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Cost-effectiveness of interventions to reduce the thrombolytic delay for acute myocardial infarction

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Objectives: The objective of the study was to estimate the costs and health benefits of a public awareness campaign aimed at shortening the delay for thrombolytic therapy in patients with acute myocardial infarction (AMI) and to estimate the incremental costs and benefits of an additional telemedicine program.
Methods and Results: By using trial data on the impact of a Swedish campaign, a model was developed to simulate the current distribution of thrombolytic delay in Denmark and the delay after a campaign. The reduction in delay was translated into reduced fatality assuming reductions from the campaign and additional effects of a telemedicine program. The costs of the campaign were based on trial data and Danish unit costs while telemedicine costs were taken from a Danish demonstration program. The analyses indicate that the awareness campaign will translate into five fewer fatal AMIs (sixty-two life years gained) and a cost per life year of DKK283,300, with both costs and benefits discounted at 5 percent. When combining the public campaign with prehospital telemedicine diagnostics, the incremental cost per life year gained was DKK854.700.
Conclusions: Programs aimed at reducing delay of thrombolysis in patients with AMI are likely to have a limited impact on AMI fatality. Information campaigns may have acceptable cost-effectiveness ratios, while telemedicine programs lead to threefold greater ratios. Whether such programs can be considered cost-effective will depend on how life year gains are valued by society.

Keywords: Myocardial infarction, Thrombolytic therapy, Delay, Economics

Coronary heart disease (CHD) accounted for approximately 20 percent of all deaths in Denmark in 1996 (32). The number of acute myocardial infarctions (AMI) was approximately 13,000, of which 5,000 proved fatal. Approximately half of these fatalities occurred outside hospitals. However, the AMI mortality has declined over the past ten to fifteen years, partly because of improved medical treatment, including intravenous thrombolytic therapy.

It is well established that thrombolytic therapy reduces the mortality during the first month after an AMI and that the benefit of the therapy is greatest if it is started shortly after the onset of the symptoms (1;2;8). It has now been demonstrated that primary percutaneous coronary intervention (PCI) provides a better survival (also time dependent) after transmural AMI than thrombolytic therapy (4;25;27). The full potential benefit of the thrombolytic is not achieved because of unnecessary delay from debut of the AMI symptoms until thrombolytic therapy is initiated.

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Public campaigns have been organized to increase people's awareness of AMI symptoms (6;11;16;21;26;31), but findings from studies have been conflicting with respect to shortening of patients' delay (the time from onset of symptoms until contact to the health-care system) (6;7). In some studies, the median as well as the mean patient delay has been reduced (6;11) whereas in others, there has been no apparent effects. Prehospital AMI diagnosis through telemedicine has reduced door-to-needle delay (the time from admission to hospital until start of thrombolytic therapy) by approximately 50 percent (19;20). The health benefit in terms of reduced mortality, however, will depend on the distribution of delay before and after an intervention as the association between delay and reduction in mortality is not necessarily linear (2;8).

The aim of this study was to estimate health and economic consequences of a public awareness campaign aimed at reducing patients' delay in order to start thrombolytic therapy earlier—alone and in combination with prehospital AMI diagnosis through telemedicine. Both health and economic consequences were modeled by comparing the current situation in Denmark to a situation of reduced delay due to the interventions.

METHODS

To estimate costs and health benefits, we developed a model to simulate all cases of AMI during one year in Denmark with the current and the reduced delay. Studies on the effects of public awareness campaigns and telemedicine programs were identified by a Medline search using the terms myocardial infarction, thrombolytic therapy, delay, mortality, long-term survival, media campaign, prehospital diagnosis. While earlier thrombolytic therapy may have several health benefits, we focused on the increased survival, applying life years gained as the measure of health benefit.

With delay time as the key variable, the current use of thrombolytic therapy was simulated, applying data on the Danish AMI-population and the current delay, and compared it with a reduced delay from a public campaign, adapting Swedish data to a Danish setting. Health benefits were modeled by estimating the increased number of AMI survivals during the first month after the infarction (avoided fatalities) as a result of earlier thrombolytic treatment, assuming—in the base case—that the beneficial effect of thrombolytic therapy is diminishing as a nonlinear function of time from onset of symptoms to start of thrombolytic therapy. The additional avoided fatalities due to the combination with prehospital telemedicine diagnosis were modeled, reducing the door-to-needle delay for patient transferred by ambulance. The reduced one-month case fatality was translated into life years gained by estimating remaining life years, according to age (groups of five years) and sex, for AMI patients who survive one month after the infarction. The costs of the campaign were modeled along with economic consequences in terms of more patients contacting the hospitals and the cost of prehospital telemedicine diagnosis.

