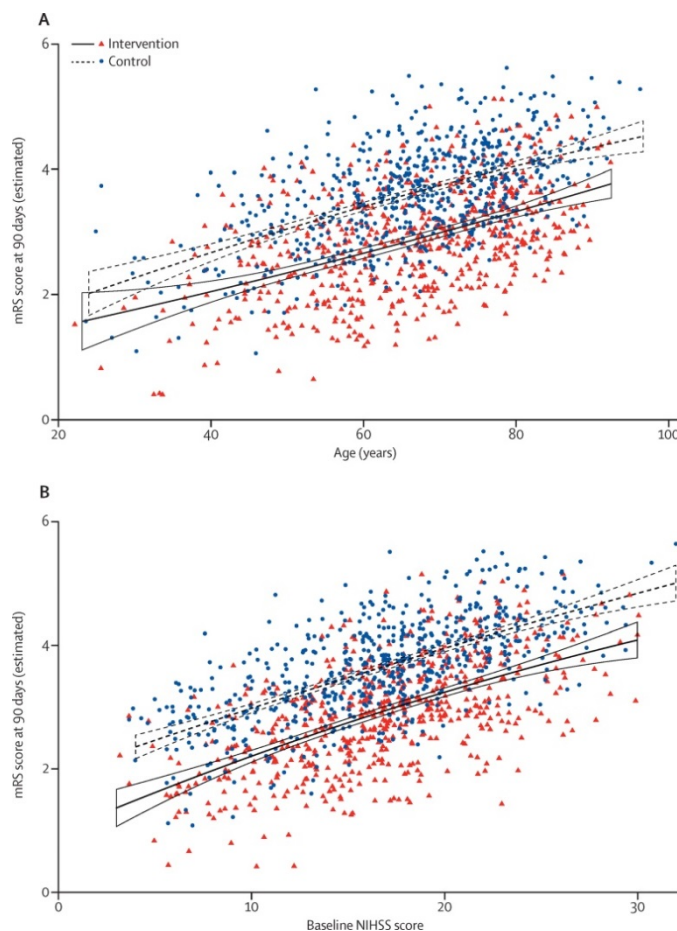


**SUPPLEMENTAL DIGITAL CONTENT-1**  
**DETERMINANTS OF ENDOVASCULAR THROMBECTOMY EFFECTIVENESS**

Before considering the potential effects of anesthetic management on endovascular thrombectomy (EVT), it is necessary to first understand the patient and procedural determinants of EVT effectiveness. Only with this understanding can the limitations and findings of observational reports of anesthetic management for EVT be placed into context.

**A. Age and National Institutes of Health Stroke Scale (NIHSS) Score**

When data from the five randomized control trials (RCTs) that first established the effectiveness of EVT were combined, two factors were independently associated with less favorable functional outcome: 1) increasing patient age; and 2) increasing pre-EVT NIHSS score;<sup>1</sup> see Figure S1-1.

