Supplement

Sensitivity Analysis

Sensitivity analysis removing the three most heavily-weighted studies was performed, with data presented graphically in Supplementary Figure 2. Sensitivity analysis removed 1 record from each of the following DTN reduction strategies (adjusted values in brackets): Pre-hospital notification systems (SMD = 1.322, 95% CI = 0.738 – 1.906, $\tau^2 = 0.747$), Stroke Tools (SMD = 1.690, 95% CI = 0.178 – 3.203, $\tau^2 = 1.166$), and Combination DTN reduction Initiatives (SMD = 1.850, 95% CI = 1.500 – 2.200, $\tau^2 = 1.289$). Weighted sensitivity analyses did not change the significance or heterogeneity of the primary analyses. Weighted sensitivity analysis did not affect data for other DTN reduction strategies.

Weighted sensitivity analysis altered the meta-analysis such that the DTN reduction rank order changed. Substantial improvement of the Prehospital Notification SMD was attributed to elimination of the most heavily weighted and lowest SMD study within that group, improving Prehospital Notification's relative DTN improvement rank from 5th to 3rd. Similar elimination of a low SMD outlier in the Stroke Tools group resulted in a relative category rank increase from 4th to 2nd in strategy efficacy. The record eliminated from Combination Interventions was slightly above the median for that group, causing a corresponding drop in SMD upon removal with no rank change.

Sensitivity analysis removing Poor-quality studies was performed, with data presented graphically in Supplementary Figure 3. Quality sensitivity analysis removed 14 records total, comprised of 2 from Prompt Data Feedback (SMD = 1.518, 95% CI = 0.625 – 2.410, $\tau^2 = 0.865$), 2 from Non-Target Strategies (SMD = 0.966, 95% CI = 0.616 – 1.315, $\tau^2 = 0.486$), and 10 from Combination DTN reduction Initiatives (SMD = 2.052, 95% CI = 1.635 – 2.469, $\tau^2 = 1.501$). Quality sensitivity analysis improved the relative DTN reduction rank of Prompt Data Feedback from 3rd to 2nd.Quality sensitivity analysis did not change the significance or heterogeneity of the primary analyses. Quality sensitivity analysis did not affect data for other DTN reduction strategies.

Within the combination DTN reduction strategies, the weighted-sensitivity analysis removed one study employing 10 DTN reduction strategies, although no significant relationships found in the raw analysis were affected. Quality-sensitivity analysis removed ten studies from the total 44 combination studies, and introduced a significant relationship between DTN improvement and the inclusion of Pre-Hospital Notification (p=0.022) and Non-Target Strategies (p=0.009) into chosen combinations. No other relationships were different from the raw analysis findings.

Sensitivity analysis did not affect the significance of any other meta-regression characteristic (both Intervention Duration and use of Combination Strategies (vs. Single Strategies) remained significant).

Funnel plots were inspected for evidence of publication bias. Tweedie & Duval (2000) Trim and Fill test using random-effects modeling imputed 29 additional studies in the weighted sensitivity analysis, 38 additional studies in the quality sensitivity analysis, and 35 additional studies in the sensitivity analysis restricted to observational studies. In each sensitivity analysis, the imputed studies were less than that in the raw analysis (51 records imputed in the raw analysis).