Assuming that the initial delay reduction of the campaign would persist for at least three years (as was the case in the Swedish campaign) and that the initial campaign in Denmark would be followed by a short "fresh-up" campaign, we adopted a time horizon of five years to capture avoided fatalities from the campaign and the consequent costs during a realistic period of time. The inclusion of future health care costs has been subject to discussion (10), and we chose to exclude them. In line with this strategy, we also excluded also the potential value of increased production due to gained life years; thus, we applied the perspective of the health-care provider. In line with common practice, we excluded the economic consequences of additional survivors of AMI. All future costs and life years gained were discounted at 5 percent and expressed in year 1999 Danish Crowns (DKK; 1 US$ = 8 DKK).

The model has 7 main components. The data and the assumptions will briefly be described in the following sections.

Current Danish Delay among Patients with AMI

Current Presentation Delay (patient delay plus the prehospital delay: time from onset of symptoms until hospital admission): In line with Ottesen et al. (28), we assumed that 34 percent of patients with AMI arrive at hospital within two hours after onset of symptoms and 81 percent arrived within twelve hours (Table 1). Seven percent of the AMI patients

Table 1. Presentation Delay (Current and after a Campaign) and Proportion with Thrombolytic Therapy

	Presentation delay (min)						
	0–60	61–120	121–240	241–360	361–720	721–1440	Total
Current delay by intervals (%)[a]	7.0*	27.0	24.0	10.0	13.0	19.0	100%
Delay after a campaign by intervals (%)[b]	7.0	30.9	29.5	9.4	14.0	(9.2)	100%
Thrombolytic therapy by intervals (%)[c]	55.8	55.8	48.5	48.5	31.5	11.9	41.8%

[a]Current proportion admitted to hospital according to intervals of presentation delay (28). *The delay in the interval 0–60 min is based on unpublished data (Rasmussen, 2000).
[b]Estimated from Swedish data (6;12–14), supposing the same relative chance in each interval of delay.
[c]Proportion given thrombolytic therapy afterward (i.e., after door-to-needle delay; 28).

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were assumed to be admitted at hospital within one hour after onset of symptom (Rasmussen CH, unpublished data, 2000).

Current Door-to-Needle Delay: Based on Rasmussen (Rasmussen CH, unpublished data, 2000), the current door-to-needle delay was assumed to be sixty minutes.

Thrombolytic Therapy Among Patients with Myocardial Infarction

Proportion of the AMI-Population Treated with Thrombolysis: From the study of Ottesen et al. (28), we applied data of the proportion of AMI patients having thrombolytic therapy as a function of intervals of presentation delay (Table 1). Of the total AMI population admitted to hospital, approximately 42 percent were assumed to have thrombolytic therapy with the current delay and with a reduced delay. In Sweden, the proportion is 30 percent (12).

Age Distribution among Patients Having Thrombolysis: The age distribution among patients having thrombolysis was estimated from a study in Copenhagen (22), where 21 percent of patients aged older than sixty-five years had thrombolytic therapy, while the proportion was 8 percent of those older than seventy-five years.

Impact of the Interventions

The Public Campaign: The impact of a Danish public campaign was estimated from the literature, and it was assumed that the campaign only would have an impact on patients' delay. Due to cultural and delay similarities between Sweden and Denmark and partly because of detailed data from the Swedish study (5–7;12–15), the change in pattern of presentation delay after a Danish campaign was estimated, applying the Swedish data on a Danish setting (Table 1). In Sweden, both the proportion of patients arriving in hospital less than one hour after symptom debut and the proportion arriving through contact with the emergency phone remained unchanged. We assumed a small increase in use of emergency phone, as the proportion is low in Denmark (30 percent) in comparison to Sweden (60 percent). As for the Swedish campaign, we assumed that the reduced delay pattern remained for at least three years.

