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**FASTTRACK CLINICAL RESEARCH**
*Acute coronary syndromes*

# 16-year follow-up of the Danish Acute Myocardial Infarction 2 (DANAMI-2) trial: primary percutaneous coronary intervention vs. fibrinolysis in ST-segment elevation myocardial infarction

**Pernille G. Thrane [1], Steen D. Kristensen[1], Kevin K.W. Olesen [1], Leif S. Mortensen[2], Hans Erik Bøtker[1], Leif Thuesen[3], Henrik S. Hansen[4], Ulrik Abildgaard[5], Thomas Engstrøm[6], Henning R. Andersen[1], and Michael Maeng[1]***

[1]Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark; [2]Spange Statistics, Elleparken 10, 8520 Lisbjerg, Denmark; [3]Department of Cardiology, Hobrovej 18-20, 9000 Aalborg University Hospital, Aalborg, Denmark; [4]Department of Cardiology, Odense University Hospital, J. B. Winsløws Vej 4, 5000 Odense C, Denmark; [5]Department of Cardiology, Copenhagen University Hospital Gentofte, Gentofte Hospitalsvej 1, 2900 Hellerup, Denmark; and [6]Department of Cardiology, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark

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**Aims** The DANish Acute Myocardial Infarction 2 (DANAMI-2) trial found that interhospital transport to primary percutaneous coronary intervention (pPCI) was superior to fibrinolysis at the local hospital in patients with ST-segment elevation myocardial infarction (STEMI) at 30 days. The present study investigates the 16-year cardiovascular outcomes.

**Methods and results** We randomized 1572 STEMI patients to pPCI or fibrinolysis at 24 referral hospitals and 5 invasive centres in Denmark. Patients randomized to pPCI at referral hospitals were immediately transported to the nearest invasive centre. The main endpoint of the current study was a composite of death or rehospitalization for myocardial infarction (MI). Outcome information beyond 3 years was obtained through Danish health registries. After 16 years, pPCI-treated patients had a sustained lower rate of composite endpoint compared to patients treated with fibrinolysis in the overall cohort [58.7% vs. 62.3%; hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.76–0.98], and among patients transported for pPCI (58.7% vs. 64.1%; HR 0.82, 95% CI 0.71–0.96). No difference in all-cause mortality was found, but cardiac mortality was reduced by an absolute of 4.4% in favour of pPCI (18.3% vs. 22.7%; HR 0.78, 95% CI 0.63–0.98). pPCI postponed a main event with 12.3 months in average compared to fibrinolysis (95% CI 5.0–19.5).

**Conclusion** The benefit of pPCI over fibrinolysis was maintained at 16-year follow-up. pPCI reduced the composite endpoint of death or rehospitalization for MI, reduced cardiac mortality, and delayed average time to a main event by approximately 1 year.

**Keywords** ST-elevation myocardial infarction • Long-term outcome • Fibrinolysis • Percutaneous coronary intervention



* Corresponding author. Tel: +45 26703237, Fax: +45 78452117, Email: michael.maeng@clin.au.dk

# Introduction

Early and efficient reperfusion is the main therapeutic goal in acute treatment of ST-segment elevation myocardial infarction (STEMI). Fibrinolysis was the mainstay in reperfusion treatment until the first studies comparing fibrinolysis to primary percutaneous coronary intervention (pPCI) documented that pPCI improved short-term clinical outcome.[1,2] However, these studies were rather small and only included patients admitted to hospitals with angioplasty facilities.

The DANish Acute Myocardial Infarction 2 (DANAMI-2) trial was the first multicentre, randomized controlled trial comparing inter-hospital transport to pPCI vs. fibrinolysis at the admission hospital. The study showed that a reperfusion strategy with pPCI improved the 30-day composite endpoint of death, clinical reinfarction or disabling stroke, when transportation could be completed within 120 min.[3] This finding was confirmed in the PRAGUE-2 study.[4] Based on these results, current European and American guidelines recommend reperfusion with pPCI if time of STEMI diagnosis or first medical contact to reperfusion (wire crossing) is within 120 min.[5–7] A sustained benefit of a pPCI strategy has been documented for up to 8 years of follow-up.[8–10] Many countries still have a poor organization of reperfusion therapy, and knowledge on very long-term outcomes may foster implementation of the best management strategy for STEMI patients.[11] The present study reports on clinical outcomes after 16 years of follow-up of the DANAMI-2 trial and will thereby be the first to provide a very long-term perspective on death and cardiovascular events when comparing pPCI with fibrinolysis in STEMI patients.