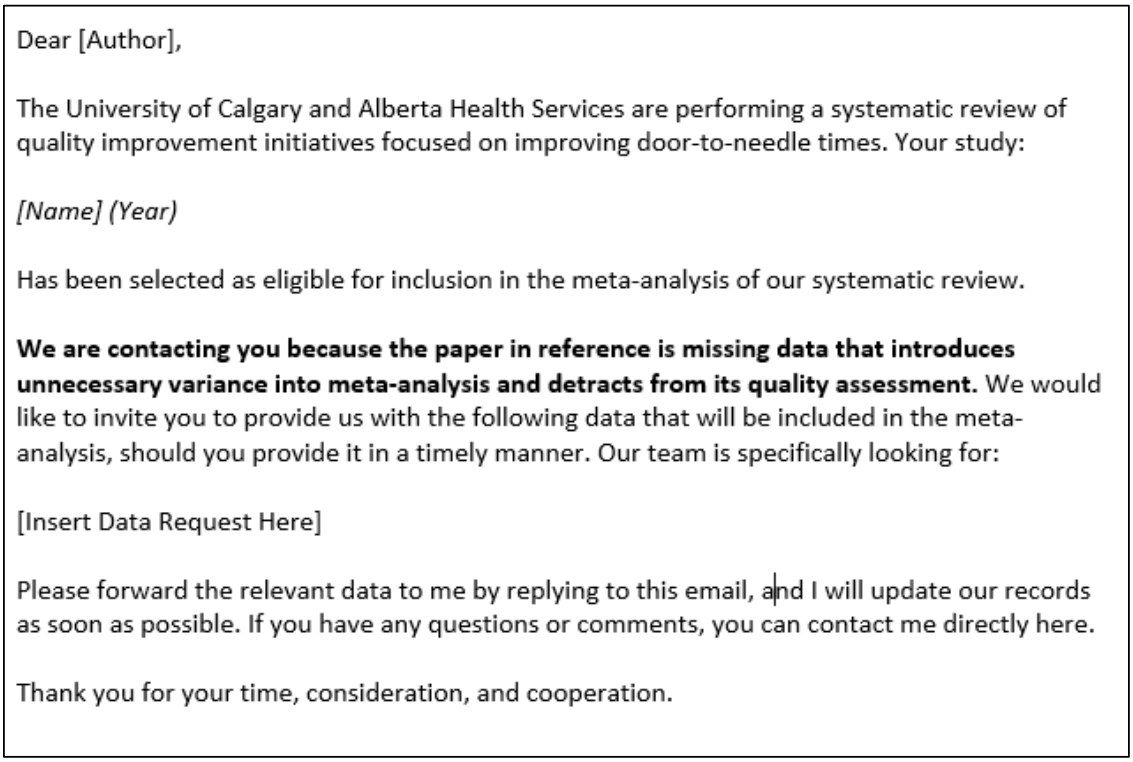
The sensitivity analyses were considered important for the review. For the weighted sensitivity analysis, removal of the studies from analysis resulted in a more balanced representation of DTN improvement associated with each DTN reduction strategy (the three most heavily-weighted studies accounted for 96.3% of the total weight of all studies). Quality sensitivity analysis was important to improve confidence in studies and conclusions.

Subgroup Analysis

Separate meta-analyses were performed for RCT and Observational studies. As only 1 Review-type study was included, no meta-analysis was performed for that study type.

Four RCT-type studies were present in the raw data, however two of these were excluded from meta-analysis within categories as they represented different DTN reduction strategies. Overall pooled SMD for RCT-type studies was (SMD = -0.101, 95% CI = -0.622 – 0.419) (Supplementary Figure 4). Only one study employing Rapid Acquisition and Interpretation of Brain Imaging showed DTN improvement (SMD = 0.591, 95% CI = 0.426 – 0.756), however this study was rated as being “low” quality and would be removed upon sensitivity analysis. Issues with imprecision and risk of bias limit conclusions about relationships between RCT investigations and DTN improvement.

Subgroup meta-analysis of only observational studies pooled 91 records (Supplemental Figure 5). One study representing Rapid Acquisition and Interpretation of Brain Imaging was not included due to RCT study-type, causing the category to be dropped from analysis. Combination Interventions remained the top ranked strategy for reducing DTN, however EMS Prenotification increased in rank from 3rd to 2nd while Prompt Data Feedback dropped in rank from 2nd ^{to} 3rd. No changes (upgrades or downgrades) were made to GRADEPro Certainty findings, except where the DTN reduction strategy was dropped entirely due to lack of studies (n=0 or 1).



Dear [Author],

The University of Calgary and Alberta Health Services are performing a systematic review of quality improvement initiatives focused on improving door-to-needle times. Your study:

[Name] (Year)

Has been selected as eligible for inclusion in the meta-analysis of our systematic review.

