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Diffusion of thrombolysis for acute myocardial infarction from 1981 to 2000 in England: Trend analysis and comparison with need

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Objectives: To describe the adoption and take up of thrombolytic agents for acute myocardial infarction since 1980 in England and compare use with the estimated ceiling of need.
Methods: Data on national sales and use of thrombolysis since 1980 (supplied by IMS Health) was used to draw an adoption and diffusion curve. The epidemiological ceiling of acute myocardial infarction, from hospital activity statistics, was modified to an estimated clinical need by accounting for diagnostic difficulty and contraindications using information from published surveys of thrombolysis use in the United Kingdom.
Results: There was a rapid uptake of thrombolytic agents in the first 2 years after availability in 1987, then a plateau, followed by a rise to a peak use in 1995. The shortfall in doses resulting from the difference between estimated ceiling of clinical need and doses purchased and provided in the 14 years since availability is estimated as 167,800 (95 percent confidence range 94,000 to 241,700).
Conclusions: Although there was a rapid initial uptake of thrombolysis in England, usage took 8 years to reach the ceiling of clinical need of 65 percent of patients with acute myocardial infarction, with many patients missing the opportunity to benefit. Monitoring of uptake of innovations known to be cost-effective is required to identify those developments that need additional stimulus for change to ensure that patients do not miss out on the opportunity to benefit.

Keywords: Myocardial infarction, Thrombolytic therapy, Diffusion of innovation, Health services need and demand

Although the incidence of acute myocardial infarction (AMI) has declined over the past decade, it remains a major cause of morbidity and mortality in England. The management and secondary prevention of myocardial infarction has also changed considerably with the role of β-blockers, aspirin, and angiotensin-converting enzyme inhibitors (ACE inhibitors) becoming clearer and the survival benefits of early thrombolysis for patients who have typical electrocardiogram (ECG) changes well established. Even though evidence of effectiveness has been strong since the mid to late 1980s, and arguably much earlier, commentators agree that the use of thrombolytic agents in England has been patchy and generally assumed not to reach all those who could benefit (1;26). Indeed, even 14 years after availability, early access to thrombolysis is still being encouraged and supported by national

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guidance and audit (10;20). A major difficulty in evaluating the use of thrombolytic agents in England is the absence of a national system for collecting information about the use of pharmaceuticals in hospital services.

We believe that it is important not only to evaluate whether thrombolysis is now reaching all those who could benefit but also to know how quickly this has been achieved. There are many published cross-sectional surveys and audits of the use of thrombolysis in the United Kingdom, the majority of which are snapshots of a moment in time, occasionally repeated after a change in service delivery, and restricted to a specific region, group of hospitals, or single sites. A recent exception is the Myocardial Infarction National Audit Project (MINAP) that started collecting data in 2000 on the speed of administration of thrombolysis to patients with acute myocardial infarction (AMI) (2). MINAP is collecting data on a voluntary basis in an increasing number of acute hospitals in the United Kingdom, but not yet with total coverage. Excluding studies reporting eligibility for entry into clinical trials, there are eleven studies undertaken in the United Kingdom that provide sufficient information to estimate the potential ceiling of clinical need for thrombolysis, given ideal circumstances, at 65.3 percent with a 95 percent confidence interval of 59.6 percent to 71.4 percent. This estimate takes into account the proportion of patients with a nondiagnostic ECG or other diagnostic difficulty at presentation and contraindications to therapy (3;6,7;11–13;16;19;21;22;24;25). We describe here the adoption and diffusion of thrombolytic agents for acute myocardial infarction over the past 20 years in England and compare usage data with the estimated ceiling of clinical need for thrombolysis. Although historical diffusion data can be hard to produce and analyze, insights gained may be applicable to the introduction of future innovation of this kind into health services.

