International Journal of Technology Assessment in Health Care, **20:4** (2004), 537–544.

Influences upon the diffusion of thrombolysis for acute myocardial infarction in England: Case study

Alison Cook
Claire Packer
Andrew Stevens
The University of Birmingham

Tom Quinn
Coventry University

Objectives: To investigate the factors that influenced the adoption and diffusion of thrombolysis in acute myocardial infarction in England and to verify usage data from 1981 to 2001.
Methods: Survey of cardiologists in England using a pre-prepared time line of historical events and a plot of thrombolysis diffusion since 1981. The cardiologists were divided into three groups that were provided with (i) the time line only, (ii) the diffusion curve only, and (iii) the time line and the diffusion curve.
Results: The GISSI and ISIS-2 clinical trials were perceived to have had a significant influence upon the initial diffusion of thrombolysis in England occurring over the 3 years after launch. Other positive influences included the initial listing in the national formulary, the change to administration in emergency departments, the rise in evidence-based medicine, and production of national guidance.
Conclusions: Although it is apparent that the overall influences on adoption and diffusion of thrombolysis were multiple; clinical trials, service developments, and national guidelines all were judged to have played a part. The GISSI and ISIS-2 clinical trials were confirmed as the major influence on initial adoption.

Keywords: Thrombolytic therapy, Myocardial infarction, Diffusion of innovation

In 1912, Herrick (7) attributed myocardial infarction to coronary artery thrombus. Fierce debate followed for the next 68 years until DeWood et al. (4) convincingly demonstrated the primary role of thrombus in 1980. Even before this debate was settled, Fletcher et al. (5) reported the first use of thrombolysis in acute myocardial infarction (AMI) in 1958. Between 1959 and 1988, thirty-three trials comparing intravenous streptokinase with placebo or no therapy were reported. A 1992 retrospective cumulative meta-analysis of these trials significantly favored treatment (15). Indeed, the case for thrombolytic drugs could have been considered proven by 1973, at which time ten studies had been conducted involving the randomization of 2,544 patients (1). To date, in excess of 200,000 patients have been randomized in clinical trials (20). Thrombolytic therapy arguably revolutionized the management of AMI in the 1980s, pushing clinical care more to active myocardial salvage. However, take-up in the United Kingdom has been inhibited by difficulty with timely delivery as well as concerns about contraindications and complications.

Influences upon the adoption and diffusion of medical technologies, such as thrombolysis, are wide ranging and include technical, medical, social, and economic factors (9). In general, three main influences on diffusion have been put forward: actors in the process—involvement of clinicians, patients, and health-care purchasers; structure and environment—health services and commercial market; and

The authors thank the cardiologists involved in the pilot and the main survey. Mr. Peter Stephens of IMS Health kindly provided national data on the supply and use of thrombolytic agents. Claire Packer and Alison Cook are funded by the Department of Health and Andrew Stevens by the National Health Service for England.

