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Applicability of ENCHANTED trial results to current acute ischemic stroke patients eligible for intravenous thrombolysis in England and Wales: Comparison with the Sentinel Stroke National Audit Programme registry

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Abstract

Background: Randomized controlled trials provide high-level evidence, but the necessity to include selected patients may limit the generalisability of their results.

Methods: Comparisons were made of baseline and outcome data between patients with acute ischemic stroke (AIS) recruited into the alteplase-dose arm of the international, multi-center, Enhanced Control of Hypertension and Thrombolysis Stroke study (ENCHANTED) in the United Kingdom (UK), and alteplase-treated AIS patients registered in the UK Sentinel Stroke National Audit Programme (SSNAP) registry, over the study period June 2012 to October 2015.

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Results: There were 770 AIS patients (41.2% female; mean age 72 years) included in ENCHANTED at sites in England and Wales, which was 19.5% of alteplase-treated AIS patients registered in the SSNAP registry. Trial participants were significantly older, had lower baseline neurological severity, less likely Asian, and had more premorbid symptoms, hypertension and atrial fibrillation. Although ENCHANTED participants had higher rates of symptomatic intracerebral hemorrhage than those in SSNAP, there were no differences in onset-to-treatment time, levels of disability (assessed by the modified Rankin scale) at hospital discharge, and mortality over 90 days between groups.

Conclusions: Despite the high level of participation, equipoise over the dose of alteplase among UK clinician investigators favored the inclusion of older, frailer, milder AIS patients in the ENCHANTED trial.

Clinical trial registration: Clinical Trial Registration-URL: http://www.clinicaltrials.gov. Unique identifier: NCT01422616

Keywords
Acute ischemic stroke, alteplase, thrombolysis, clinical trial, health outcomes

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Introduction

Reperfusion therapy with intravenous (iv) alteplase (or recombinant tissue plasminogen activator) is approved for the treatment of time-selected patients with acute ischemic stroke (AIS),[1] but controversy exists over the most safe and efficacious dose. Concerns over the risk of symptomatic intracerebral hemorrhage (sICH), the most serious complication of iv alteplase, and its affordability in low resource settings, have led to lower doses being used in many Asian AIS patients[2] after a dose of 0.6 mg/kg was approved in Japan. The Enhanced Control of Hypertension and Thrombolysis Stroke study (ENCHANTED) provided the first randomized evaluation of the effectiveness of low-dose (0.6 mg/kg body weight) compared to standard-dose (0.9 mg/kg) iv alteplase in thrombolysis-eligible AIS patients.[3] Although the study was unable to demonstrate non-inferiority between the doses on the primary endpoint of death or disability (modified Rankin scale (mRS) scores 2–6) at 90 days, it clearly showed a reduced risk of sICH with the lower dose of alteplase. The results were translated into the recent United Kingdom (UK) National Clinical Guidelines for stroke as showing:

> A lower risk of ICH and early mortality with the lower dose, without conclusively demonstrating that the doses were of equivalent efficacy, such that there may be circumstances in which the treating physician and/or patient wish to forgo some of the potential disability benefit from standard dose in order to reduce the early risk of ICH through use of the lower dose.[4]

Yet, despite being a pragmatic study with broad eligibility criteria, concerns have been expressed about the generalizability of the ENCHANTED results as, like all clinical trials, it involved selected participants.[5] We wished to assess the degree of selection bias in ENCHANTED by comparing the characteristics and outcomes of AIS patient participants with other alteplase-treated AIS patients at participating sites in England and Wales. The comparison AIS population was derived from the UK Sentinel Stroke National Audit Programme (SSNAP), a prospective, national, continuous stroke register of patients (age $\geq$16 years) in England and Wales, which captures over 90% of all hospital stroke admissions in these countries.[6] Therefore, this post hoc analysis of the ENCHANTED trial will compare: (i) the trial population with the contemporaneous registry population in England and Wales; and (ii) thrombolysis-eligible and treated patients within the trial and within the registry at participating UK centers.