# Methods

## Study design in the DANAMI-2 trial

The DANAMI-2 trial is a national, multicentre, randomized controlled trial that enrolled patients from December 1997 to October 2001. The study design has been described in detail previously.[3,12] In brief, the DANAMI-2 trial randomly assigned patients with STEMI (1:1) to reperfusion therapy with pPCI at an invasive centre or fibrinolytic treatment at the admission hospital. A total of 1572 patients with STEMI were enrolled in the trial, 443 patients from 5 invasive centres and 1129 patients from 24 referral hospitals in Denmark. A flow diagram of the patient selection is presented in *Figure 1*. The study design required that patients admitted to referral hospitals were immediately transported to an invasive centre if randomized to pPCI.

## Participants

Criteria for inclusion were age ≥18 years, presence of typical ischaemic chest discomfort symptoms ≥30 min but ≤12 h, and an electrocardiogram with cumulative ST-segment elevation ≥4 mm in ≥2 contiguous leads. Furthermore, a transfer time ≤3 h was required from randomization until arrival at a catheterization laboratory.[3,12] The main exclusion criteria were standard contraindications to fibrinolysis, left bundle branch block, myocardial infarction (MI) treated with fibrinolytic treatment within the previous 30 days, or cardiogenic shock.[3,12] The invasive centres established a 24-h service for pPCI-procedures to join the study.

The safety and efficacy committee called for termination when the third interim analysis showed superiority of pPCI in the referral hospital substudy.

## Treatment

All randomized patients were treated with aspirin, and unfractionated heparin immediately following the diagnosis.[12] Patients randomized to fibrinolysis received 15 mg bolus tissue-plasminogen-activator (alteplase) followed by infusion of 85 mg/90 min upon arrival at the admission hospital. Patients randomized to pPCI were immediately transported to an invasive centre with angioplasty facilities. The culprit lesions were stented unless the diameter of the vessel was <2.0 mm. Only the culprit lesions were treated at the index angioplasty. Platelet glycoprotein IIb/IIIA-receptor blockers were administered at the discretion of the physician. After stent implementation, patients were treated with ticlopidine 500 mg daily for 1 month until August 2001, where the PCI-CURE study was published.[13] From August through October 2001, patients received a loading dose of 300 mg clopidogrel followed by 75 mg daily for 1 month.

## Endpoints and follow-up

The original primary endpoint was a composite endpoint consisting of all-cause death, clinical reinfarction, or disabling stroke.[3,8] Since 'disabling stroke' could not be defined based on registry data alone, the main endpoint in this 16-year follow-up study was defined as a composite of all-cause death or rehospitalization for MI. Additional study endpoints were all-cause death, rehospitalization for MI, cardiac death, and non-cardiac death.

Patients were followed with visits at the randomizing hospital at 1 month and annually until 3 years after the index STEMI. A clinical endpoint committee, blinded to treatment, adjudicated the endpoints within the 3-year period. The predefined endpoints have previously been described in detail.[3,12] Beyond the first 3 years after index STEMI, the endpoints were obtained from validated national health registries.[14,15] Linkage was performed using the 10-digit unique personal identification number all Danish citizens receive at birth or upon immigration.

For the analysis of each outcome, follow-up was traced until the occurrence of an outcome event, death, emigration, or completion of 16-year follow-up. All-cause death was obtained from the Danish Civil Registration System.[16] Cardiac death was defined according to the Academic Research Consortium consensus guidelines and obtained from the Danish Register of Causes of Death.[15,17] Hence, cardiac death was defined as death caused by ischaemic heart disease, sudden cardiac death, ventricular tachycardia, other cardiac arrhythmias, heart failure, sudden undefined death, unwitnessed, or unknown cause of death (Supplementary material online, *Table S1*). All deaths with missing cause of death or missing medical record on the death certificate were defined as unregistered cause of death. All other deaths were considered non-cardiac (Supplementary material online, *Table S1*). Data on rehospitalization for MI were obtained from the Danish National Patient Registry.[14] Rehospitalization for MI was defined as the first MI after index STEMI, obtained as a primary or secondary discharge diagnosis during an acute hospital admission. This event detection algorithm has been validated and was found to have positive predictive values between 89% and 100% and a negative predictive value >99% for detection of MI beyond 3 years after index PCI.[18] Mechanical revascularization was defined as the first PCI or coronary artery bypass graft (CABG) operation from last clinical 3-year follow-up (Supplementary material online, *Table S2*).