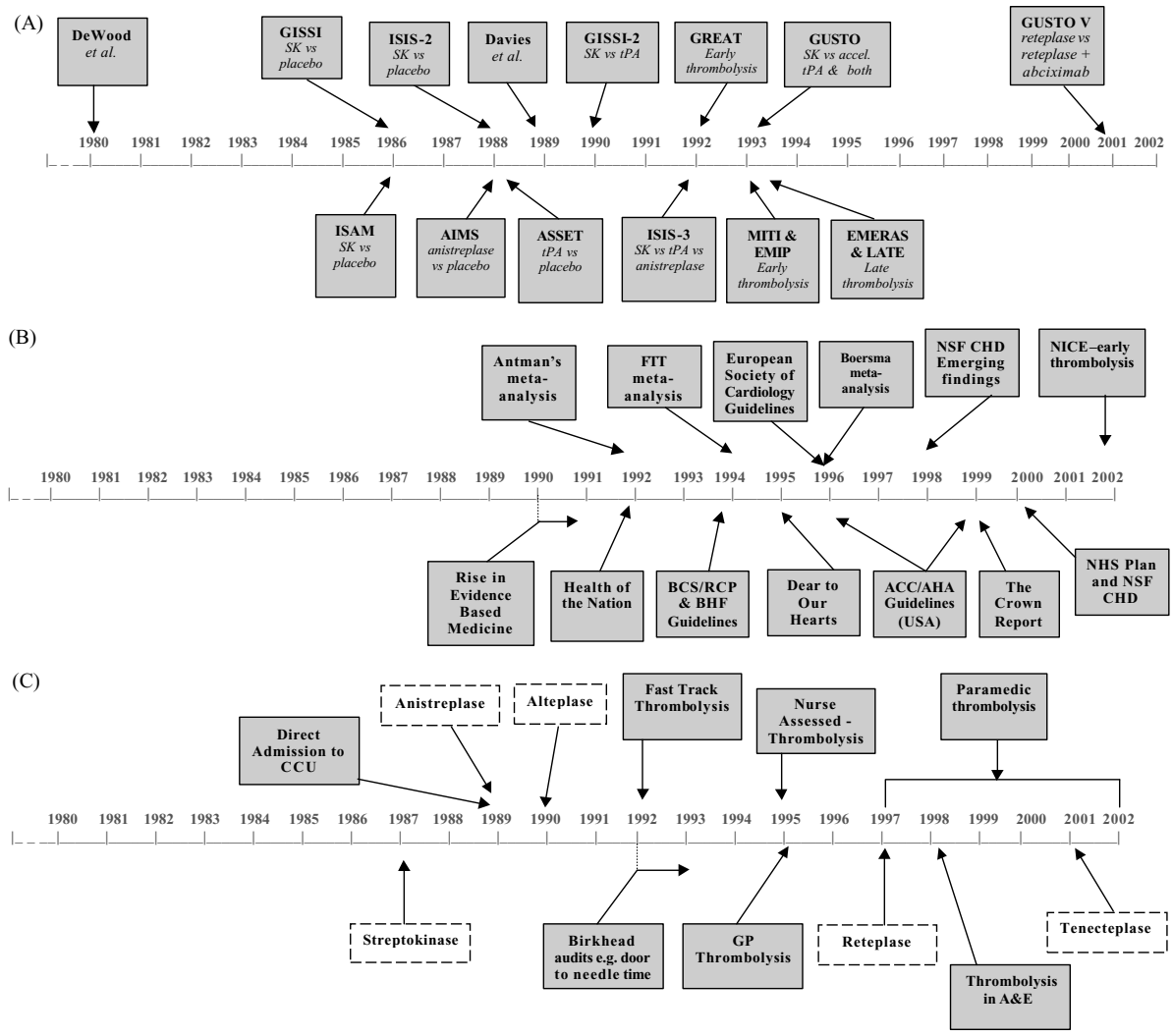

Figure 1. Time lines of the pivotal events in the use of thrombolysis in the treatment of acute myocardial infarction in England. Time lines were developed in collaboration with clinical and policy experts. **A:** Primary research: The trial name/abbreviation or the first author is given in bold. For additional information and references see Box 1. SK, streptokinase; tPA, tissue plasminogen activator; accel. tPA, accelerated tPA. **B:** Secondary research: guidelines, guidance, and reviews. **C:** Process and licensing. Boxes with the dashed border illustrate when the particular thrombolytic first appeared in the British National Formulary (BNF) with a specific indication of myocardial infarction or acute myocardial infarction.

the characteristics of the innovations—technology type and cost (2). Ultimately, the actors involved, notably the medical professionals, are the final influence on adoption within health services. Elucidation of the key influences on medical professionals and other players is not complete, but one means put forward is the publication of key research results, whereas other influences are thought to include evidence-based guidance and guidelines. In the case of thrombolysis described for the Trent region of England from 1987 to 1992, the former were suggested as critical, based principally on the slope of the adoption curve (12).

This study uses a novel means of using three separately briefed groups of senior cardiologists to verify a best estimate of the diffusion curve and investigate the links between both diffusion and the time line events using an analytical method. Time lines that illustrate the events that may have influenced thrombolysis adoption and diffusion in England from 1980 are set out in Figure 1 with supportive text in Box 1. Figure 2 using data supplied by IMS Health, a commercial agency that collects data nationally on drug use and sales, shows a diffusion curve for thrombolytic agents that clearly demonstrates a sharp rise in 1987 to a plateau in the early 1990s with a second rise in the mid 1990s (16).

METHODS

A sample of cardiologists was taken from the specialists registered on an internet directory (www.specialistinfo.com) with supplementary information from the General Medical

https://doi.org/10.1017/S0266462304001473 Published online by Cambridge University Press