Methods

Design

The ENCHANTED trial is an international, multicenter, prospective, randomized, open-label, blinded-endpoint trial with a 2×2 partial-factorial design to assess the effectiveness of low-versus standard-dose alteplase (the completed arm), and more intensive-versus guideline-recommended control of blood pressure (BP) (the ongoing arm); full details of which are outlined elsewhere.[3,7] These analyses consider the 770 AIS patients who were treated at participating sites in England and Wales between 18 June 2012 and 14 October 2015. Thrombolysis-eligible AIS patients were randomly allocated to treatment with low-dose (0.6 mg/kg; 15% as bolus, 85% as infusion over 1 h) or standard-dose (0.9 mg/kg; 10% as bolus, 90% as

infusion over 1 h) iv alteplase. The study protocol was approved by the appropriate ethics committee at each participating site, and written informed consent was obtained from patients or an appropriate surrogate. Ethical approval for use of relevant SSNAP data was granted by the Ethics and Confidentiality Committee of the National Information Governance Board. Mortality data in the ENCHANTED trial were collected up to 90 days, whereas such data in the SSNAP registry were recorded from two main sources: (i) by the treating clinical team for in-hospital mortality; and (ii) data linkage with the national death register based on the NHS number. Thereafter, 90-day mortality rates were derived from either/ both of these dates of death and the date of hospital admission.

Procedures

Key demographic and clinical characteristics of AIS patients were recorded at the time of enrollment in ENCHANTED, and within a median of 20 days of hospital admission in SSNAP. Stroke severity was measured with the National Institutes of Health stroke scale (NIHSS) at baseline and at 24 h (in those patients receiving thrombolysis). The primary clinical outcome of ENCHANTED was the combined endpoint of death or disability (mRS scores 2–6) at 90 days. However, mRS scores at hospital discharge and mortality within 90 days were used for these analyses as these outcomes were common to both datasets. The safety outcome was sICH, defined according to the National Institute of Neurological Disorders and Stroke (NINDS) criteria (i.e. any ICH associated with neurological deterioration, $\geq$1 point increase in NIHSS scores from baseline or death within 24 to 36 h) was also common to both datasets.[8] The evaluation of sICH was by independent assessors blinded to clinical data, treatment, and date and sequence of scan in the ENCHANTED trial, but was uploaded without adjudication by the treating clinical team for SSNAP registry patients.

Statistical analysis

Key baseline characteristics and 90-day outcomes are summarized as mean (SD), median (interquartile range (IQR)) and percent for normally distributed, skewed, and categorical data, respectively. *P* values were obtained from the Kruskal–Wallis test for continuous data or Chi-squared for categorical data. A two-sided P value < 0.05 was set as the level for statistical significance, and no adjustment was made for multiplicity of testing. All statistical analyses were performed using SAS version 9.3 (SAS institute, Cary, NC, USA).

Role of the funding source

The sponsors had no role in the study design, data collection, data analysis, data interpretation or writing of the report. All authors had full access to the study data. The corresponding author had final responsibility for the decision to submit the paper for publication.

Results

These analyses involve the 770 AIS patients (41.2% female; mean age 72 years) randomized to the alteplase-dose arm of ENCHANTED in England and Wales, which corresponds to 1.9% of 39,835 hospitalized stroke patients correspondingly entered onto the SSNAP registry over respective recruitment time periods at these 30 trial sites. Of 34,932 AIS patients registered in SSNAP, 5937 were potentially eligible for ENCHANTED according to the inclusion and exclusion criteria of the study, and 3957 did receive thrombolysis treatment. Thus, ENCHANTED included approximately one-fifth (19.5%) of all thrombolysis-eligible and treated AIS patients in England and Wales.

Overall, 213,886 stroke patients were registered with SSNAP across 206 sites in England and Wales during the study period. Of these, 187,283 had AIS and 28,800 fulfilled eligibility criteria for ENCHANTED, with 18,109 (62.9%) actually receiving thrombolysis treatment.

Table 1 outlines the key baseline characteristics of the AIS population eligible for ENCHANTED at all SSNAP sites in England and Wales. Compared to AIS patients in the SSNAP registry, ENCHANTED participants were older, less often Asian, had lower mean baseline NIHSS scores, and more pre-morbid symptoms, hypertension and atrial fibrillation. In addition, ENCHANTED participants were less likely to be treated in a stroke unit, although more received ICU care. However, no significant differences were evident in median (IQR) times from the onset of symptoms to treatment between ENCHANTED participants and potentially eligible AIS patients, and between those AIS patients thrombolyzed at ENCHANTED sites (137 [107–180] min) and all SSNAP sites (142 [111–181]). Other key baseline characteristics and data on alteplase use and management over the first seven days among trial participants, as compared to the total ENCHANTED population, are provided in Supplementary Tables S1 and S2, respectively.