Prehospital Telemedicine Diagnostics: The additional health benefit of combining prehospital telemedicine diagnostics with a public campaign was modeled reducing the door-to-needle delay by 50 percent (base case estimate) for patients admitted by ambulance, as demonstrated in the literature (19;20). This is, however, optimistic with the actual Danish organization of the health care system. Due to the short distances in Denmark, it is not realistic to administer prehospital thrombolytic therapy. The mean prehospital delay (the time from contact to the health-care system to hospital admission) for patient using the emergency phone is assumed to be thirty minutes.

Of patients with suspected AMI, 32 percent call the emergency phone and are transported by ambulance, while 64 percent contact a general practitioner (Rasmussen CH, unpublished data, 2000). For the latter group, approximately 80 percent are transferred by ambulance to hospital.

Mortality Reduction Due Thrombolytic Therapy as a Function of Delay

Based on the pathophysiology of myocardial infarction, we assumed as base case estimate that the mortality reduction from thrombolytic therapy declines nonlinearly with delay time as proposed in a meta-analysis by Boersma et al. (8), applying discrete intervals of delay. According to their analysis, the mortality reduction due to thrombolytic treatment declines nonlinearly as a function of the delay time, that is, the mortality reduction relative to placebo will be 65, 37, 29, 23, 18, and 9 per 1,000 given thrombolytic therapy with a delay of, respectively, less than one hour, 1–2, 2–4, 6–12, and more than 12 hours. In contrast, The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group (2) concluded that the absolute mortality reduction declines linearly with time since onset of AMI symptoms, and the estimated loss of benefit is 1.6 lives per 1,000 for each hour of delay. The initial mortality reduction was estimated at thirty-five per 1,000 treated patients compared with no thrombolysis. As will appear from Fig. 1, the difference between the linear and the nonlinear model is only important during the first two hours of delay, where the nonlinear model predicts greater effect.

Danish Population of AMI-Patients

The occurrence of AMI in Denmark was based on recent statistics of the occurrence of AMI in Denmark (32), and the gender-specific thirty days fatality after admission with AMI has been calculated, applying data for the age and gender distribution of the out-of-hospital AMI fatality (Søren Rasmussen, National Institute of Public Health, Copenhagen, unpublished data, 2000). In line with Maggioni et al. (23), we assumed that the age-specific mortality increases by 6 percent per year of age, assuming that the exponential increase in mortality is true for all patients with AMI up to one year after the infarction.

Life Expectancy after the First Month after AMI

Remaining life expectancy for patients who survived an AMI was estimated on the basis of age- and sex-specific mortality risks in the general Danish population (3). The risk was adjusted upward due to the higher mortality risk among those who have had AMI and expressed as remaining life expectancy in age groups of five years for each sex. As base case estimate, the excess mortality risk of AMI patients was estimated on the basis of survival data from the Danish part of the MONICA project (Monitoring of Trends and Determinants in Cardiovascular Disease Project), where standardized mortality ratios have been calculated successively fifteen years