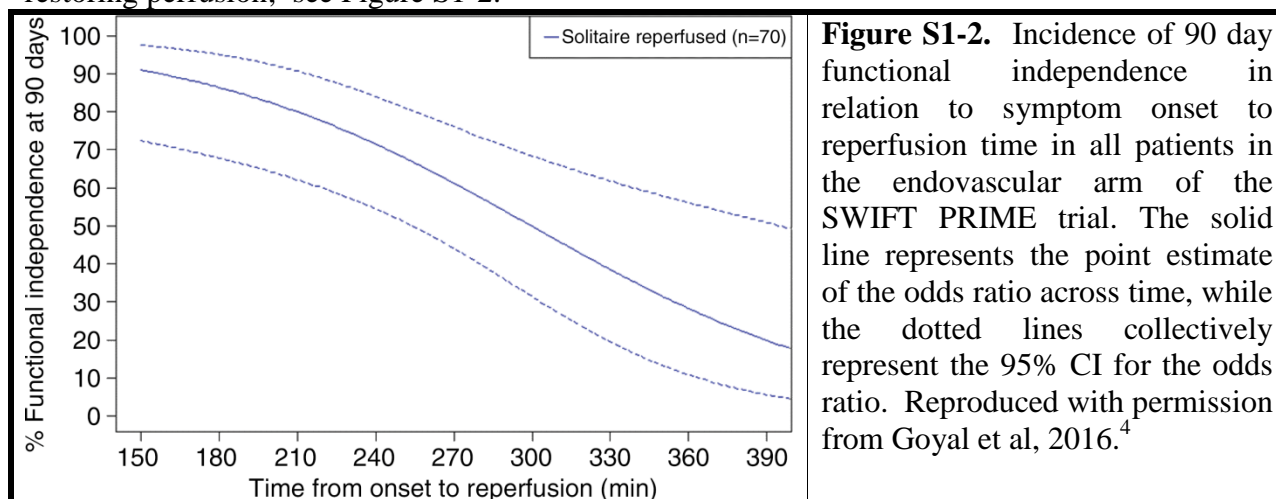


**Figure S1-1.** Modified Rankin Score (mRS) at 90 days versus patient age (A, top) and pre-EVT National Institutes of Health Stroke Scale Score (NIHSS) (B, bottom). Data are stratified by intervention (e.g., endovascular thrombectomy; red data points) versus control (e.g., medical therapy; blue data points). Models adjust for covariates (age, sex, baseline stroke severity, site of occlusion, intravenous tPA [yes vs. no], Alberta Stroke Program Early Computed Tomography Score) and time from onset to randomization. Reprinted from The Lancet 387(10029), Goyal M, Menon BK, van Zwam WH, et al., Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomized trials, 1723-1731, 2016, with permission from Elsevier.<sup>1</sup>

In fact, in virtually all EVT studies, outcomes are strongly associated with the severity of the initial stroke symptoms. Greater initial symptom severity correlates with a greater volume of ischemic brain—some of it potentially salvageable (the penumbra) and some of it not (the ischemic core—infarct). Therefore, when considering the findings of observational reports regarding anesthesia for EVT, it is essential to consider patient age and NIHSS score at presentation.

#### B. Time between Stroke Onset and Reperfusion

As previously discussed, a key determinant of EVT effectiveness is the time between stroke onset and establishing reperfusion.<sup>2</sup> In the MR CLEAN trial, both: 1) the likelihood of successful reperfusion; and 2) the likelihood of neurologic improvement after successful reperfusion decreased with increasing time.<sup>3</sup> There was no significant benefit of EVT when the time from symptom onset to reperfusion exceeded 6 hours. In the SWIFT PRIME trial, the likelihood of 3-month functional independence was 91% if reperfusion was achieved within 150 minutes after symptom onset. The likelihood of good outcome decreased by ~10% (absolute) over the next 60 minutes, and then by 20% (absolute) with every subsequent hour before restoring perfusion;<sup>4</sup> see Figure S1-2.



Importantly, two recent RCTs (DAWN, DEFUSE 3) demonstrated there are some acute stroke patients who can benefit from EVT when treated more than 6 hours after symptom onset.<sup>5,6</sup> In both trials, computed tomography (CT)-perfusion or magnetic resonance (MR) imaging was used to select patients who had both: 1) an ischemic core (infarct) that was small; and 2) a relatively large penumbral region that, although moderately ischemic and dysfunctional, was still potentially viable. In these studies, EVT performed 6-24 hours (DAWN) and 6-16 hours (DEFUSE 3) after symptom onset improved functional outcome compared with patients receiving medical therapy (controls). Notably, in this subset of stroke patients, EVT effectiveness did not appear to be time sensitive;<sup>6</sup> see below, Collateral Perfusion Prior to Reperfusion..

#### C. Occlusion Location

Several studies report EVT outcomes depend on the location of the occlusion. In general, patients who have occlusions limited to the middle cerebral artery (MCA) have more favorable outcomes than patients who have occlusions of the intracranial internal carotid artery (ICA)<sup>7-10</sup> or

basilar artery.<sup>10</sup> Using pooled data from 4 RCTs (IMS III, SWIFT, STAR, DEFUSE 2), good 90-day functional outcome (mRS $\leq$ 2) was more common in patients who had MCA occlusions than ICA occlusions: 170/389 (44%) vs. 53/161 (33%), respectively;  $P=0.022$  (Fisher's exact test calculated by the author of this review).<sup>11</sup> One reason for this difference may be that a common (~40%) subtype of distal intracranial ICA occlusions (referred to as a "T" occlusion) prevents flow in *both* the ipsilateral MCA and ipsilateral ACA.<sup>12</sup> Because ipsilateral collateral (leptomeningeal) flow from the distal ACA to the distal MCA territory is prevented, a T-subtype of ICA occlusion is likely to result in a larger zone of dense ischemia than MCA occlusion alone. In addition, because of a larger clot burden, more device passes are required to reestablish perfusion (delaying reperfusion), and good reperfusion is less frequent.<sup>12</sup> For these three reasons, outcomes from T-subtype of ICA occlusions are less favorable than other ICA occlusion subtypes,<sup>12</sup> and may largely explain why there is slightly less favorable outcome with intracranial ICA occlusion vs. MCA occlusion overall.