Table 2 shows comparable 90-day mortality between ENCHANTED participants, and eligible and thrombolysis-treated SSNAP patients at ENCHANTED participating sites. ENCHANTED participants were significantly less likely to have moderate-to-severe disability (mRS score 4: requiring assistance with daily

Table 1. Selected baseline and management characteristics of ENCHANTED participants compared to eligible and treated patients at ENCHANTED and all SSNAP sites in England and Wales

	SSNAP sites participating in ENCHANTED				All SSNAP sites	
Variable	Trial participants ($n = 770$)	Eligible patients ($n = 5937$)	Eligible/treated patients ($n = 3957$)	P value[§]	Eligible patients ($n = 28,800$)	Eligible/treated patients ($n = 18,109$)
Age, years >80	72 (14) 252/ 770 (32.7)	71 (14) 1751/5937 (29.5)	70 (14) 1143/3957 (28.9)	0.001 0.032	71 (14) 9018/28800 (31.3)	71 (14) 5362/18109 (29.6)
Female	317/ 770 (41.2)	2573/5937 (43.3)	1716/3957 (43.4)	0.26	12596/28800 (43.7)	7914/18109 (43.7)
Non-Asian ethnicity	753/ 770 (97.8)	5724/5937 (96.4)	3811/3957 (96.3)	0.039	28033/28800 (97.3)	17617/18109 (97.3)
NIHSS score[a]	7.0 (5.0–13.0)	7.0 (3.0–14.0)	10.0 (6.0–16.0)		7.0 (3.0–13.0)	10.0 (6.0–16.0)
Onset to treatment, mins	139 (110–177)	N/A	137 (107–180)		N/A	142 (111–181)
Medical history						
Hypertension	471/ 770 (61.2)	3257/5937 (54.9)	2109/3957 (53.3)	<0.0001	15094/28800 (52.4)	9380/18109 (51.8)
Atrial fibrillation[b]	187/ 768 (24.3)	982/5937 (16.5)	679/3957 (17.2)	<0.0001	4847/28800 (16.8)	3135/18109 (17.3)
Diabetes	134/ 770 (17.4)	1049/5937 (17.7)	633/3957 (16.0)	0.34	4752/28800 (16.5)	2811/18109 (15.5)
Antiplatelet therapy[c]	77/187 (41.2)	413/982 (42.1)	299/679 (44.0)	0.56	2187/4847 (45.1)	1462/3135 (46.6)
Anticoagulation[c]	14/187 (7.5)	237/982 (24.1)	125/679 (18.4)	0.0001	1271/4847 (26.2)	641/3135 (20.4)
Pre-morbid symptoms[d]	238/769 (30.9)	1180/5937 (19.9)	750/3957 (19.0)	<0.0001	5129/28800 (17.8)	3034/18109 (16.8)
Management						
Stroke unit	680/763 (89.1)	5856/5937 (98.6)	3926/3957 (99.2)	<0.0001	28269/28800 (98.2)	17962/18109 (99.2)
ICU	20/762 (2.6)	112/5937 (1.9)	95/3957 (2.4)	0.71	812/28800 (2.8)	731/ 18109 (4.0)
Withdrawal care	21/764 (2.7)	105/5937 (1.8)	80/3957 (2.0)	0.20	593/28800 (2.1)	434/18109 (2.4)

Note: Data are presented as *n/N* (%), mean (SD), median (IQR).

[a]Denominator of patients with fully completed NIHSS (not all patients had completed NIHSS at admission recorded in the SSNAP database).

[b]Defined from admission electrocardiogram and known diagnosis (history from primary or secondary health care record or from regular prescribed medication) in SSNAP.

[c]This refers to aspirin (or other antiplatelet) or warfarin therapy on admission in atrial fibrillation patients only.

[d]Pre-morbid mRS of 1.

§*P* values refer to the comparison between ENCHANTED trial participants (column 2), and SSNAP eligible and treated patients (column 4) participating in ENCHANTED.

ENCHANTED : enhanced control of hypertension and thrombolysis stroke study; ICU: intensive care unit; mRS modified Rankin: NIHSS: National Institutes of Health Stroke Scale; SSNAP: sentinel stroke national audit program; SU: stroke unit.