## Statistical design and analysis

Data were analysed according to the intention-to-treat principle. Analyses were performed for the total study population and the referral and invasive hospital group separately, as prespecified in the original trial protocol.[3] Kaplan–Meier curves were constructed for the composite endpoint and all-cause death. The 16-year cumulative incidence proportions were calculated for each endpoint. Competing risk analysis was

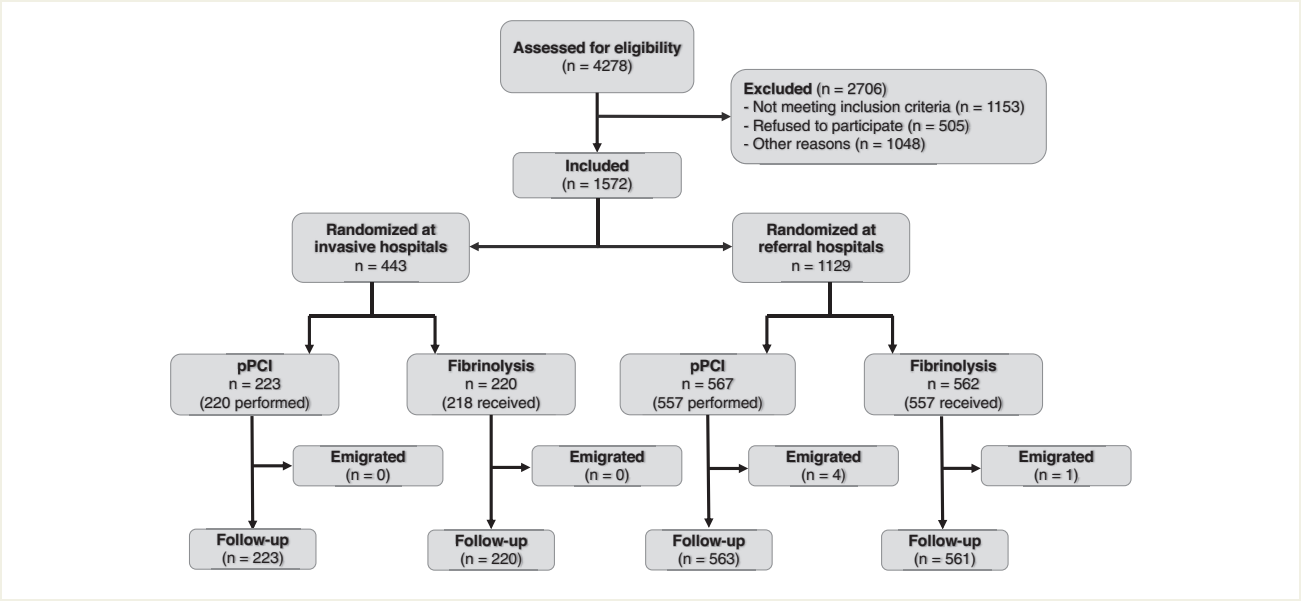



**Figure 1** Flow diagram presenting the patient flow in the DANAMI-2 trial and follow-up. Information on excluded patients is described in detail in a previous publication.[7]

used to estimate the 16-year cumulative incidence proportions of rehospitalization for MI, cardiac death, and non-cardiac death. A landmark analysis of mechanical revascularization was performed for patients alive after clinical 3-year follow-up. A competing risk model was used to estimate cumulative incidence proportions and hazard ratio (HR) from year 3 to 16. To estimate the difference in risk of the composite endpoint and all-cause death, the log-rank test and Cox proportional HRs were calculated using the fibrinolysis group as reference. To account for competing risks in cause-specific mortality and rehospitalization for MI, the Fine and Gray proportional subhazard model was used to estimate cumulative event curves and HRs.[19] The proportionality assumption was assessed by log–log plots.

To provide an alternative and intuitive measurement of the time to first event a restricted mean survival or event time method was used.[20] The difference in restricted mean is equivalent to the difference in area under the survival curves. Differences in average time to the first event were estimated for the composite endpoint, death, and rehospitalization for MI at 16-year follow-up.[20] Finally, subgroup analyses were performed according to predefined baseline characteristics, but with additional age groups to examine a potential effect of younger or older age. *P*-values <0.05 were considered significant. All statistical analyses were performed using Stata/MP version 15.0 (StataCorp, College Station, TX, USA).