Box 1. Explanatory Texts for the Time Lines

ACC/AHA GUIDELINES (USA)—American College of Cardiology/American Heart Association guidelines acute myocardial infarction (AMI) (8;9).
AIMS (APSAC Intervention Mortality Study)—trial of APSAC (anisoylated plasminogen streptokinase activator complex—Anistreplase, Eminase®) versus placebo (1).
ANTMAN'S META-ANALYSIS—meta-analysis of trials of thrombolytics (2;25).
ASSET (Anglo-Scandinavian Study of Early Thrombolysis)—trial of tissue plasminogen activator (tPA) versus placebo (45).
BCS/RCP & BHF GUIDELINES—British Cardiac Society/Royal College of Physicians & British Heart Foundation guidelines for myocardial infarction (MI) (11;44).
BIRKHEAD AUDITS—measurement of delays between onset of symptoms and admission to hospital, and thrombolysis provision and trends in AMI patients. (3–5)
BOERSMA META-ANALYSIS—meta-analysis of timing of thrombolytic therapy (6).
CROWN REPORT—this review highlighted how the legal authority to prescribe could be extended to professional groups other than doctors or dentists (32).
DAVIES—histopathological data (10).
DEAR TO OUR HEARTS—Audit Commission report on the prevention and treatment of CHD for purchasers of health care (12).
DeWOOD—convincingly demonstrated the primary role of thrombus in MI (13).
DIRECT ADMISSION TO CCU (Coronary Care Unit)—admitting patients directly to the CCU can significantly reduce the delay to thrombolysis (7).
EMERAS (Estudio Multicentrico Estretoquinasa Republicas de America del Sur)—trial of late thrombolysis (14).
EMIP (The European Myocardial Infarction Project Group)—trial where patients received either anistreplase before admission, followed by placebo in the hospital, or placebo before admission, followed by anistreplase in the hospital group (35).
EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES—guidelines on the pre-hospital and in-hospital management of acute myocardial infarction (42).
FAST TRACK THROMBOLYSIS—an evaluation of the impact of a fast track triage system for AMI patients (29).
FTT (Fibrinolytic Therapy Trialists') **META-ANALYSIS**—a systematic review concerned with the indications and contraindications to thrombolytic therapy (15).
GISSI (Gruppo italiano per lo studio della streptochinasi nell'infarcto miocardio)—trial of streptokinase versus placebo (18).
GISSI-2 (Gruppo Italiano per lo studio della sopravvivenza nell'infarto miocardico)—trial of streptokinase versus alteplase (17).
GP (General Practitioner)**THROMBOLYSIS**—practicality and safety of thrombolysis when administered by GPs (19). A later survey to GPs suggested they do not wish to give thrombolysis themselves (33).
GREAT (Grampian Region Early Anistreplase Trial)—study of intravenous anistreplase versus placebo given at home (by a GP) or in hospital (16).
GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries)—trial to test the hypothesis that early and sustained infarct-related vessel patency was associated with improved survival in patients with AMI (36;37).
GUSTO V (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries V)—trial of reteplase alone versus reteplase and abciximab (38).
HEALTH OF THE NATION—from 1992–1997 this strategy was at the centre of health policy in England and formed the context for planning of services provided by the NHS (39).
ISAM (Intravenous Streptokinase in Acute Myocardial Infarction)—trial randomising patients presenting within 6 hours after the onset of symptoms to receive one-hour intravenous streptokinase or placebo (40).
ISIS-2 (Second International Study of Infarct Survival)—trial of intravenous streptokinase, oral aspirin, both or neither (22).
ISIS-3 (Third International Study of Infarct Survival)—trial of streptokinase versus t-PA versus anistreplase (23).
LATE (Late Assessment of Thrombolytic Efficacy)—trial of late thrombolysis, 6-24 hours after symptom onset patients were randomised to alteplase or matching placebo (24).
MITI (The Myocardial Infarction Triage and Intervention Trial)—trial of aspirin and alteplase treatment initiated before or after hospital arrival (43).
NHS (National Health Service) **PLAN**—outlines investment in the NHS (41).
NICE (National Institute for Clinical Excellence)—guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction (26).
NSF (National Service Framework) **FOR CHD** (Coronary Heart Disease) **EMERGING FINDINGS**—defines the scope of the NSF for CHD (28).
NSF CHD—sets national standards and defined service models for CHD (27).
NURSE ASSESSED—THROMBOLYSIS—investigated the ability of coronary care nurses to manage patients with suspected AMI, compared with junior medical staff (30).
PARAMEDIC THROMBOLYSIS—reports & discussions exploring place of paramedics in thrombolysis development (20;31;34).
THROMBOLYSIS IN A&E (Accident and Emergency)—questionnaires sent to consultants in UK A&E departments surveying thrombolysis provision and policy (21).

Council's database (www.gmc-uk.org). Cardiologists were selected if they had a work-based address in England and a date of first qualification before 1977. One hundred and thirty-eight study eligible cardiologists were identified, from which 69 (50 percent) were randomly selected and randomized to one of three study groups.