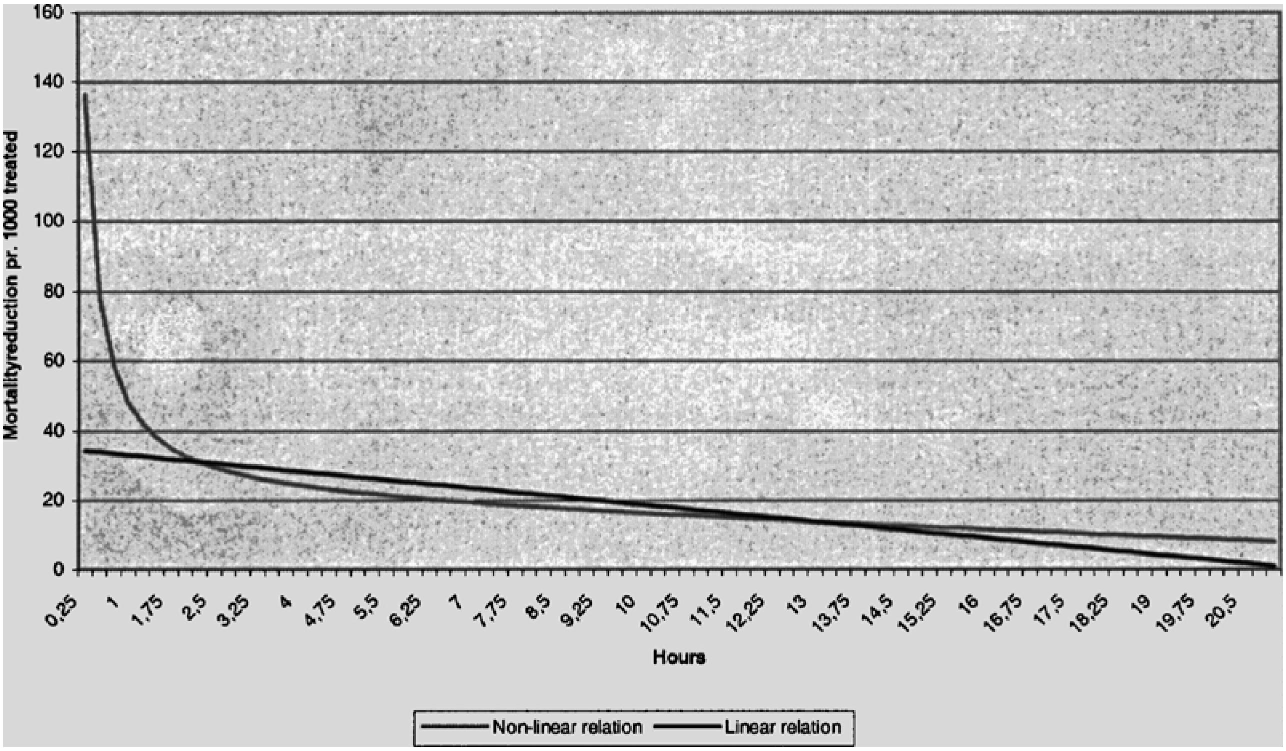

Figure 1. Linear versus nonlinear relation between delay and mortality. The figure illustrates the difference between a linear end a nonlinear relationship between hours of delay and the effect (mortalityreduction) of thrombolytic therapy to patients with acute myocardial infarction. Thrombolytic therapy is compared to placebo. Sources: nonlinear relation (8), linear relation (2).

after acute myocardial infarction for cohorts of Danish patients with nonrecurrent AMI in the period 1982–1991 (9).

Cost Consequences

Cost Consequences of Danish Public Campaign: The economic consequences of a Danish campaign was estimated adopting the Swedish cost data from 1987 (in U.S. dollars) (6;14) converting U.S. dollars into DKK (100 DKK = 684.36 U.S. dollars [1987]) and adjusting for the different size of populations and the inflation in Denmark between 1987 and 1999. The estimated costs of a one year Danish campaign—human resources exclusive—were 40 million DDK.

Adjusting Swedish data to the size of the Danish population (13;14), we estimated that the campaign initially would increase the number of patients seeking care at the emergency rooms at the hospitals for noncardiac chest pain with approximately 6,500 per year at a cost of 1.2 million DKK. The potential for increased number of hospital admissions was accounted for only in the sensitivity analysis. Assuming that more patients will contact the ambulance services directly and, thereby, bypass the family doctor, we estimated a saving equivalent to 6 percent less contacts to the family doctor.

Costs of Prehospital Telemedicine Diagnostics: The economic consequences of establishing and running telemedicine diagnostics in all ambulances (500) in Denmark were based on information of the need (and costs) for equipment and for upgrading ambulance staff (electronic information, Ole Qvist Pedersen, 2000) and on the assumption that prehospital diagnostics will require telemedicine teams with cardiologic specialist in five hospitals to provide AMI diagnostics in Denmark. Capital equipment was assumed to last five years. In the sensitivity analysis, the equipment alternatively was assumed to be out-dated in three years, using standard techniques.

RESULTS

Assuming an unchanged door-to-needle delay (sixty minutes), a public campaign will increase the proportion of patients having thrombolysis in the interval two to four hours after onset of AMI symptoms from 20.8 percent to 24.0 percent, whereas the proportion of patients treated in hospital within the first two hours of onset of symptom will remain the same (Table 2).