METHODS

Thrombolysis Use

There are four thrombolytic agents currently licensed for use in the United Kingdom: streptokinase has been available for acute myocardial infarction since 1987, alteplase from late 1988, reteplase from 1997, and tenecteplase from 2001. Anistreplase was also licensed during this time but was withdrawn in 2000. By using past editions of the British National Formulary (BNF), we identified and contacted each drug company known to have marketed a thrombolytic agent for myocardial infarction in the United Kingdom (UK) at any point since licensing with a request for data on sales (5). We also approached IMS Health, a commercial agency that collects data nationally and internationally on drug use and sales. We contacted the chief pharmaceutical officer of each health region in England to find any regional audits or other data collections. We also talked to key clinicians and researchers in the field to identify any other relevant data sources.

The pharmaceutical companies were unable to supply sufficient data on sales because of the time lapse since initial launch, company mergers and acquisitions, and the numerous changes to the marketing license holders over time. IMS Health provided data on drug sales in England from 1981 to 1996 and on administration to patients in England from 1995 to 2001. Information was found in two health regions—the West Midlands (West Midlands Regional Pharmacy Service) and Trent (17;18).

Data identified and supplied were converted to the equivalent number of single doses using the World Health Organization Collaborating Center for Drug Statistics Methodology tables of daily defined doses (DDDs). Data from the West Midlands were presented in the form of the amount of money spent on thrombolytic agents. This amount was converted to estimated doses in England using the cost per dose in the relevant year's BNF and mid-year population estimates. As patients with myocardial infarction receive only one dose or infusion of a thrombolytic agent during each episode, we assumed that the number of doses sold or administered to patients in any 1 year is equivalent to the number of episodes of infarction.

Need for Thrombolysis

We extracted data on the number of hospital admissions for acute myocardial infarction in England from the Hospital In-Patient Enquiry (HIPE, 1981 to 1985: ICD9 410) and Hospital Episode Statistics data (HES, 1990 to 2001: ICD9 4100 and ICD10 I21X and I22X) (9). Data from the HIPE are based on discharges from hospital. We used admission episodes (the first spell of in-patient treatment) from the HES data sets. We estimated data for the missing years, arising from a change in the data collection system in England, using a straight line between 1985 and 1990. By using the hospital activity data and the estimated number of doses of thrombolytic agents, we estimated the ratio of thrombolysis use to patients with acute myocardial infarction admitted to hospital for each year.

RESULTS

Thrombolysis Use

Figure 1 illustrates the diffusion curve in patient doses for thrombolytic agents in England since 1981. The curve shows a low level of use during the mid 1980s with a rapid increase in 1988 and 1989. There is a plateau from 1989 to 1992 followed by an increase to a peak in 1995. From 1995, there is a slow decline in the number of doses purchased. This reduction occurred principally in streptokinase. We found no differences in the data collection methods in 1990 to 1992 to explain the plateau.

Triangulation of national data with regional data from West Midlands and Trent shows some consistency during the rapid increase of 1988 and 1989 as well as the decline

