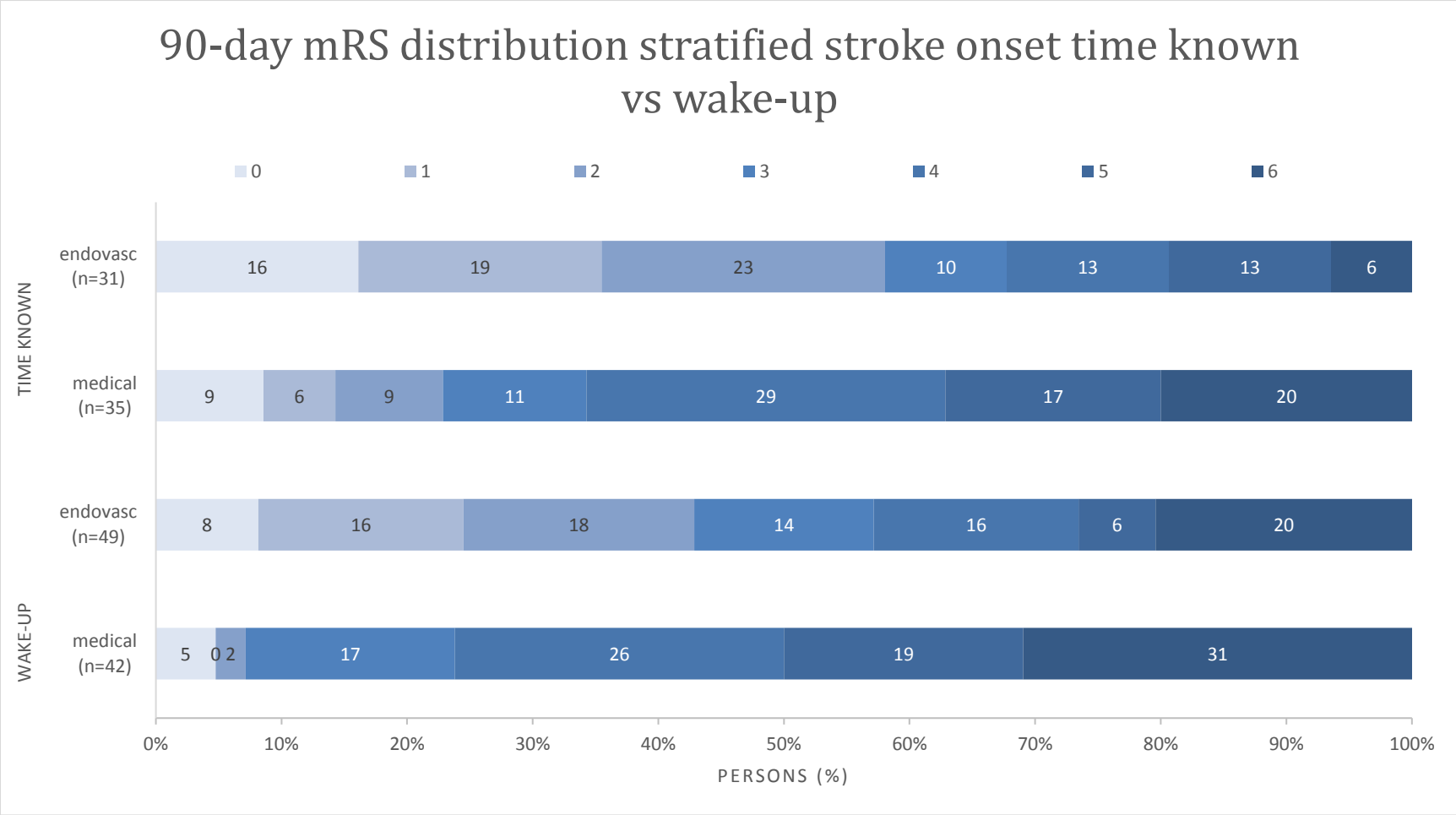
Onset to Randomization >11 hours, OR 5.65 (2.44, 13.12); ≤11 hours, OR 1.70 (0.85, 3.41), P value for interaction = 0.066



Age ≥ 80 years, OR = 2.31 (0.80, 6.68); Age < 80 years, OR= 2.86 (1.55, 5.27), P value for interaction = 0.70



Baseline NIHSS ≥ 16 OR= 4.51 (2.07, 9.83) Baseline NIHSS < 16 OR= 2.28 (1.08, 4.81), P value for interaction = 0.47



Stroke onset time known, OR= 3.41 (1.40, 8.32); Wake-up stroke, OR= 3.44 (1.60, 7.38), P value for interaction = 0.94