GROUP A: Received the time lines (Figure 1—with supportive text, shown in a shortened form in box 1) and a blank diffusion grid. Respondents were asked to grade each of the thirty-nine events outlined on the time lines according to the effect it had, in their opinion, on the overall diffusion of thrombolytics in the treatment of AMI in England. The grades were as follows: "1", marked increase; "2", increase; "3", little/no effect; "4", decrease; "5", marked decrease; and "X", not familiar or difficult to say.

In addition, this group was asked to sketch a diffusion curve for thrombolysis use from 1980 using the grid while considering their grading responses. On the y-axis,

https://doi.org/10.1017/S0266462304001473 Published online by Cambridge University Press

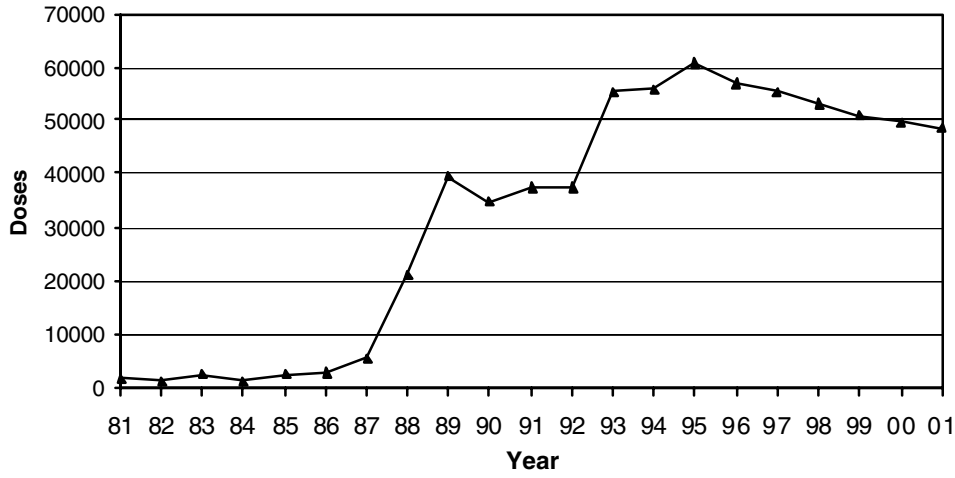

Figure 2. Estimated doses of thrombolytic agents in England. Source: IMS Health.

thrombolytic use was marked from "no usage" at the origin to "maximum usage." Maximum usage was defined as "the numbers of patients presenting to medical services with an AMI."

GROUP B: Received the diffusion curve (Figure 2) and was asked to describe, with no prompts, the events that may explain its shape.

GROUP C: Received the time lines and the diffusion curve. As in Group A, respondents were asked to assign a code to each event considering the diffusion curve.

Respondents in Groups B and C were instructed to make amendments to the shape of the diffusion curve, if they wished, so as to reflect their opinion of thrombolysis use in England.

All documentation was comprehensively piloted before the main study. The questionnaires were sent out to the main sample in 2002. A £50 book token incentive was offered for the return of a completed questionnaire. A week after the deadline, follow-up calls were made to those cardiologists who had not responded. Twenty completed questionnaires were received. On exclusion of the one invalid response, nineteen questionnaires were analyzed—seven in Group A, five in Group B, and seven in Group C.

RESULTS

Group A—Time Line Only

An increase in thrombolytic use during the late 1980s to early 1990s was highlighted in all the sketches from the respondents. Six respondents included a plateau in diffusion after this initial adoption. Three respondents also sketched a second rise in the mid- to late 1990s following this plateau.

We summarized the grades given to each event into two categories—"increase" and "no change." "Increase" represents the number of respondents in Group A that assigned either a "1" (marked increase) or a "2" (increase) to that particular event. "No change" represents the total number of respondents in this group that assigned a "3" (little/no effect) to the event. A very small number assigned either a "4" (decrease) or an "X" (not familiar/difficult to say). No respondent assigned a "5" (marked decrease) to an event. The grading of the events on the time lines is summarized in Table 1 for the respondents in Group A.

The events thought to have increased the use of thrombolysis were as follows:

- from all *seven* respondents: ISIS-2 (Second International Study of Infarct Survival—clinical trial of intravenous streptokinase, oral aspirin, both, or neither), first appearance of streptokinase in the British National Formulary (BNF) for this indication, "fast-track" thrombolysis (i.e., rapid access to cardiac-care team), and thrombolysis in Accident & Emergency (A&E) departments;
- from *six* respondents: GISSI (Gruppo italiano per lo studio della streptochinasi nell'infarcto miocardio—clinical trial of intravenous streptokinase versus placebo), rise in evidence-based medicine, British Cardiac Society/Royal College of Physicians & British Heart Foundation (BCS/RCP & BHF) guidelines for AMI management;
- from *five* respondents: the National Health Service (NHS) Plan & National Service Framework for Coronary Heart Disease (NSF for CHD), direct admission to the cardiac-care unit at the request of the patient's general practitioner, Birkhead audits (measurement of delay between onset of symptoms and thrombolysis provision and proportion of patients receiving thrombolysis within specified time targets).