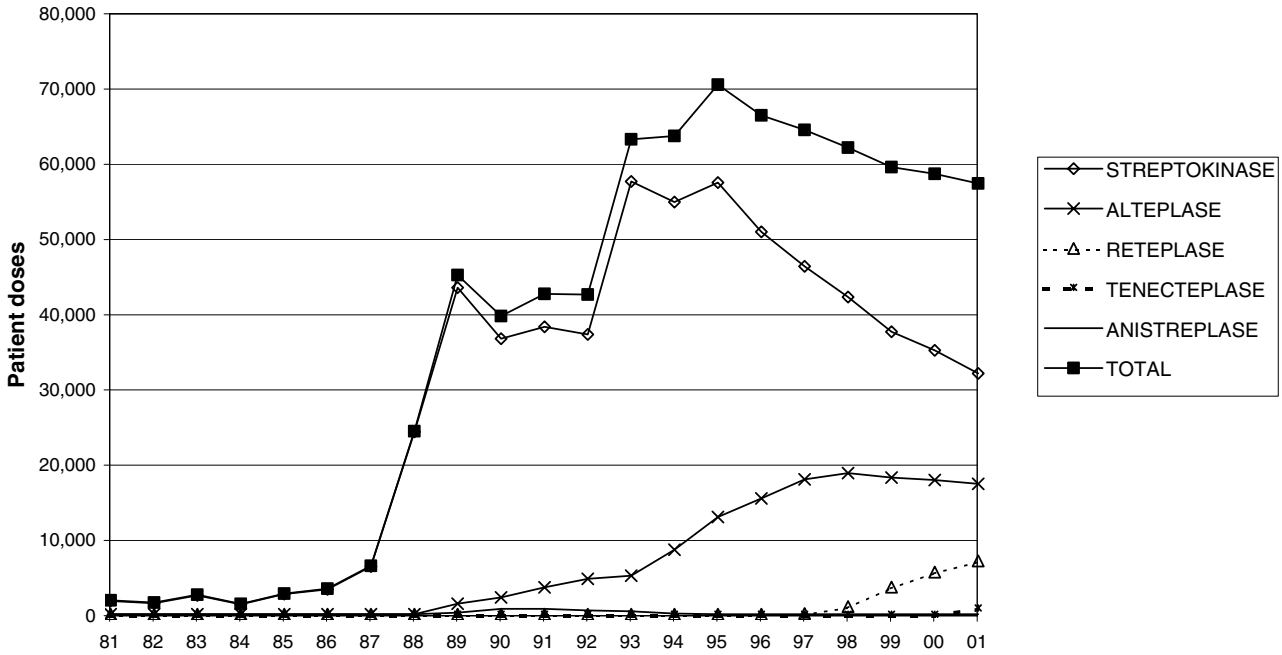

Figure 1. Estimated patient doses of thrombolysis purchased in England (by individual drugs). Source: IMS Health

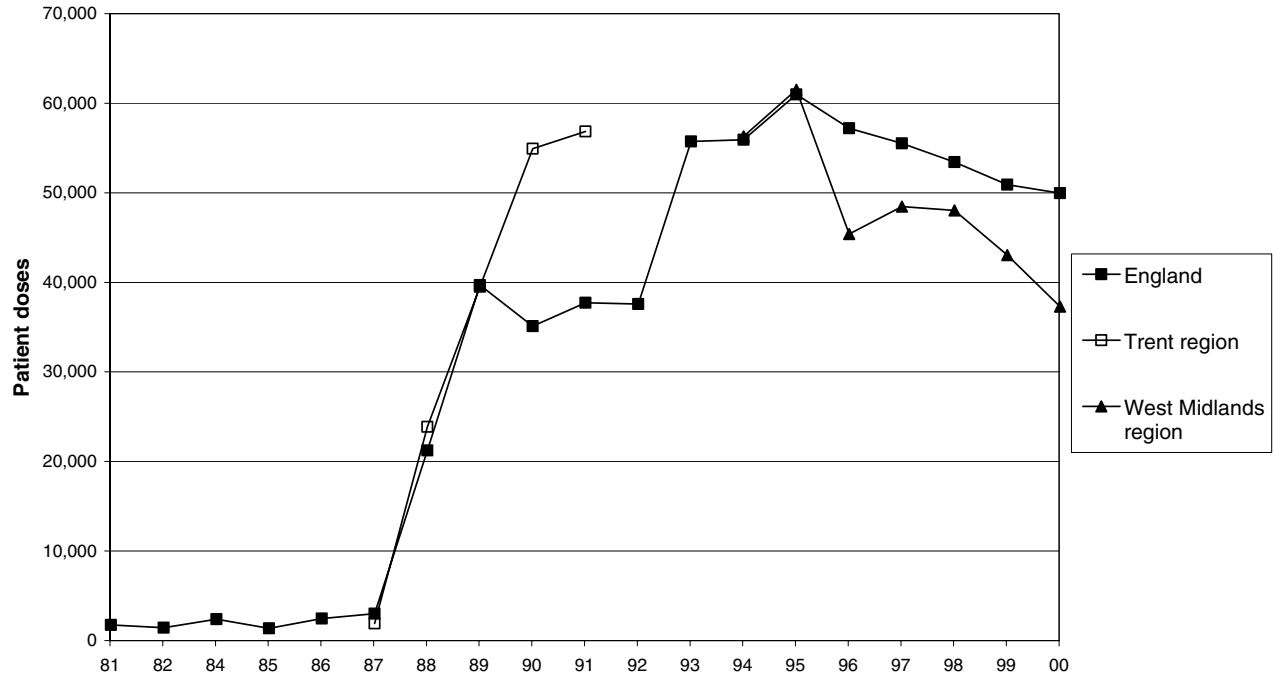

Figure 2. Triangulation of estimated patient doses of thrombolysis purchased in England.