In addition, it is important to differentiate between EVT patients who have occlusions in the anterior vs. the posterior (vertebrobasilar) circulation. In general, EVT outcomes appear to be less favorable with posterior circulation occlusions. For example, compare the results of ESCAPE (anterior circulation, presentation NIHSS=16, post-EVT mTICI 2b-3=72%)<sup>13</sup> with a recent report of patients undergoing posterior circulation EVT (presentation NIHSS=16, post-EVT mTICI 2b-3=79%).<sup>14</sup> Although both presentation NIHSS scores and the degree of reperfusion were comparable between the two studies, both good 90-day functional outcome (mRS $\leq$ 2: 35/95 [37%] vs. 87/164 [53%];  $P=0.0141$ ) and mortality (42/95 [44%] vs. 17/164 [10%];  $P<0.0001$ ) were less favorable in patients who had posterior circulation strokes (Fisher's exact tests calculated by the author of this review). Therefore, when considering the findings of observational reports regarding anesthesia for EVT, it is essential to control for occlusion location (ICA vs. MCA; anterior vs. posterior).

#### D. Collateral Perfusion Prior to Reperfusion

A key determinant of EVT effectiveness is the adequacy of collateral perfusion to the ischemic brain *prior* to establishing reperfusion.<sup>15,16</sup> In the MR CLEAN trial, EVT patients who had moderate to good collaterals (~67%) benefited from EVT, whereas patients who had poor or absent collaterals (~33%) did not.<sup>17</sup> The modification of EVT treatment effect by collateral status was significant ( $P=0.018$ ); see Table S1-1.

**Table S1-1. EVT Effectiveness as a Function of Collateral Grade in MR CLEAN Trial**

	Collateral Perfusion Grade to Ischemic Hemisphere Prior to Reperfusion in 493 EVT Patients			
	0 (Absent): n=26, 5%	1 (Poor): n=136, 28%	2 (Moderate): n=198, 40%	3 (Good): n=133, 27%
Odds Ratio for 90 day mRS $\leq$ 2, EVT vs. Control (95% CI) <sup>a</sup>	<sup>b</sup>	0.8 (0.3-2.3)	2.2 (1.1-4.5)	4.2 (1.9-9.3)

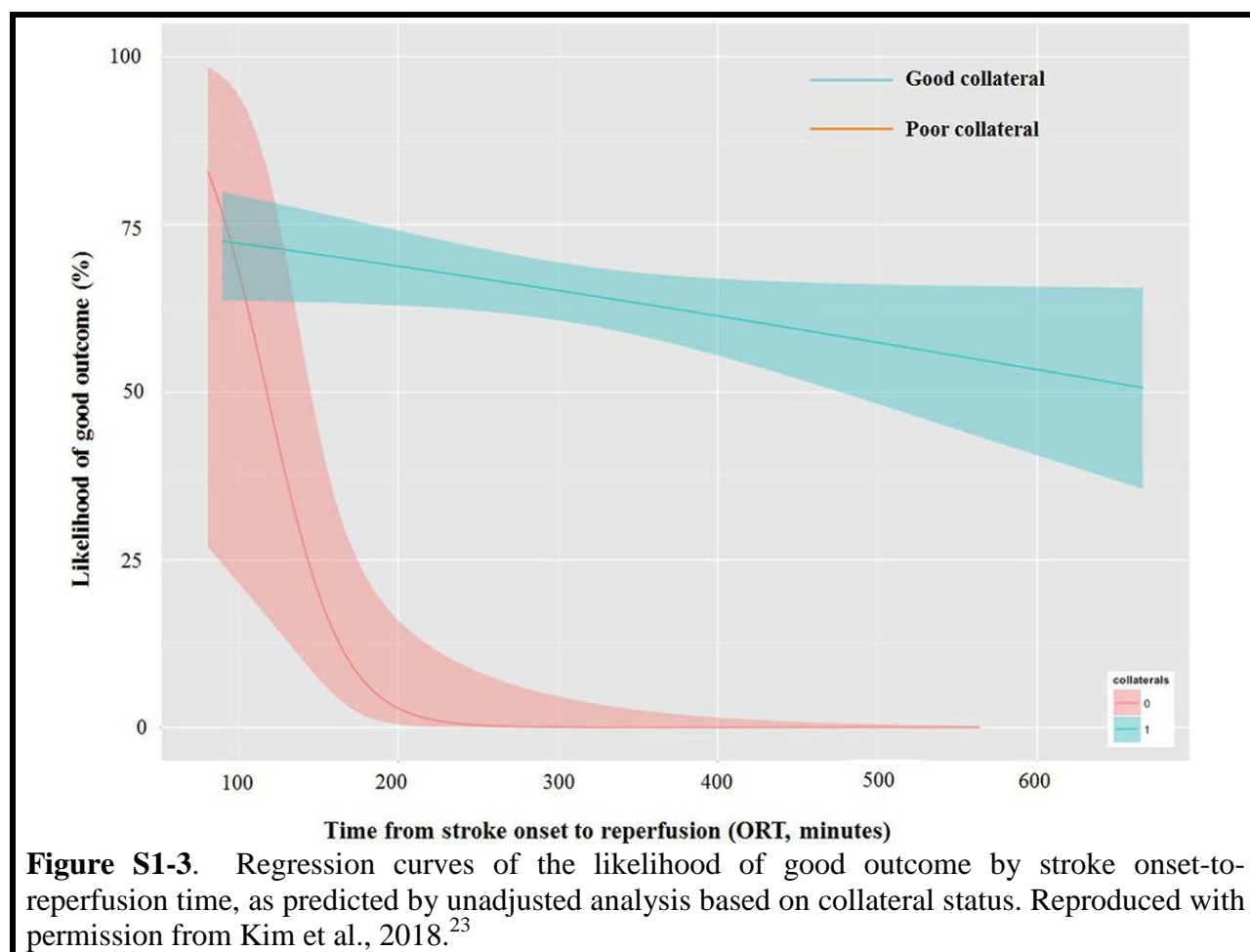
Data abstracted from Berkhemer et al, 2016.<sup>17</sup>