## Ethical considerations

The DANAMI-2 trial was approved by the National Ethics committee of Denmark and complies with the declaration of Helsinki. All patients provided written informed consent before inclusion. The current study was approved by the Danish Data Protection Agency (J No 1-16-02-194-18). There are no further ethical approvals required for registry-based studies according to Danish law.

# Results

## Baseline characteristics and follow-up

Baseline characteristics did not differ between patients randomized to pPCI and fibrinolysis.[3] All events were traced until 16 years after randomization. During follow-up, five patients emigrated and were censored on the date of emigration; hence, vital status was known for 99.7% of the study population (*Figure 1*). Cause of death was missing for 18 patients (2.2% of 799 deaths).

## Study endpoints

The 16-year cumulative incidence proportions are shown in *Table 1* and cumulative event curves are presented in *Take home figure*. The composite endpoint was reached in 60.0% of patients, and 50.8% of patients died during follow-up.

pPCI patients had a lower rate of the composite endpoint compared to patients treated with fibrinolysis with an absolute difference of 3.6% [pPCI 58.7% vs. fibrinolysis 62.3%; HR 0.86, 95% confidence interval (CI) 0.76–0.98]. This reduction was primarily caused by a lower rate of rehospitalization for MI in patients treated with pPCI (pPCI 19.0% vs. fibrinolysis 24.5%; HR 0.75, 95% CI 0.60–0.93). No significant difference was found in all-cause mortality between the treatment groups (pPCI 50.5% vs. fibrinolysis 51.3%; HR 0.95, 95% CI 0.83–1.09). However, pPCI was associated with a reduced risk of cardiac death compared to fibrinolysis with an absolute difference of 4.4% (pPCI 18.3% vs. fibrinolysis 22.7%; HR 0.78, 95% CI 0.63–0.98), while non-cardiac death was 2.5% higher in the pPCI group (pPCI 30.5% vs. fibrinolysis 28.0%; HR 1.11, 95% CI 0.92–1.33). In a sensitivity analysis, we reclassified missing cause of death as either cardiac or non-cardiac death. Either reclassification was robust. The landmark analysis from 3 to 16 years showed that mechanical revascularization rates were 21.0% ($n = 151$) in the fibrinolysis group and 18.3% ($n = 135$) in the pPCI group (HR 0.86, 0.68–1.08).

The results of the subgroup analyses of the referral and invasive hospital align with the findings in the overall cohort. In the referral hospital substudy, pPCI treatment was associated with a reduction in composite endpoint (HR 0.82, 95% CI 0.71–0.96), while the composite endpoint in the prematurely terminated invasive hospital substudy

**Table 1 Number of events, cumulative incidence proportions (%), and hazard ratios in patients randomized to pPCI compared to fibrinolysis at 16-year follow-up**

| | pPCI | Fibrinolysis | HR (95% CI) |
|---|---|---|---|
| Overall cohort | | | |
| *n* | 790 | 782 | |
| Composite endpoint | 463 (58.7) | 487 (62.3) | 0.86 (0.76–0.98) |
| Rehospitalization for MI | 151 (19.0) | 190 (24.5) | 0.75 (0.60–0.93) |
| All-cause death | 398 (50.5) | 401 (51.3) | 0.95 (0.83–1.09) |
| Cardiac death | 144 (18.3) | 178 (22.7) | 0.78 (0.63–0.98) |
| Non-cardiac death | 242 (30.5) | 217 (28.0) | 1.11 (0.92–1.33) |
| Referral hospitals | | | |
| *n* | 567 | 562 | |
| Composite endpoint | 332 (58.7) | 360 (64.1) | 0.82 (0.71–0.96) |
| Rehospitalization for MI | 115 (20.2) | 142 (25.4) | 0.77 (0.60–0.98) |
| All-cause death | 285 (50.5) | 294 (52.3) | 0.91 (0.77–1.07) |
| Cardiac death | 110 (19.4) | 135 (24.3) | 0.79 (0.61–1.01) |
| Non-cardiac death | 167 (29.2) | 157 (28.2) | 1.04 (0.84–1.30) |
| Invasive centres | | | |
| *n* | 223 | 220 | |
| Composite endpoint | 131 (58.7) | 127 (57.7) | 0.97 (0.76–1.24) |
| Rehospitalization for MI | 36 (15.9) | 48 (22.1) | 0.69 (0.45–1.07) |
| All-cause death | 113 (50.7) | 107 (48.6) | 1.08 (0.83–1.40) |
| Cardiac death | 34 (15.3) | 43 (19.4) | 0.77 (0.49–1.21) |
| Non-cardiac death | 75 (33.7) | 60 (27.1) | 1.30 (0.93–1.82) |