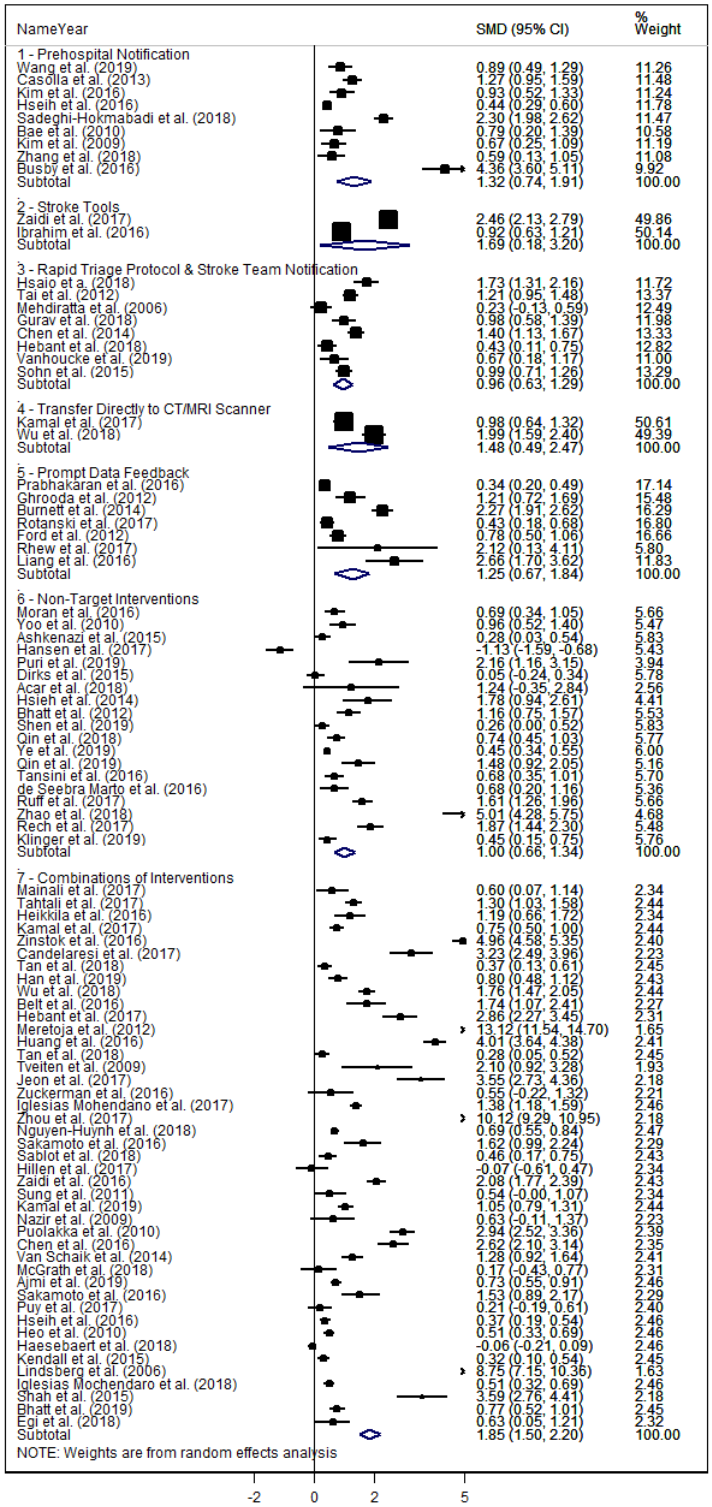
We are contacting you because the paper in reference is missing data that introduces unnecessary variance into meta-analysis and detracts from its quality assessment. We would like to invite you to provide us with the following data that will be included in the meta-analysis, should you provide it in a timely manner. Our team is specifically looking for:

[Insert Data Request Here]

Please forward the relevant data to me by replying to this email, and I will update our records as soon as possible. If you have any questions or comments, you can contact me directly here.