According to the model, of approximately 9,800 patients admitted alive to hospital for AMI during one year, approximately five more patients than today will avoid a fatal outcome in the subsequent month (Table 3). During five years of reduced delay, the avoided fatalities translate into 177 life years gained (discounted at 5 percent). The estimated net five-year cost of the public campaign (intervention

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Table 2. Proportion Treated by Intervals of Total Thrombolytic Delay[a]

Intervention	Total thrombolytic delay (min)						
	0–60	61–120	121–240	241–360	361–720	721–1440	Total
Current (%)	0,00	3,91	20,84	8,27	5,86	2,95	41,82
Campaign (%)	0,00	3,91	24,03	8,69	3,67	1,53	41,82
Telemedicine (%)	0,00	11,31	16,37	6,56	4,98	2,60	41,82
Combination (%)*	0,00	12,23	19,31	5,83	3,14	1,31	41,82

[a]All percentages of thrombolytic delay are percentages of the total acute myocardial infarction population admitted alive at hospital. The asterisk indicates the marginal/additional consequences of adding the telemedicine strategy to the public campaign.

costs minus savings) will be 51.3 million DKK (50.2 million DKK when discounting at 5 percent). Consequently, the base case estimate for the cost per life year gained (cost/LY) is DKK283,300, discounting both life years and costs at 5 percent or DKK161.500 when not discounting.

If the public campaign were combined with prehospital telemedicine diagnostics—reducing the door-to-needle delay by 50 percent—approximately fourteen patients would avoid a fatal AMI outcome. The base case estimate for cost/LY for the combination is DKK563,800, when discounting at 5 percent, or DKK321,400 undiscounted. The marginal cost/LY of adding the telemedicine strategy to the public campaign is DKK854,700. This marginal cost/LY approximately DKK80,000 less than for the telemedicine strategy alone (Table 3) and is explained by the fact that the relation between reduced fatality and earlier thrombolysis is assumed to be nonlinear and that a slightly greater proportion is assumed to use the emergency phone due to the campaign.

In the sensitivity analysis, we varied, one by one, the assumptions upon which the analysis were based and compared the consequences with the base case estimates of discounted cost/LY for the campaign alone and the marginal cost/LY for the combination. Assuming that 25 percent of the patients with noncardiac chest pain in the emergency departments will be admitted to the cardiologic department, the cost/LY for the campaign will be DKK577,000, an increase of 103 percent. With a reduced cost of information materials from DKK40 million to DKK20 million, the cost/LY was DKK170,000, a decrease of 40 percent. With a reduced proportion of 33.5 percent (instead of 41.8 percent) treated with—or with effect—thrombolysis, cost/LY was DKK373,000. Assuming a different age distribution among those having thrombolysis (i.e., more elderly treated and fewer younger treated), cost/LY was DKK346,000. Realistic changes in other parameters had little influence on the cost-effectiveness ratio.

Assuming that the relationship between delay and mortality reduction is linear (2), the marginal cost/LY of the combination will be DKK 1,743,300. This change in assumption is only important for the telemedicine strategy. If the telemedicine equipment was assumed to last three years instead of five years, the marginal cost/LY will be DKK981,300. (It is possible, however, that equipment prices will be lower in the future. We could not account for this possibility.) The cost/LY will decrease with approximately the same amount if the ongoing upgrading of ambulance staff is less costly. If it is possible in the future to eliminate the door-to-needle delay by the telemedicine strategy, the marginal cost/LY of the combination will be DKK223,500, a decrease of 74 percent and DKK50,000 less than the campaign alone.

DISCUSSION

An information campaign aimed at getting patients with AMI to hospital earlier appears to result in approximately five avoided fatalities (of 2,400 fatalities per year) among 9,800 AMI patients admitted alive to the hospital at a cost of DKK283,300 per life year gained (discounted at 5 percent). The limited impact on the total fatality can partly be explained by the fact that, although the median delay will be reduced due the campaign, almost the same number as before a campaign will be treated within the first two hours after

Table 3. Results by Base Case Estimates[a]

Intervention	1 year GL	5 years					
		LY	LY*	Cost	Cost*	Cost/LY	Cost/LY*
Telemedicine	8,45	537	306	304.858.899	285.563.649	532.134	933.306
Campaign	4,90	311	177	51.303.477	50.229.843	161.459	283.304
Combination	14,13	897	511	304.711.536	288.310.158	321.440	563.771
Marginal	9,23	586	334	304.858.899	285.563.649	487.449	854.736

[a]Marginal, Extra number gained if the campaign is combined with prehospital telemedicine diagnostics in relation to the campaign alone; GL, gained life or avoided fatalities each year; LY: life years gained during 5 years; Cost/LY, cost per life years gained, all costs are in DKK (1999). Asterisks indicate that the numbers are discounted by 5%.