The composite endpoint includes all-cause death and rehospitalization for MI. Cumulative incidence proportions and hazard ratios are based on a competing risk model for the endpoints: rehospitalization for MI, cardiac-, and non-cardiac death. CI, confidence interval; HR, hazard ratio; pPCI, primary percutaneous coronary intervention.

did not reach statistical significance (HR 0.97, 95% CI 0.76–1.24). However, point estimates of rehospitalization for MI and cardiac death in both subgroups favoured pPCI. *Figure 2* illustrates the HRs of the composite endpoint in a number of prespecified subgroups according to baseline characteristics.

The average time from randomization to first main endpoint (death or rehospitalization for MI) was 10.6 years for pPCI and 9.5 years for fibrinolysis, leading to a pPCI-related average postponement of main event of 12.3 months (95% CI 5.0–19.5) after 16 years of follow-up. The average postponement of rehospitalization for MI in 16 years was 11.5 month (95% CI 4.8–18.3) with pPCI treatment compared to fibrinolysis (13.7 vs. 12.8 years). The average survival after index STEMI was 11.2 years with fibrinolysis and 11.6 years with pPCI, with a difference in mean survival time of 4.9 months (95% CI −1.8 to 11.6) at 16 years of follow-up.

# Discussion

This study reports the 16-year outcomes of the DANAMI-2 trial, which was the first to document that transfer for pPCI was superior to on-site fibrinolysis. The current study represents the longest follow-up comparing pPCI vs. fibrinolysis in STEMI patients. With a median age of 63 years in each treatment group at baseline, a 16-year follow-up study provides an extensive cardiovascular perspective of pPCI vs. fibrinolysis in STEMI patients. We found that the superiority of pPCI on the composite endpoint of death or rehospitalization for MI was sustained, both in the total cohort and in patients transported from a referral hospital to a pPCI-capable tertiary hospital. Moreover, the study is the first to document a significant reduction of cardiac mortality compared to fibrinolysis. The average time to first event of the composite endpoint was 10.6 years with pPCI, with an average postponement of 12.3 months of either death or rehospitalization for MI with pPCI as compared to fibrinolysis.