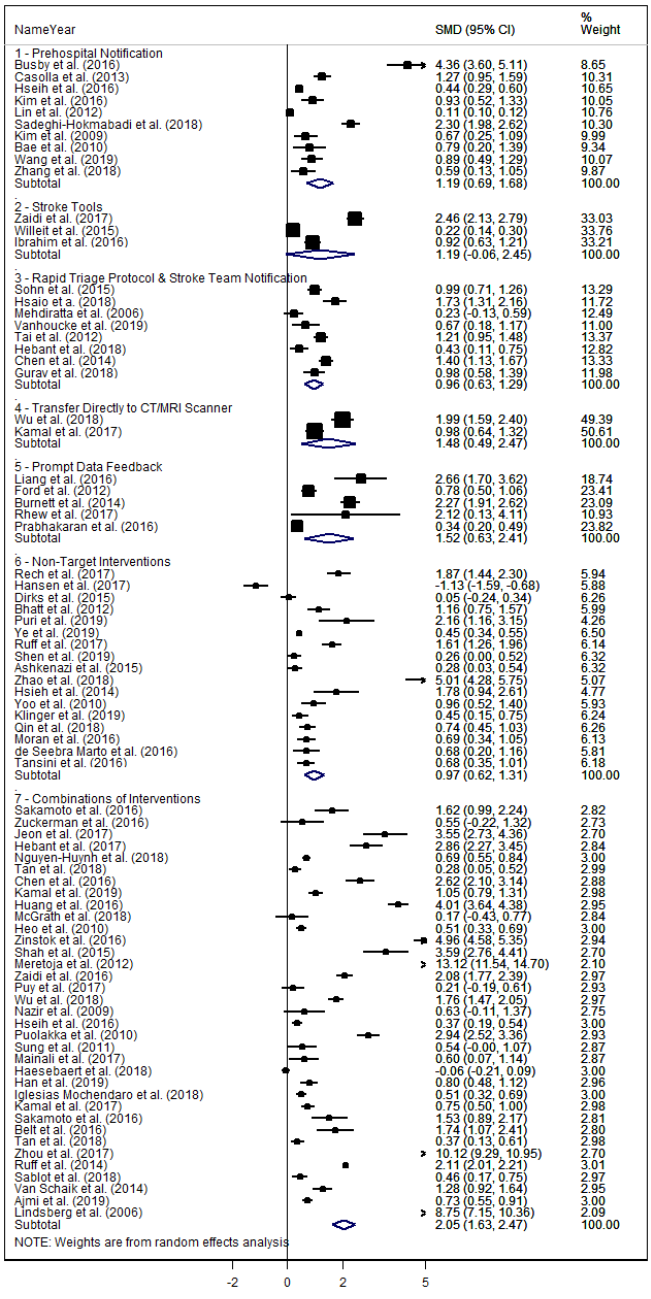
Thank you for your time, consideration, and cooperation.

Supplementary Figure 1. Sample information request form used to contact authors where data was missing.



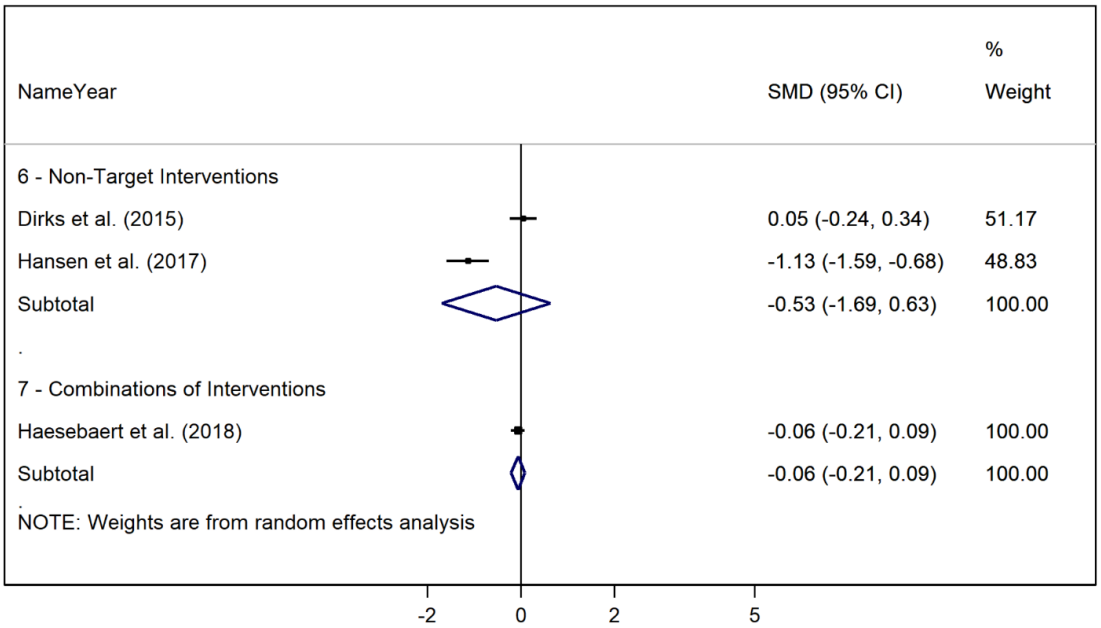
Supplementary Figure 2. Sensitivity analysis: Forest Plot after removal of three

most heavily weighted studies. Standard mean differences (SMD) for studies, 95% confidence intervals (95% CI), and weighting for individual studies and categories of quality improvement door-to-needle time reduction initiatives of acute ischemic stroke management pathways are organized by category.