in use from 1995 (see Figure 2). There is a suggestion in the Trent region that the plateau in the national data may not reflect actual practice or that hospitals in the Trent region had a different pattern of use from the rest of England. There was also a good agreement between national data and the West Midlands region in use of reteplase from 1987 to 2000, and alteplase and streptokinase from 1994 to 2000.

Need for Thrombolysis

The number of patients admitted to hospital with acute myocardial infarction rose slowly in the early 1980s and declined

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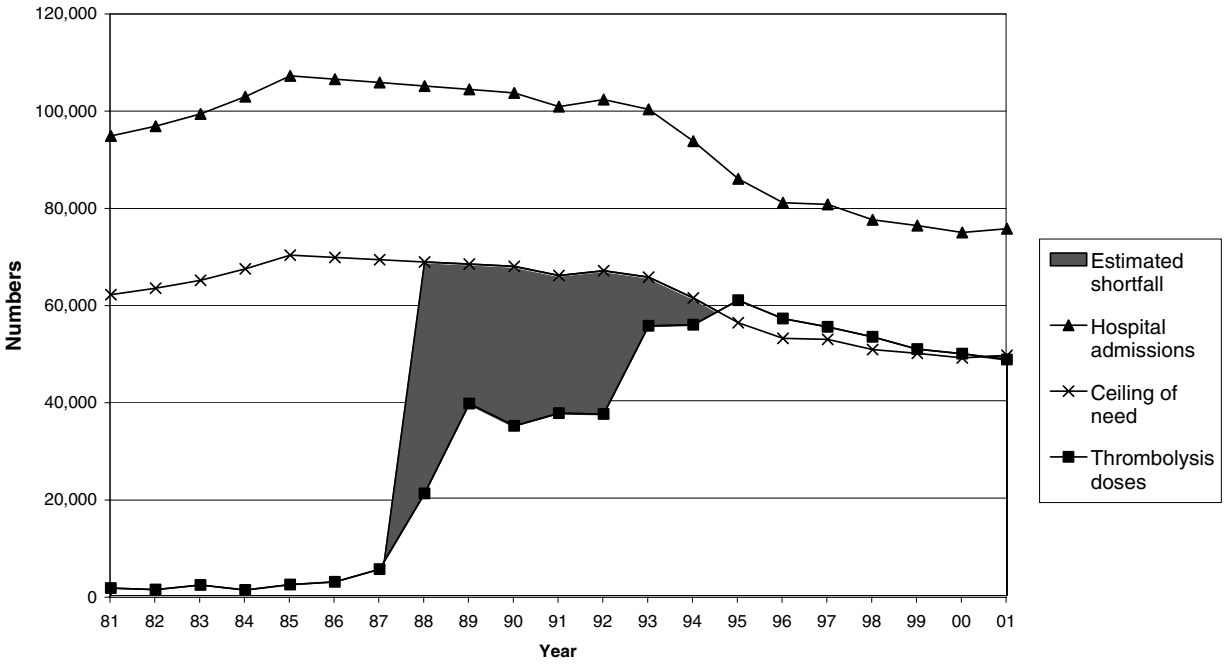

Figure 3. Hospital admissions for acute myocardial infarction, doses of thrombolysis, and estimated shortfall. Hospital admission: 1981–1985 Hospital In-Patient Enquiry. 1990–2001 Hospital Episode Statistics: admissions to hospital (first spell in hospital). 1986–1989 Straight line estimated trend.

throughout the 1990s (see Figure 3). The ratio of thrombolysis use to the number of patients with acute myocardial infarction shows a sharp increase to 35 percent–40 percent in the late 1980s followed by a second steep rise in the mid-1990s, reaching an estimated 70 percent by 1995 before falling slightly to 64 percent in 2001.