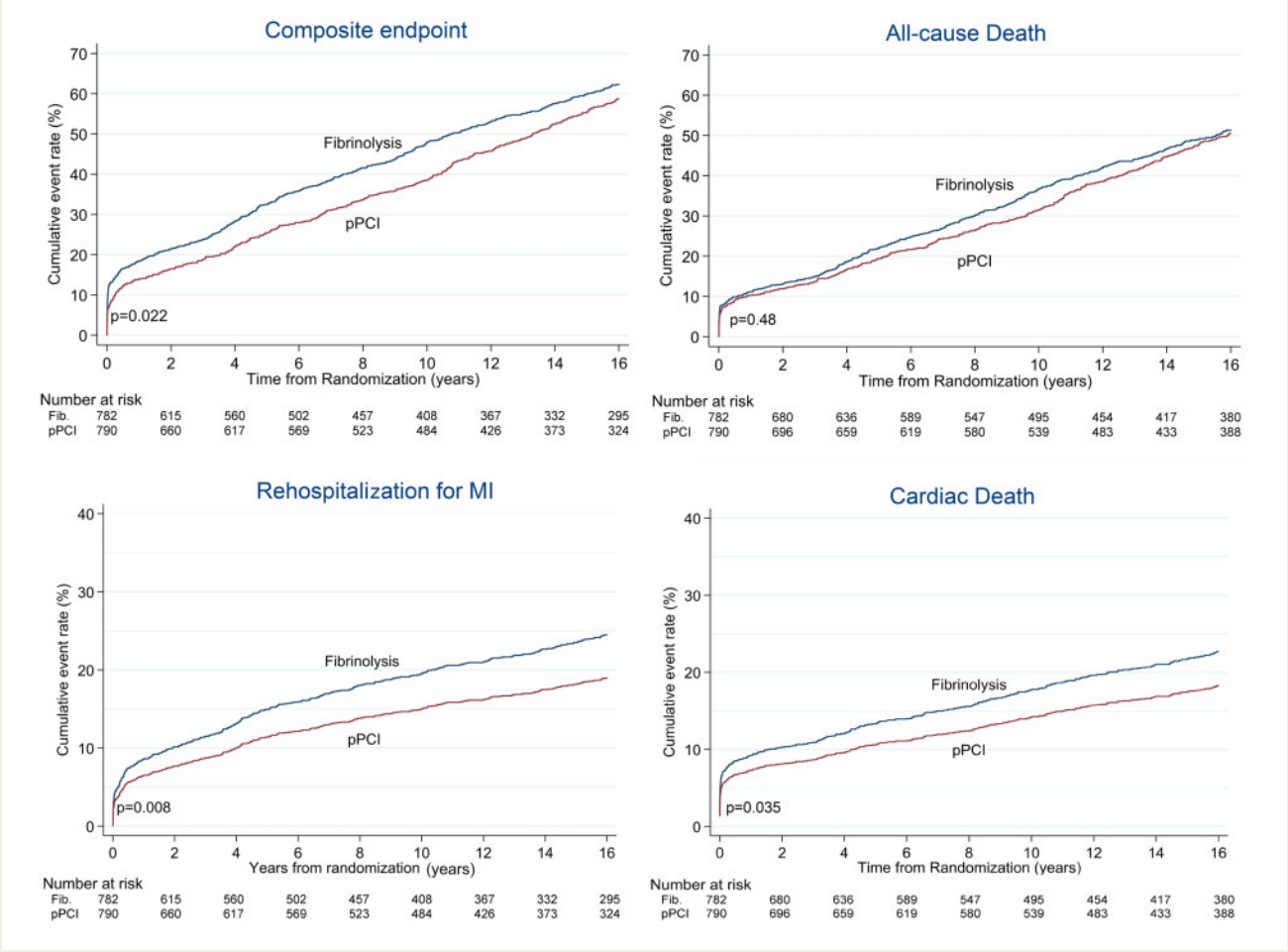
## Composite endpoint

Here, we report a sustained lower rate of the composite endpoint of death or rehospitalization for MI in patients treated with pPCI compared to fibrinolysis. After 16 years the absolute difference in composite endpoint in the total DANAMI-2 population was 3.6%. Compared to the trend found in previous studies reporting up to 8 years of follow-up,[3,4,8–10] the difference in composite endpoint tended to level out over time. We found that the curves of the composite event converge after 12–13 years (*Take home figure*). This convergence might be explained by a diluted effect of the initial randomization over time, especially with regards to all-cause mortality as many patients in this age group die from non-cardiac causes such as cancer.[21]

The maintained difference in the composite endpoint was primarily driven by a 5.5% higher rate of rehospitalization for MI in patients treated with fibrinolysis compared to pPCI. This finding is concordant with shorter-term follow-up studies.[3,8–10]

We previously reported that 96% of patients randomized at referral hospitals arrived at the catheterization laboratory within 120 min.[3] This delay is reported to be even lower in more recent trials.[22] Moreover, our previous results showed that interhospital transportation was associated with a median treatment delay of 55 min.[9] The present study shows that pPCI treatment remains associated with lower rates of the composite endpoint, even in patients transported from the referral hospital to the nearest invasive centre.

Very long-term follow-up of landmark studies are important to support the practice-changing benefits of implementation of STEMI centres with 24/7 interventional facilities for immediate pPCI. While hitherto not reported in STEMI patients, follow-up studies of major randomized trials in non-STEMI patients have reported conflicting results on very long-term outcomes following an early invasive strategy vs. a non-/selective invasive strategy.[23,24] A 15-year follow-up of the FRISC-II trial reported a lasting postponement of death or next MI by an average of 18 months in patients treated with an invasive strategy compared to a non-invasive strategy in non-STEMI patients.[23] In contrast, the 10-year outcomes of the ICTUS trial showed no benefit of an early invasive strategy in reducing death or spontaneous MI in non-STEMI patients.[24] In concordance with the FRISC-II trial, we found that an invasive strategy for STEMI patients provides a lasting postponement of the composite endpoint over 16 years, with an average postponement of 12.3 months with pPCI treatment compared to fibrinolysis.