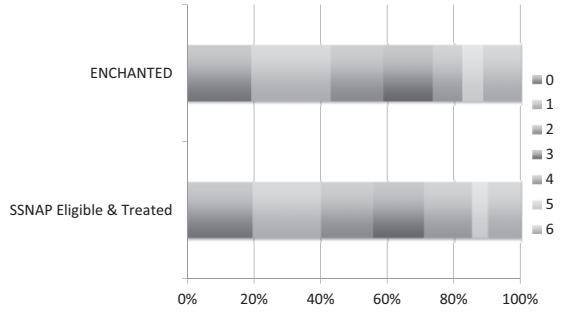
Table 2. Death and disability in ENCHANTED trial participants compared to eligible and treated patients at ENCHANTED and all SSNAP sites in England and Wales[a]

	ENCHANTED participants ($n = 770$)	SSNAP eligible and treated patients at ENCHANTED sites ($n = 3957$)	*P* value
Death or disability (mRS score 2–6)	411/719 (57.2)	2244/3736[b] (60.1)	0.15
Death or disability (mRS score 3–6)	298/719 (41.5)	1660/3736 (44.4)	0.14
Death	83/770 (10.8)	462/3957 (11.7)	0.48
mRS score			
0	137 (19.1)	723 (19.4)	0.85
1	171 (23.8)	769 (20.6)	0.054
2	113 (15.7)	584 (15.6)	0.95
3	106 (14.7)	566 (15.1)	0.78
4	64 (8.9)	535 (14.3)	<0.0001
5	45 (6.3)	181 (4.8)	0.11
6	83 (11.5)	378 (10.1)	0.25

Note: Data are *n*/*N* (%).
[a]mRS data are at hospital separation and mortality data at 90 days for both datasets.
[b]Only available in SSNAP for records locked to discharge.
mRS: modified Rankin scale.

living) at hospital separation as compared to ENCHANTED-eligible and thrombolysis-treated SSNAP patients (8.9% vs. 14.3%; $P < 0.0001$), and they tended to be free of substantial disability (mRS score 1: 23.8 vs. 20.6%; $P = 0.054$). There were no other differences in outcomes (Table 2, Figure 1). Although ENCHANTED participants had significantly higher rates of sICH than ENCHANTED eligible and thrombolysis-treated SSNAP patients (5.1 vs. 3.4%; $P = 0.028$), there was no difference in deaths, and neurological deterioration was significantly lower in the former (6.9 vs. 11.7%; $P < 0.0001$) (Table 3).

Figure 1. Global functional outcome at 90 days in participants of the ENCHANTED trial and in patients with acute ischemic stroke in the SSNAP register who were eligible and treated with intravenous alteplase. The figure shows the raw distribution of scores on the modified Rankin scale (mRS) at 90 days. Scores on the mRS range from 0 to 6, with 0 indicating no symptoms; 1 symptoms without clinical significant disability; 2 slight disability; 3 moderate disability; 4 moderately severe disability; 5 severe disability; and 6, death.



Discussion

Our study compared participants of the multi-center ENCHANTED trial that assessed two different doses of iv alteplase, with the contemporaneous population of hospitalized AIS patients who fulfilled the study eligibility criteria and were thrombolyzed at sites in England and Wales over the study period. The use of a pragmatic design with simple criteria and data collection requirements resulted in ENCHANTED achieving a high level of recruitment, approximately one in five of potentially thrombolysis-eligible AIS patients within the research network. However, these analyses show the trial had a degree of selection bias, reflected in differences in the characteristics and outcomes between AIS patients within and outside the trial. Compared to background AIS patients, trial participants were

Table 3. Symptomatic intracerebral hemorrhage in ENCHANTED participants compared to eligible and treated patients at ENCHANTED and all SSNAP sites in England and Wales

	ENCHANTED participants ($n = 770$)	SSNAP eligible and treated patients at ENCHANTED sites ($n = 3957$)	*P* value
sICH	39/770 (5.1)	136/3957 (3.4)	0.028
Death/neurological deterioration in 24 h	53/770 (6.9)	462/3957 (11.7)	<0.0001

Note: Data are *n*/*N* (%).
sICH: symptomatic intracerebral hemorrhage, defined by National Institute of Health for Neurological Disorders and Stroke criteria.

older, had greater premorbid health problems, and presented at later times after the onset of symptoms, all of which may have contributed to their higher rate of sICH despite presenting with milder neurological severity. These findings are likely to reflect the equipoise of investigators over the AIS patients to be included in the trial to address the research question under investigation.