Abbreviations: EVT, endovascular thrombectomy; mRS, modified Rankin Scale.

a. Odds ratios were adjusted for age, presentation National Institutes of Health Stroke Scale score, time to randomization, previous stroke, atrial fibrillation, diabetes mellitus, and presence of internal carotid artery terminus occlusion.

b. No patient in either the EVT or control group who had absent collaterals had  $mRS \leq 2$  at 3 months

The most likely reason is that good collaterals result in a smaller ischemic core and greater cerebral blood flow to the ischemic penumbra.<sup>18,19</sup> For example, in the DEFUSE 2 trial, EVT patients who had good collaterals presented with lesser NIHSS scores and lesser volumes of ischemic tissue.<sup>20</sup> In addition, greater collateral flow to the penumbra slows the progression from cerebral ischemia to cerebral infarction.<sup>18,21,22</sup> As a result, good collaterals afford greater time to achieve reperfusion;<sup>23</sup> see Figure S1-3.



Consistent with the preceding discussion regarding occlusion location,<sup>12</sup> in DEFUSE 2, good collaterals were less common in patients who had intracranial ICA occlusions than patients with MCA occlusions.<sup>20</sup> This observation was also reported by Kim et al.<sup>23</sup> In DEFUSE 2, reperfusion was more successful in patients with good collaterals, even when adjusted for occlusion location.<sup>20</sup> Many other studies have reported EVT reperfusion success is associated with more favorable collateral status,<sup>24-26</sup> although some studies have not observed this.<sup>17</sup> Thus, to the extent it is possible, preventing any decrease in collateral flow prior to reperfusion is imperative.

Several modalities to evaluate collaterals using non-invasive imaging have been developed. The Alberta Stroke Program Early CT Score (ASPECTS) is a CT-based 10-point

scale to assess the magnitude of early ischemic changes in the MCA distribution. One point is subtracted from 10 for any evidence of early ischemic change in each of the defined regions. A normal CT scan receives ASPECTS of 10 points, whereas a score of 0 indicates diffuse involvement throughout the MCA territory. A lesser pre-EVT ASPECTS is associated with less favorable outcome. Numerous studies have established that patients who have less favorable ASPECTS have less favorable collaterals.<sup>17,25-29</sup> Thus, ASPECTS can be considered to be correlate of collateral status. Other, more advanced, imaging methods are used to quantify collateral perfusion to the affected hemisphere, such as multiphase CT angiography, and/or CT- and MR-perfusion imaging.

Less favorable collaterals are associated with increasing patient age<sup>17,30</sup> and history of chronic hypertension.<sup>23,25,27,30,31</sup>

#### E. Adequate Reperfusion

The effectiveness of EVT depends on restoring near normal arterial perfusion throughout the territory of the affected vessels. Post-EVT reperfusion is classified using the modified Thrombolysis in Cerebral Infarction (mTICI) scale.<sup>32</sup> After EVT, mTICI classes 2b or greater are the desired levels of reperfusion: class 2b (> 50%, but less than complete antegrade reperfusion of the target downstream territory); class 2c (>90%, but not complete antegrade reperfusion); class 3 (complete antegrade reperfusion of the target downstream territory with absence of visualized occlusion in all distal branches).<sup>32</sup> When adequate reperfusion is achieved (mTICI class 2b, 2c, or 3; denoted 2b-3) functional outcomes are significantly more favorable than when lesser degrees of reperfusion are achieved (mTICI 2a or less).<sup>23,32-35</sup> As EVT devices have evolved, reperfusion success has increased and procedural times have decreased.<sup>36</sup> Specifically, second generation EVT devices have been shown to result in a greater percentage of patients who have adequate (2b-3) reperfusion and better functional outcomes than first generation devices.<sup>37-40</sup> Therefore, when considering the findings of observational reports regarding anesthesia for EVT, it is essential to control for the EVT devices used and/or whether the devices that were used changed over the time period of the study.

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