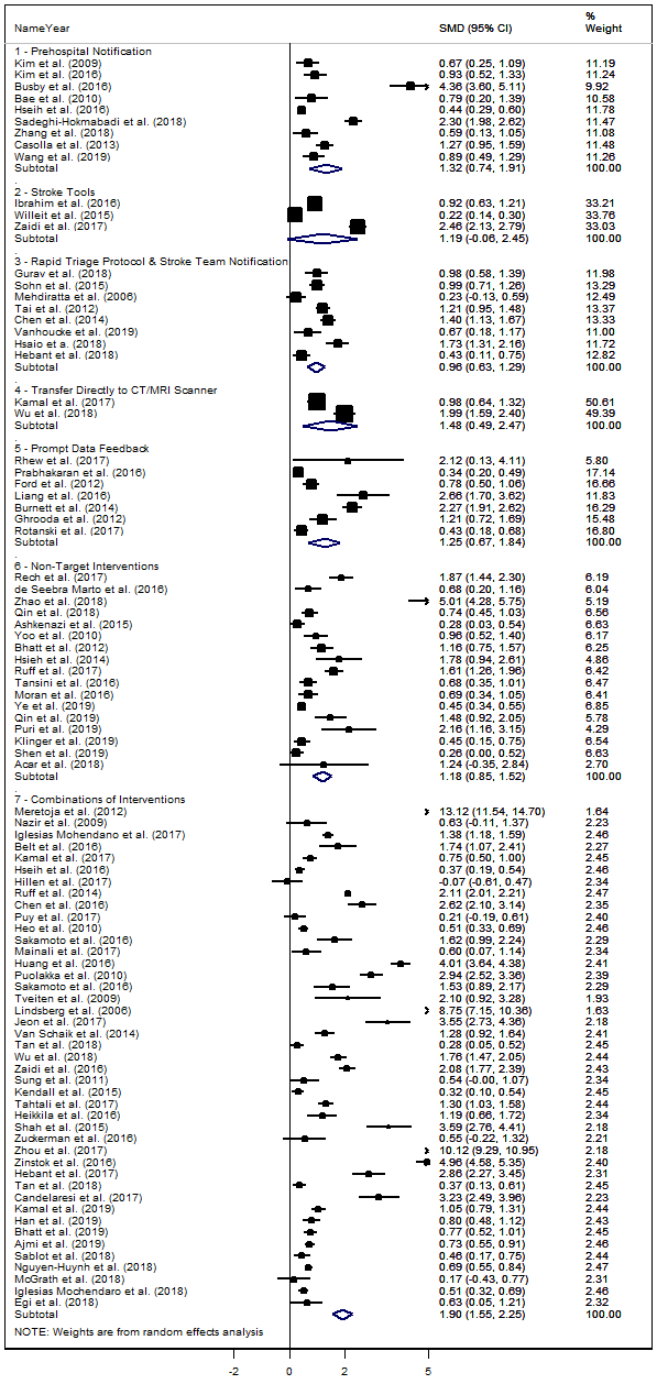


Supplementary Figure 3. Sensitivity analysis: Forest Plot after removal of Poor quality studies, as assessed by the respective NIH quality assessment tool. Standard

mean differences (SMD) for studies, 95% confidence intervals (95% CI), and weighting for individual studies and categories of quality improvement DTN reduction initiatives of acute ischemic stroke management pathways are organized by category.



Supplementary Figure 4. Subgroup analysis: Forest Plot for Randomized Control Studies only. Standard mean differences (SMD) for studies, 95% confidence intervals (95% CI), and weighting for individual studies and categories of quality improvement DTN reduction initiatives of acute ischemic stroke management pathways are organized by category.



Supplementary Figure 5. Subgroup analysis: Forest Plot for Observational studies only. Standard mean differences (SMD) for studies, 95% confidence intervals (95% CI), and weighting for individual studies and categories of quality improvement DTN

reduction initiatives of acute ischemic stroke management pathways are organized by category.

Supplementary Table 1: See attached.

Supplementary Table 2: Individual meta-regression characteristics and output. Duration of door-to-needle time (DTN) reduction protocols and the use of combinations of DTN reduction strategies were found to be significantly associated with DTN reduction.