Randomized controlled trials provide the highest level of quality in evaluating interventions, but they are limited by a degree of external validity, or generalizability, from selection bias associated with the necessity to restrict including patients based on certain inclusion/exclusion criteria. In the era of 'big data', disease registries add value in determining 'real life' efficacy, provision of outcomes on rare diseases, and providing rapid review of the application of treatments as data accumulate.[9] As demonstrated in Scandinavia, registries can complement clinical trial data to monitor and continuously improve health services and patient outcomes.[10]

With its high level of data acquisition and coverage,[6] the SSNAP registry provided an ideal opportunity to compare our trial participants with the near whole, hospitalized, AIS population in England and Wales. In general, though, clinical trials tend to include younger and healthier 'diseased' participants. For example, in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) of ezetimibe compared to simvastatin, patients with an acute coronary syndrome tended to be younger, healthier and to have had more optimal therapies compared to those in the ambulatory cardiology practice-performance registry of the American College of Cardiology.[11] It is apparent that due to their concerns about the risks of sICH, ENCHANTED investigators narrowed their clinical equipoise over the dose of alteplase in favor of older, milder AIS patients, whereas younger AIS patients with more severe deficits tended to be excluded from participation and treated with standard-dose alteplase.

In the United States, participation in the Get-with-the-Guidelines-Stroke registry of the American Heart Association/American Stroke Association has been shown to increase adherence to various performance measures related to patient outcomes, independent of hospital size, teaching status, and geographical location.[12] We were unable to find any significant differences between trial and non-trial AIS patients, in relation to the clinical outcomes of mortality and disability, but our analyses were limited by the patient and site numbers. Another limitation of our study is that it was a post hoc analysis within a single region, which together with open nature of the trial raises the potential for bias and chance associations. Moreover, the ENCHANTED trial used the primary outcome measure at the conventional time point of 90 days post-randomization, but the mRS was only routinely collected at the time of hospital discharge in the SSNAP registry. Thus, as well as variability around the reliability of the mRS outcome measure between studies,[13] there may be concerns about the utility of discharge mRS score in predicting 90-day outcome.[14] In addition, while the key secondary safety outcome of sICH was independently adjudicated for ENCHANTED trial patients, this information was uploaded without adjudication by the treating clinical teams to the SSNAP registry. Finally, the ENCHANTED trial participants were randomized to low versus standard-dose alteplase. It may be considered that a more appropriate comparison was between trial participants randomized to standard-dose and registry patients eligible and treated with thrombolysis. However, Supplementary Table S3 shows similar differences between the trial participants treated with standard-dose compared to those thrombolysis-eligible and treated in the SSNAP registry. Nonetheless, we consider the more relevant comparison between all trial participants and the thrombolysis-eligible and treated registry population to understand better important differences between the trial and registry populations.

In summary, we have shown significant differences between trial and hospital populations in participating English and Welsh centers in the ENCHANTED trial and SSNAP registry, respectively. Importantly,

the trial population tended to be older, and have pre-existing co-morbidities and milder neurological severity, which likely reflect the treating clinician's decision to include them. However, these factors were associated with a higher rate of sICH, although this did not translate into worse mortality or disability compared to the broader AIS population. This study highlights the degree of selection bias underlying clinical trials but also the importance of disease registries in monitoring systems of care and health outcomes.

Contributors

TGR drafted the manuscript for content; TGR, BDB, LP, AGR, and CSA contributed to acquisition of the data; TGR and CSA were responsible for the study concept and co-ordination; BDB, LP and XW were responsible for statistical analyses; TGR, BDB, LP, NS, XW, AGR and CSA were responsible for interpretation of the data. All authors contributed to writing and editing of the manuscript, and approved the final version.

Declaration of conflicting interests

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Ethics approval

The study protocol was approved by the National Research Ethics Service Yorkshire and Humber – Leeds West Committee for UK centers (11/YH/0442), and written informed consent was obtained from the patient or an appropriate surrogate.

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