Group B—Diffusion Curve Only

One respondent in this group amended the diffusion curve provided by sketching a rise in use from 1998 onward. Table 2 sets out the main themes to emerge from the five respondents in Group B.

https://doi.org/10.1017/S0266462304001473 Published online by Cambridge University Press

Table 1. Summary of the 'Increase' and 'No Change' Responses to the Time Lines from Group A (n = 7)

Time line primary research	No. of responses		Time line secondary research	No. of responses		Time line process & licensing	No. of responses	
	Increase	No change		Increase	No change		Increase	No change
DeWood	2	5	Rise in EBM	6	1	Streptokinase in BNF	7	0
GISSI	6	1	Antman meta-analysis	2	5	Direct CCU admission	5	2
ISAM	3	3	Health of the Nation	2	4	Anistreplase in BNF	1	6
ISIS-2	7	0	FTT meta-analysis	4	3	Alteplase in BNF	4	3
AIMS	2	5	BCS/RCP & BHF Guidelines	6	1	Fast Track Thrombolysis	7	0
ASSET	2	5	Dear to our Hearts	0	5	Birkhead audits	5	2
Davies	2	5	European Guidelines	4	3	GP thrombolysis	2	3
GISSI-2	1	6	Boersma meta-analysis	0	6	Nurse assessed thrombolysis	4	2
GREAT	2	5	ACC/AHA Guidelines	3	3	Reteplase in BNF	0	7
ISIS-3	2	5	NSF CHD Emerging Report	3	4	A & E thrombolysis	7	0
GUSTO	4	3	Crown Report	0	4	Paramedic thrombolysis	4	1
MITI & EMIP	2	5	NHS Plan & NSF CHD	5	2	Tenecteplase in BNF	2	5
EMERAS & LATE	3	4	NICE—early thrombolysis	3	4			
GUSTO V	2	5						

ACC, American College of Cardiology; A&E , Accident and Emergency; AHA, American Heart Association; BCS, British Cardiac Society; BHF, British Heart Foundation; BNF, British National Formulary; CCU, Coronary Care Unit; EBM, evidence-based medicine; FTT, Fibrinolytic therapy trialists; GP, General Practitioner; NHS, National Health Servcie; NICE, National Institute for Clinical Excellence; NSF CHD, National Service Framework for Coronary Heart Disease; RCP, Royal College of Physicians.

Table 2. Summary of the Main Themes from Group B

Time period	Number of respondents commenting specifically	Comments that postulate reasons for shape illustrated
1981–1986/7 Marginal increase	4	• Only used by enthusiastic innovators and enthusiasts • Insufficient data as at that time the good quality trials had not been published • Mostly used for non-cardiac indications such as pulmonary embolus
1986/7–1989 Sharp increase	5	• Response to the publication of favourable trials i.e. GISSI-1 and ISIS-2
1989/90–1992 Plateau	4	• Concerns about possible side effects, higher incidence of stroke and doubts/reluctance to use thrombolytics in the elderly
1992/3–1994/5 Increase	4	• Increase in the patients who are eligible through the greater definition of those who could benefit • The drive from audits of pain-to-needle and door-to-needle times
1995–2001 Overall decrease	5	• Falling incidence of myocardial infarcts • The increase of angioplasty as an alternative • A better understanding of risk/benefit, side-effects and contraindications surrounding thrombolysis

Group C—Time Line and Diffusion Curve

No respondent amended the curve. The grading of the events on the time lines is summarized in Table 3 for the respondents in Group C. The events thought to have increased the use of thrombolysis were as follows:

- from *seven* respondents: GISSI, ISIS-2 and the first appearance of streptokinase in the BNF for this indication
- from *six* respondents: thrombolysis in A&E departments
- from *five* respondents: BCS/RCP & BHF guidelines, NHS Plan & NSF for CHD, the first appearance of alteplase in the BNF for this indication, "fast-track" thrombolysis, Birkhead audits, nurse-assessed thrombolysis