**Take home figure** Cumulative event curves of 16-year outcomes in the DANAMI-2 study. The composite endpoint includes all-cause death and rehospitalization for MI. Fib., fibrinolysis; pPCI, primary percutaneous coronary intervention.

## Mortality

Previous randomized trials have shown numerically lower rates of short-term mortality with pPCI treatment compared to fibrinolysis. However, neither of the individual studies showed a significant mortality difference, nor were they powered to this purpose.[1–3] Meta-analyses of randomized trials have reported a 30-day absolute mortality reduction of 2–3% in favour of pPCI.[25,26] The previous 8-year follow-up of the DANAMI-2 trial reported a significant absolute difference in all-cause mortality in the referral hospital subgroup of 6.6% and point estimates favouring pPCI in the total DANAMI-2 cohort.[9]

In the current study, no difference in all-cause mortality between the treatment groups could be demonstrated after 16 years. While mortality curves diverged within the first 10 years, the curves started moving towards each other through the last 6 years. However, we found an absolute difference in cardiac mortality of 4.4% in patients treated with pPCI compared to fibrinolysis. The HRs in both subgroup analyses supported this finding, and the cumulative event curve show a consistent divergence during the follow-up period (*Take home figure*). It seems likely that this effect is caused by the increased rate of rehospitalization for MI in patients treated with fibrinolysis compared to patients treated with pPCI. This finding provides evidence of a long-term benefit of pPCI treatment, even after 16 years.

## Limitations

Several important diagnostic and therapeutic improvements have been implemented since the enrolment of patients in the DANAMI-2 trial in the years from 1997 to 2001. These include improvements in the prehospital diagnosis and triage,[27,28] important developments in pharmacological treatment including longer treatment with the newer potent platelet inhibitors ticagrelor or prasugrel[29], and also advances in stent technology with the current use of newer-generation drug-eluting stents and better implantation techniques.

Fibrinolysis has evolved too. In the DANAMI-2 trial, patients were treated according to 1997–2001 standards. Consequently, patients with failed fibrinolytic treatment often were conservatively treated. Some patients with failed fibrinolysis were treated with repeated fibrinolysis ($n = 26$) while only a few underwent rescue PCI ($n = 15$).[3] We have previously reported that mechanical revascularization within the first 3 years was considerably more common in the fibrinolysis group.[8] Within these first 3 years, PCI was performed in 16% of the