Variable	Coefficient	Standard Error	T	P > |t|	95% Confidence Interval	
Hospital Type	-0.04	0.426	-0.1	0.924	-0.888	0.806
Physician Type	-0.071	0.286	-0.25	0.804	-0.64	0.497
Registered with a Database	0.513	0.485	1.06	0.294	-0.452	1.479
Stroke Centre Designation (Primary or Comprehensive)	0.199	0.489	0.41	0.684	-0.773	1.172
Study implementation after ECASSIII	-0.22	0.513	-0.43	0.669	-1.242	0.801
Duration of DTN reduction program	0.017	0.006	2.81	0.006	0.005	0.03
Use of Combinations of DTN Strategies (vs. Single)	1	0.405	2.47	0.016	0.193	1.807

DTN = Door-to-Need Time

Supplementary Table 3: See attached.

Supplementary Table 4: See attached.

Supplementary Table 5: See attached.

Supplementary Table 6: GRADEpro evidence profile and quality assessment. Observational studies were given a default certainty of "low", which was upgraded or downgraded with modifications. Rationale for upgrading was based on strong ($1 \geq SMD > 2$) or very strong associations ($SMD \geq 2$).

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality improvement strategies	No quality improvement strategies	Absolute (95% CI)		
Prehospital Notification (assessed with: Door-to-Needle Time Improvements)											
10	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected strong association	250633	123415	SMD **1.22 SD more** (0.683 more to 1.757 more)	⨁⨁◯◯ LOW	CRITICAL
Stroke Tools (assessed with: Door-to-Needle Time Improvements)											
3	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected strong association	1477	1482	SMD **1.193 SD more** (0.064 more to 2.451 more)	⨁⨁◯◯ LOW	CRITICAL
Rapid Triage Protocol and Stroke Team Activation (assessed with: Door-to-Needle Time Improvements)											
8	observational studies	not serious	not serious	not serious	not serious	none	939	555	SMD **0.958 SD more** (0.63 fewer to 1.286 more)	⨁⨁◯◯ LOW	CRITICAL
Transfer Directly to CT / MRI (assessed with: Door-to-Needle Time Improvements)											
2	observational studies	not serious	not serious	not serious	serious [a]	strong association	89	332	SMD **1.48 SD more** (0.489 more to 2.471 more)	⨁⨁◯◯ LOW	CRITICAL
Rapid Acquisition and Interpretation of Imaging (assessed with: Door-to-Needle Time Improvements)											
1	randomised trials	serious[b]	not serious	not serious	not serious	none	372	243	SMD **0.591 SD more** (0.426 more to 0.756 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Rapid Access and Administration of IV tPA (assessed with: Door-to-Needle Time Improvements)											
1	observational studies	not serious	not serious	not serious	serious [a]	very strong association	156	82	SMD **2 SD more** (1.677 more to 2.322 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Prompt Data Feedback (assessed with: Door-to-Needle Time Improvements)											
7	observational studies	not serious	not serious	not serious	not serious	strong association	807	779	SMD **1.225 SD more** (0.666 more to 1.843 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Non-Target Interventions (assessed with: Door-to-Needle Time Improvements)											
19	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected	2196	1673	SMD **0.999 SD more** (0.664 more to 1.335 more)	⨁◯◯◯ VERY LOW	CRITICAL
Combinations of Interventions (assessed with: Door-to-Needle Time Improvements)											
44	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected very strong association	4004	3558	SMD **1.857 SD more** (1.51 more to 2.205 more)	⨁⨁◯◯ LOW	CRITICAL

Rationale for downgrading included Publication Bias, a = Imprecision (Criteria based on number of patients, Very Serious = <200, Serious = 201-399), and b = Inconsistency (Criteria based on heterogeneity as a $\tau 2$ score: Not serious = $0 \leq \tau 2 < 1$; Serious = $1 \leq \tau 2 < 2$; Very Serious = $\tau 2 \geq 2$).

Supplementary Table 7: Relative ranking of Door-to-Needle Time quality improvement strategies presented in observational study types. Ranking is performed according to Standard Mean Differences. Previous rank refers to Table 6, reflecting meta-analysis of all study types.

Standard Mean Difference Improvement	Standard Mean Difference DTN Improvement Rank	Previous Rank
1.903	Combination Strategies	1
1.322	EMS Pre-hospital Notification	3
1.255	Prompt Data Feedback	2
1.183	Non-Target Interventions	4