DISCUSSION

The construction of retrospective diffusion curves is always problematic because of a variety of data difficulties 16;19). This study, however, gives confidence that the daily dose data for a class of drugs has been acceptably accurate. Only one respondent from the twelve that received the diffusion curve amended it by sketching an increase from 1998 onward (in contrast to the decline illustrated). The respondents in Group A who had no data-driven curve to go on produced a remarkably consistent composite picture, including a plateau or a slowing of diffusion after the initial adoption in most cases. We can say that we have no evidence to suggest that the diffusion curve in Figure 2 does not

https://doi.org/10.1017/S0266462304001473 Published online by Cambridge University Press

Table 3. Summary of the 'Increase' and 'No Change' Responses to the Time lines from Group C ($n = 7$)

Time line primary research	No. of responses		Time line secondary research	No. of responses		Time line process & licensing	No. of responses	
	Increase	No change		Increase	No change		Increase	No change
DeWood	0	6	Rise in EBM	2	5	Streptokinase in BNF	7	0
GISSI	7	0	Antman meta-analysis	0	6	Direct CCU admission	4	3
ISAM	1	5	Health of the Nation	3	3	Anistreplase in BNF	1	6
ISIS-2	7	0	FTT meta-analysis	1	6	Alteplase in BNF	5	2
AIMS	1	6	BCS/RCP & BHF Guidelines	5	2	Fast Track Thrombolysis	5	2
ASSET	3	4	Dear to our Hearts	0	5	Birkhead audits	5	2
Davies	2	5	European Guidelines	2	5	GP thrombolysis	0	7
GISSI-2	1	6	Boersma meta-analysis	0	6	Nurse assessed thrombolysis	5	2
GREAT	1	5	ACC/AHA Guidelines	1	5	Reteplase in BNF	1	6
ISIS-3	4	3	NSF CHD Emerging Report	0	7	A & E thrombolysis	6	1
GUSTO	4	3	Crown Report	0	5	Paramedic thrombolysis	0	7
MITI & EMIP	1	6	NHS Plan & NSF CHD	5	2	Tenecteplase in BNF	1	6
EMERAS & LATE	2	4	NICE—early thrombolysis	2	4			
GUSTO V	1	6						

Abbreviations as in Table 1.

represent the adoption and diffusion pattern of thrombolytic agents in England.

The clinical trials GISSI (6) and ISIS-2 (11) were deemed to be key influences upon thrombolysis diffusion in this study. It is worth noting that, while grading ISIS-2, respondents may have been considering this trial's interim results that were published in 1987 (10). It is possible that this publication heightened awareness of the trial before the main results were published in 1988. Previously, evidence from trials has been demonstrated to have a variable impact on cardiology practice, although rigorously conducted, highly relevant randomized control trials published in high impact journals have been shown to result in a measurable influence on clinical behavior (3;13;14).

To our respondents, the influence of service developments, for example, A&E thrombolysis and fast-track thrombolysis and the drive for improved performance initiated by the clinical audit were also important (8;17). National guidelines were influential but were lower order compared with clinical trials. Indeed, concern has been expressed around implementation costs of cardiology guidelines in the United Kingdom (18).

The novel method outlined here represents a viable approach to the investigation of influences upon technology diffusion. Clear themes emerged from the study groups, and although all three had differing data sets, they all came to the same broad conclusions. However, it would require several further case studies with varying technologies before any generalizable statements could be inferred about diffusion influences from the perspective of clinicians. In the case study presented here, we believe that our sample was large enough to ensure that we have probably heard most of the perceptions that might be important.

Although it is apparent that the overall influences on adoption and diffusion of thrombolysis were multiple, clinical trials, service developments and national guidelines all were judged to have played a part. The GISSI and ISIS-2 clinical trials were confirmed as the major influence on initial adoption.

Policy Implications

This study challenges the assumption that guidelines/guidance are an overriding influence in the directing of clinician behavior. The power of the landmark clinical trial is clearly critical in this example. It will be interesting to observe whether this continues to be the case in the United Kingdom, where compulsory guidance is issued by the National Institute for Clinical Excellence (NICE). Further such research could inform policy-makers, who wish to influence the adoption of clinically effective health technology.

REFERENCES

1. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomised control trials and recommendations of clinical experts. *JAMA*. 1992;268:240-248.
2. Bonnair A, Persson J. Innovation and diffusion of health care technologies. In: Szcepura A, Kankaanpää J, eds. *Assessment of health care technologies*. Chichester: Wiley; 1996:17-28.
3. Col NF, McLaughlin TJ, Soumerai SB, et al. The impact of clinical trials on the use of medications for acute myocardial infarction. *Arch Intern Med*. 1996;156:54-60.
4. DeWood MD, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med*. 1980;303:897-902.
5. Fletcher AP, Alkjaersig N, Smyrniotis FE, Sherry S. The treatment of patients suffering from early myocardial infarction with massive and prolonged streptokinase therapy. *Transcripts Assoc Am Physicians*. 1958;71:287-296.
6. Gruppo italiano per lo studio della streptochinasi nell'infarcto miocardio (GISSI). Effectiveness of intravenous thrombolytic