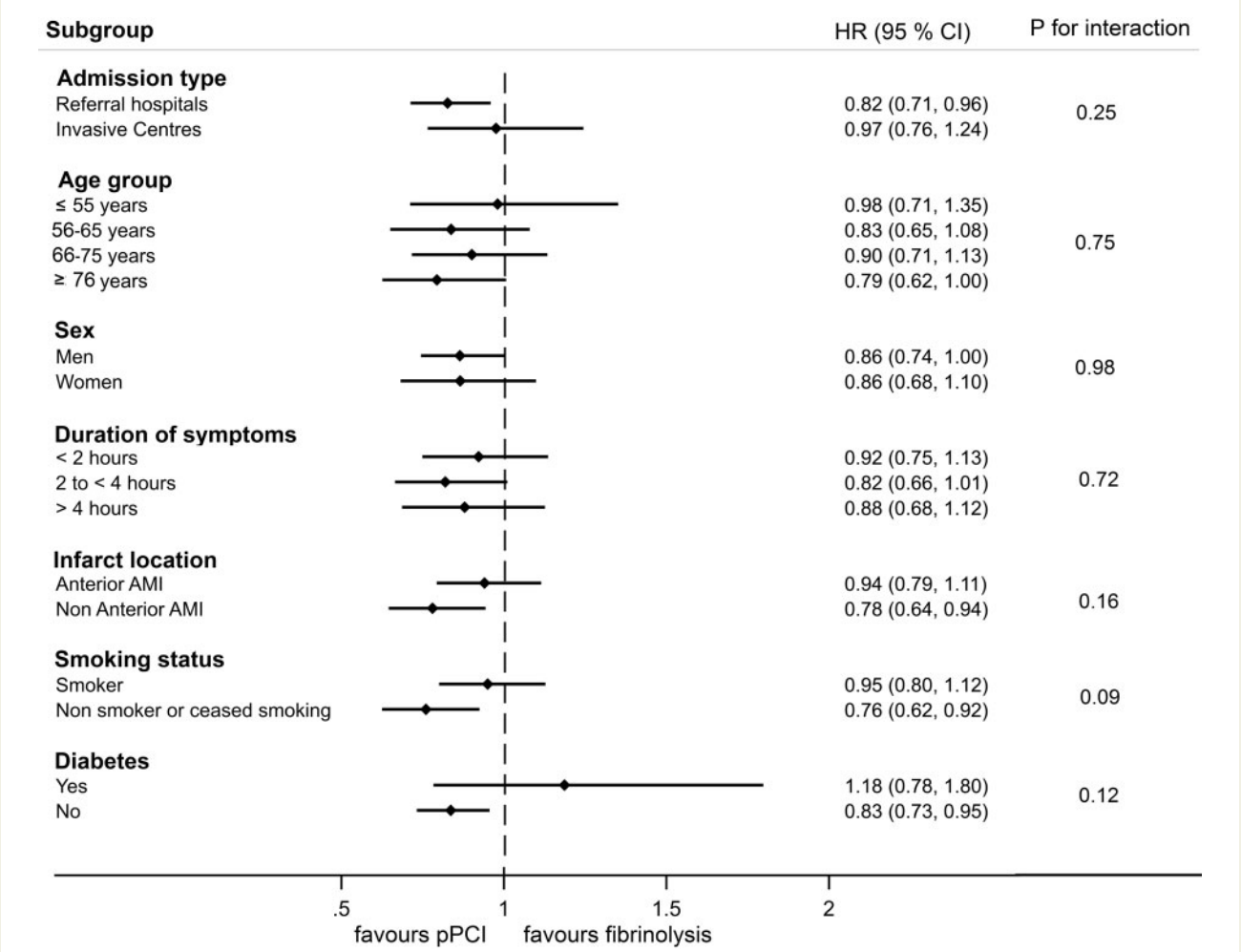



**Figure 2** Forest plot illustrating subgroup analyses of primary percutaneous coronary intervention vs. fibrinolysis according to baseline characteristics in the DANAMI-2 trial. AMI, acute myocardial infarction; pPCI, primary percutaneous coronary intervention.

patients after index pPCI compared to 34% after fibrinolysis ($P = 0.001$) while CABG was performed in 9% vs. 12%.[8] This difference was most pronounced within the first 6 months.[8] In our present landmark analysis from 3 to 16 years we report a small, but insignificant, additional increase in mechanical revascularization in the fibrinolysis group.

In 2013, the STREAM trial provided evidence that when pPCI cannot be achieved within 1 h after first medical contact, a pharmacoinvasive strategy with fibrinolytic treatment and subsequent pPCI if needed provides an alternative to a pPCI strategy, although bleedings were increased in the pharmacoinvasive group.[22] Further support to this approach arises from 5-year results of the French FAST-MI registry.[30] Thus, it is very likely that a facilitated pharmacoinvasive approach with coronary angiography and, if relevant, revascularization early after fibrinolysis might provide a superior strategy as compared to the conservative fibrinolysis therapy in DANAMI-2, in particular with regard to the risk of rehospitalization for MI. In this context, one must keep in mind that the Danish geography and infrastructure is ideal for fast transfers for pPCI. In many other countries, a pharmacoinvasive approach will be the option of choice when transfer to pPCI cannot be reached within a 120 min timeframe.[22,30]

Finally, we used a combination of clinical follow-up and follow-up by national health registries. To assure high accuracy in the registry-based event detection from 3 to 16 years, we used validated algorithms and definitions.[17,18]

## Conclusion

The superiority of pPCI over fibrinolysis was maintained at 16-year follow-up. Patients treated with fibrinolysis have a sustained increased rate of rehospitalization for MI and an increased long-term risk of cardiac death compared to patients treated with pPCI. This conclusion supports the current international guidelines which state that pPCI should be offered if time of STEMI diagnosis or first medical contact to reperfusion (wire crossing) is within 120 min,[5–7] and reinforce that a pPCI strategy with fast access to pPCI-capable hospitals should be implemented in countries or regions where this strategy is possible.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

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**Conflict of interest:** S.D.K. has received lecture fees from Aspen, AstraZeneca, Bayer, and BMS/Pfizer. K.K.W.O. has received speakers fee from Bayer. T.E. has received advisory board or speakers fee from Abbot, MSD, and Bayer. M.M. has received advisory board or lecture fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Novo Nordic foundation, and Boston Scientific. All the other authors report no conflicts of interest in this work.

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