The shortfall in patient doses for thrombolysis from 1988 to 2001 compared with the epidemiological ceiling of people attending hospital for AMI modified by the estimated clinical ceiling is 167,800 doses (95 percent confidence range 94,000 to 241,700 doses).

DISCUSSION

Our estimation that almost two-thirds of people discharged from hospital in England with an acute myocardial infarction received thrombolysis in 2001 is almost identical to the estimated ceiling of clinical need of 65 percent. Although this is good, it is over 13 years since streptokinase was licensed for use in AMI in England and there has been a significant short-fall in the number of people who could have benefited from thrombolysis of an estimated 167,800 doses. Although there is some uncertainty relating to the proportion of patients with AMI with diagnostic difficulty and clinical contraindications on admission, particularly changes in these parameters over time, this deficit is considerable.

There are some factors that may affect the interpretation of our results. Although we assumed that all doses of thrombolytic agents purchased were for patients experiencing AMI, streptokinase and alteplase are licensed for other indications (acute pulmonary embolism and life-threatening venous thrombosis), which may have led to some overestimation of the number doses assigned to AMI. During the 1980s, before the ready availability of thrombolysis, a proportion of people experiencing an AMI were managed at home and would not be counted in hospital activity. Even after availability, there was much debate on the value of hospital admission and thrombolysis in the elderly and many of those who could have benefited from thrombolysis did not (12;15). Patients who die soon after admission to hospital will not be considered for thrombolysis, although they would be included in the hospital activity data. Conversion of money spent on thrombolytic agents into patient doses for the West Midlands region may have led to an underestimation of the number of doses purchased because of hospital-negotiated price reductions and bulk buys. Additionally, there will have been some wastage.

Advocates of evidence-based policy can be encouraged with the rapid uptake of thrombolysis in the initial 2 years after licensing. This discussion is rapid for a newly licensed therapy and probably represents use by enthusiastic individuals and early adopters. However, the following plateau and slow increase to a peak use in 1995 before a slight decline, over and above that due to a decline in AMI occurrences, is not so encouraging. This phase may represent a slow-down in individuals becoming converts, concern over possible adverse side effects, patient-management

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systems being slow to adapt, or the threat of a negative impact on hospital budgets. This finding is especially worrying as evidence of clinical and cost-effectiveness was continuing to be generated over this time and such evidence was becoming more accessible to general clinicians both as reviews of the evidence and in national policy and consensus guidelines that included targets and guidance on the use of thrombolysis (1;4;8;14;23). These reports may have eventually supported the increase in use to its peak in 1995. We have undertaken a separate study to relate the pattern of uptake to the publication of individual clinical trials, meta-analyses, service change, clinical guidelines, and other management tools (Cook et al., this issue).

The identification and use of national usage data were key factors that enabled this diffusion study to move beyond the static time slices of individual data points to a dynamic picture. Although data collected by IMS Health would have been suitable to use for the monitoring of the headline figure of the proportion of people with AMI receiving thrombolysis, it cannot contribute to monitoring the timing of administration, so important in thrombolytic use. The MINAP is now collecting data in the United Kingdom on the timing of thrombolysis in relation to symptom onset, calling for help, and arriving at hospital, but this audit started late in relation to drug availability and does not yet have full coverage. In the future, a combination of data collection by agencies such as IMS Health and health service national audits could be used to build up a composite picture of technology usage in England.

We conclude that, although there was a rapid initial uptake of thrombolysis in England, use took 8 years to reach the level of estimated clinical need and continues to require support in the form of national guidance and national audit for effective delivery. During those 8 years, many patients were not given the opportunity to benefit from thrombolysis. In England, data from national audits undertaken by health professionals could be supplemented by commercially collected data to ensure a complete picture of use.

Policy Implications

This study suggests that new innovations that are judged to be cost-effective and require both clinical and system changes for delivery would benefit from monitoring of their adoption and uptake on a national basis to identify those developments that need additional stimulus for change and to ensure that patients do not miss out on the opportunity to benefit. We can go further, in that the debate over which thrombolytic agent is best in which circumstances is a second-order concern, unless the choice impacts on the assurance of accessibility for all who can benefit.

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