therapy in acute myocardial infarction. *Lancet*. 1986;i:397-402.
7. Herrick JB. Clinical features of sudden obstruction of coronary arteries. *JAMA*. 1912;59:2015-2020.
8. Hood S, Birnie D, Swan L, Hills WS. Questionnaire survey of thrombolytic treatment in accident and emergency departments in the United Kingdom. *BMJ*. 1998;316:274.
9. Hummel MJ, van Rossum W, Verkerke GJ, Rakhorst G. Assessing medical technologies in development. A new paradigm of medical technology assessment. *Int J Technol Ass Health Care*. 2000;16:1214-1219.
10. ISIS Steering Committee. Intravenous streptokinase given within 0-4 hours of onset of myocardial infraction reduced mortality in ISIS-2. *Lancet*. 1987;i:502.
11. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;ii:349-60.
12. Ketley D, Woods KL. Impact of clinical trials in clinical practice: Example of thrombolysis for acute myocardial infarction. *Lancet*. 1993;342:891-894.
13. Ketley D. *Beyond clinical trials: Translation of evidence into practice in the treatment of acute myocardial infarction* [dissertation]. Leicester University; 1996.
14. Lamas GA, Peeffer MA, Hamm P, et al. for the SAVE investigators. Do the results of randomised clinical trials of cardiovascular drugs influence medical practice. *N Engl J Med*. 1992;327:241-247.
15. Lau J, Antman E, Jimenez-Silva J, et al. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med*. 1992;327:248-254.
16. Packer C, Stevens A, Cook A, Raftery J. Diffusion of Thrombolysis for acute myocardial infarction from 1981 to 2000 in England: Trend analysis and comparison with need. *Int J Technol. Assess Health Care*. 2004; 20:531-536.
17. Pell ACH, Miller HC, Robertson CE, Fox KAA. Effect of 'fast track' admission for acute myocardial infarction on delay to thrombolysis. *BMJ*. 1992;304:83-87.
18. Petch MC. Heart disease, guidelines, regulations, and the law. *Heart*. 2002;87:472-479.
19. Raftery J, Stevens A, Roderick P. The potential use of routine datasets in health technology assessment. In: Stevens A, Abrams K, Brazier J, Fitzpatrick R, Lilford R, eds. *The advanced handbook of methods in evidence based healthcare*. London: Sage Publications; 2001:136-148.
20. White HD, Van de Werf F. Thrombolysis for acute myocardial infarction. *Circulation*. 1998;97:1632-1646.

REFERENCES FOR BOX 1

1. AIMS Trial Study Group. Effects of intravenous APSAC on mortality after acute myocardial infarction: Preliminary report of a placebo-controlled clinical trial. *Lancet*. 1988;i:545-549.
2. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomised control trials and recommendations of clinical experts. *JAMA*. 1992;268:240-248.
3. Birkhead JS on behalf of the joint committee of the British Cardiac Society and a cardiology committee of Royal College of Physicians of London. Time delays in provision of thrombolytic treatment in six district hospitals. *BMJ*. 1992;305:445-448.
4. Birkhead JS on behalf of the Myocardial Infarction Audit Group. Thrombolytic treatment for myocardial infarction: An examination of practice in 39 UK hospitals. *Heart*. 1997;78:28-33.
5. Birkhead JS on behalf of the Myocardial Infraction Audit Group. Trends in the provision of thrombolytic treatment between 1993 and 1997. *Heart*. 1999;82:438-442.
6. Boersma E, Maas ACP, Deckers JW, Simoons ML. Early thrombolytic therapy in acute myocardial infarction: Reappraisal of the golden hour. *Lancet*. 1996;348:771-775.
7. Burns JMA, Hogg KJ, Rae AP, Hillis WS, Dunn FG. Impact of a policy of direct admission to a coronary care unit on use of thrombolytic treatment. *Br Heart J*. 1989;61:322-325.
8. Committee on Management of Acute Myocardial Infarction. ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 1996;28:1328-1428.
9. Committee on Management of Acute Myocardial Infarction. 1999 Update: *ACC/AHA guidelines for the management of patients with acute myocardial infraction*. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Available at: www.acc.org
10. Davies MJ, Bland JM, Hangartner JRW, Angelini A, Thomas AC. Factors influencing the presence or absence of acute coronary artery thrombi in sudden ischaemic death. *Eur Heart J*. 1989;10:203-208.
11. De Bono DP, Hopkins A. The management of acute myocardial infarction: Guidelines and audit standards. Report of a workshop of the Joint Audit Committee of the British Cardiac Society and the Royal College of Physicians. *J R Coll Physicians*. 1994;28:312-317.
12. Dear to Our Hearts? *Commissioning services for the treatment and prevention of coronary heart disease*. Audit Commission; 1995.
13. DeWood MD, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med*. 1980;303:897-902.
14. EMERAS (Estudio Multicentrico Estretoquinasa Republicas de America del Sur) Collaborative Group. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. *Lancet*. 1993;342:767-772.
15. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview or early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet*. 1994;343:311-322.
16. GREAT Group. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian region early anistreplase trial. *BMJ*. 1992;305:548-553.
17. Gruppo Italiano per lo studio della sopravvivenza nell'infarto miocardico. GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet*. 1990;336:66-71.
18. Gruppo italiano per lo studio della streptochinasi nell'infarcto miocardio (GISSI). Effectiveness of intravenous thrombolytic therapy in acute myocardial infarction. *Lancet*. 1986;i:397-402.