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onset of symptoms. Combining the campaign with prehospital telemedicine diagnosis—and thereby reducing the door-to-needle delay by 50 percent (for those admitted by ambulance)—will result in approximately nine more avoided fatalities yearly (DKK854.700 per additional life year saved). These estimates of costs and benefits, however, should be seen against the limitations of the study. The main limitation of our study lies in the fact that the beneficial effect of earlier thrombolytic therapy was modeled as a *discrete function of time,* that is, the *time interval* from onset of symptoms rather than as a *continuous function of time*. This simplification has limited impact for delay times over two hours (Figure 1) and, consequently, not for the campaign alone, but the number of avoided fatalities might be slightly higher for the combination. The beneficial effect of thrombolysis was estimated on the basis of meta-analyses of randomized clinical trials (RCTs; 2;8). Although results from meta-analyses are widely seen as the best evidence (of efficacy), it may not necessarily yield the best measure of effectiveness in routine clinical practice. Patients included in RCTs normally represent a selected group of patients in clinical practice. The effectiveness in routine practice may be inferior to that of the trials, because it is more likely that cases without beneficial effect from thrombolysis are having thrombolysis in clinical practice.

Another limitation is the rather rough estimate of the costs of the campaign. The cost/LY for the campaign, thus, was very sensitive to the imperfection of the data related to costs.

Although several studies aimed to evaluate the effect of thrombolysis and/or to evaluate interventions aimed to reduce the delay in thrombolytic therapy have been published, we have not found studies similar to our study; consequently, the present analysis cannot directly be compared with others. In a cost-effectiveness study of different thrombolytic agents (24), the marginal cost/LY for accelerated tissue plasminogen activator versus Streptokinases was US$32,678 or DKK265,000, compared with DKK283,300 for the campaign alone in our model. Estimates of costs per life year gained for Streptokinases versus placebo has been approximately of US$17,000 or DKK138,000 per life year gained (29).

POLICY IMPLICATIONS

The present analysis gives no unequivocal answer to the question of whether public campaigns should be implemented, partly because there is no official threshold value with respect to how much society is willing to pay for gaining a life year. Moreover, a general awareness of symptoms of AMI might not only have an impact on the case fatality among patients admitted alive to hospital but also on prehospital fatality. A substantial number of patients die before arrival in hospital, and this number is likely to decline when patients contact the health-care system earlier (17;18;30). The fact that a public campaign also might lead to a reduction of "out of hospital ischemic heart disease deaths" could make it more reasonable to conduct a campaign.

In planning a campaign, it is critical to prepare nurses and doctors to handle adequately the increased burden in emergency departments and to expect increased demand for health care, especially in the beginning of the campaign. Furthermore, the possible increase in anxiety in the entire population should be considered.

The marginal cost/LY of a combination of a public campaign with prehospital telemedicine AMI diagnostics aimed to reduce the thrombolytic delay in Denmark is likely to be considerably less cost-effective than a public campaign alone. The high marginal cost/LY of the telemedicine strategy (and of the telemedicine strategy alone) is explained by the high costs of equipments that is needed in every ambulance and staff in both hospitals and ambulances, while few patients actually will gain health benefit from the service. Few AMI patients in Denmark contact directly the emergency service during the first hour of unset of symptoms. Rather, general practitioners are *de facto* "door keepers" to the hospitals, and the general practitioner is often the first health professional to be contacted in case of chest pain. If a public campaign should be combined with the telemedicine strategy, it is urgent to focus on the direct contact to the emergency service. Total elimination of the door-to-needle delay due to telemedicine strategy is necessary if the strategy should be cost-effective—and this elimination will call for structural changes. This holds only if the time-dependent reduction in mortality in fact is nonlinear. It has been beyond the scope of this study to evaluate costs and health benefit of prehospital telemedicine diagnostics aimed at directly admitting patients to a cardiology center to perform primary PCI.

CONCLUSIONS

Programs aimed at reducing delay of thrombolysis in patients with AMI are likely to have a limited impact on AMI fatality. This conclusion can be explained by the finding that neither of the strategies seems to increase much the proportion of patients with a thrombolytic delay less than two hours. Not accounted for in the model, the public campaign may also lead to a reduction in the out-of-hospital fatality. Due to the high costs of the telemedicine strategy the cost per life year gained is more than threefold higher than that of the public campaign. Whether such programs can be considered cost-effective will depend on how life year gains are valued by society. In a Danish context, they are in "the gray zone" in which factors other than cost-effectiveness may influence policies.

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