19. Hannaford P, Vincent R, Ferry S *et al*. Assessment of the practicality and safety of thrombolysis with anistreplase given by general practitioners. *Br J Gen Pract*. 1995;45:175-179.
20. Harrop SN. Can paramedics help accelerate thrombolysis in myocardial infarction*? Prehosp Immediate Care*. 1998;2:18-24.
21. Hood S, Birnie D, Swan L, Hills WS. Questionnaire survey of thrombolytic treatment in accident and emergency departments in the United Kingdom. *BMJ*. 1998;316:274.
22. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;ii:349-360.
23. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: A randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet*. 1992;339:753-770.
24. LATE Study Group. Late assessment of thrombolytic efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. *Lancet*. 1993;342:759-766.
25. Lau J, Antman E, Jimenez-Silva J, et al. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med*. 1992;327:248-254.
26. National Institute for Clinical Excellence. *Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction*. London: National Institute for Clinical Excellence; 2002.
27. National Service Framework for Coronary Heart Disease. London: Department of Health; 2000. Available at: www.doh.gov.uk/nsf/coronary.htm
28. National Service Framework on Coronary Heart Disease—*Emerging findings report*. London: Department of Health; 1998. Available at: www.doh.gov.uk/pub/docs/doh/coronary.pdf
29. Pell ACH, Miller HC, Robertson CE, Fox KAA. Effect of 'fast track' admission for acute myocardial infarction on delay to thrombolysis. *BMJ*. 1992;304:83-87.
30. Quinn T. Can nurses safely assess suitability for thrombolytic therapy? A pilot study. *Intensive Crit Care Nurs*. 1995;11:126-129.
31. Rawles J. Pre-hospital coronary care. *Prehosp Immediate Care*. 1997;1:12-18.
32. *Review of prescribing, supply and administration of medicines*. The Crown Report. London: Department of Health; 1999. Available at: www.doh.gov.uk/prescrib.htm
33. Round A, Marshall AJ. Survey of general practitioners' prehospital management of suspected acute myocardial infarction. *BMJ*. 1994;309:375-376.
34. Rowley JM, Mounser P, Harrison EA, Skene AM, Hampton JR. Management of myocardial infarction: Implications for current policy derived from the Nottingham Heart Attack Register. *Br Heart J*. 1998;67:255-262.
35. The European Myocardial Infarction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *N Engl J Med*. 1993;329:383-389.
36. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med*. 1993;329:1615-1622.
37. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673-682.
38. The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinoloytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: The GUSTO V randomised trial. *Lancet*. 2001;357:1905-1914.
39. *The health of the nation: A strategy for health in England*. London: HMSO; 1992.
40. The I.S.A.M Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M). Mortality, morbidity, and infarct size at 21 days. *N Engl J Med*. 1986;314:1465-1471.
41. *The NHS plan*. London: HMSO; 2000. Available at: www.nhs.uk/nationalplan
42. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Acute myocardial infarction: Pre-hospital and in-hospital management. *Eur Heart J*. 1996;17:43-63.
43. Weaver WD, Cerqueira M, Hallstrom AP, et al. Prehospital-initiated vs hospital-initiated thrombolytic therapy. The myocardial infarction triage and intervention trial. *JAMA*. 1993;270:1211-1216.
44. Weston CFM, Penny WJ, Julian DG. Guidelines for the early management of patients with myocardial infarction. *BMJ*. 1994;308:767-771.
45. Wilcox RG, Von der Lippe G, Olsson CG, et al. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet*. 1988;2:525-530.