And fibrinolysis became pharmacoinvasive.

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ABBREVIATIONS:

DANAMI-2: DANish trial in Acute Myocardial Infarction-2; PRAGUE-2: PRimary Angioplasty for patients with acute myo-cardial infarction, transported from the General non-PCI hospitals tocatheterization Units with or without Emergency thrombolysis; RCT: randomized clinical trial; STEMI: ST-segment elevation myocardial infarction; percutaneous coronary intervention (PCI).

Timely reperfusion is the cornerstone of treatment for patients presenting with ST-segment elevation myocardial infarction (STEMI).[1] In fact, the development of reperfusion therapy for STEMI is one of the most successful stories in the history of medicine, since it was associated with impressive mortality reductions in less than 3 decades.[2] In the late 1980s and early 1990s, several randomized clinical trials (RCT) demonstrated that, compared to a conservative management, pharmacological reperfusion with intravenous fibrinolysis was associated with reduced mortality in patients presenting with STEMI.[3, 4] Mechanical reperfusion with percutaneous coronary intervention (PCI), first with balloon angioplasty[5-7] and then with stenting,[8, 9] was shown to be clinically superior to fibrinolysis in head-to-head studies. Mortality benefit of PCI over fibrinolysis was only shown in metaanalyses including all head-to-head studies published up to 2003.[10, 11] Most of the studies included in these metaanalyses enrolled patients being admitted to hospitals with PCI facilities; however, many times PCI is not an immediate option and requires transport to another facility. Two landmark trials published almost simultaneously in 2003, DANAMI-2[12] (n=1572) and PRAGUE-2[13] (n=850), studied the clinical impact of transfer to PCI vs. onsite fibrinolysis (in DANAMI-2 one third of the population was recruited in a center with PCI facilities). The primary outcome in PRAGUE-2 (all cause death at 30 days) was not significantly different between groups (6.8% in PCI vs 10% in fibrinolysis, p=0.12), but the main secondary outcome (composite of death, re-myocardial infarction (re-MI) or stroke at 30 days) was significantly less in the PCI arm. Conversely, the primary endpoint in DANAMI-2 (composite of death, re-MI or disabling stroke at 30 days) was significantly reduced in the PCI group.[12] All individual components of the primary endpoint favored PCI, but the statistical significance was mainly driven by the large reduction in the rates of re-MI at 30 days (1.6% vs 6.3%, p<0.001). As in PRAGUE-2,[13] all cause death rates in DANAMI-2 trial were numerically lower in the PCI but differences did not reach statistical significance (6.6% vs 7.8%, p=0.35). Outcomes rate in the subpopulation of patients enrolled in non-PCI centers were consistent with the entire population. The rates of 30 days repeat revascularizations were significantly less in the PCI arm (9.1% vs 18.9%, p>0.001).[12] In the 3 years pre-specified follow-up of the DANAMI-2,[14] the rates of the primary composite endpoint were still significantly lower in the PCI group, and again the differences were driven by a significant reduction in the cumulative rates of re-MI (8.3% vs 12.3%, p=0.007). Differences in the incidence of cumulative repeat revascularizations were even larger than in the earlier follow-up (25% vs 46%, p<0.001). A 5 years follow-up of the PRAGUE-2 RCT showed similar results, with significant differences favoring PCI for re-MI (12% vs 19%, p=0.009) and for repeat revascularizations (33% vs 51%, p<0.001). In DANAMI-2, cardiac death rates were non-significantly less in the PCI arm at 3 years.[14]

In this issue of the journal, the very long-term follow-up of the DANAMI-2 RCT (16 years) are presented.[15] The primary outcome of this not pre-specified follow-up (composite of death or re-hospitalization for MI) remained significantly less in the PCI arm, and again this was only driven by a significant reduction in the rates of re-MI (19% vs 24.5%). The 16 years cumulative rate of repeat revascularizations were less in the PCI group (42% vs 65.3%). Of special note, the 16 years incidence of cardiac mortality was significantly lower in the PCI group (18.3% vs 22.7%). Conversely, non-cardiac death rate was numerically higher in the PCI group (30.5% vs 28%). As a result, all cause death was very similar between groups (50.5% vs 51.3%) at 16 years follow up.

The results here reported[15] are unique from several perspectives. First, this study represents the longest follow-up ever reported in a RCT comparing 2 reperfusion strategies for STEMI. The study demonstrates that transfer for PCI (as long as it can be done timely after STEMI diagnosis) is overtly superior to stand-alone fibrinolysis. Compared to stand-alone fibrinolysis, PCI is associated with a long-lasting benefit in terms of reduction of re-MI and repeat revascularizations. Second and more importantly, this is the first time that primary PCI is shown to be associated with less cardiac mortality than stand-alone fibrinolysis in a RCT (4.4% absolute difference), and this is a major result. Thanks to the very long-term follow-up, this study is able to show differences not found by other trials. The fact that PCI was associated with numerically higher rates of non-cardiac death, and that all cause death was virtually identical in both treatment arms does not reduce the clinical relevance of the findings of the trial. The competing risks of cardiac and non-cardiac deaths and the very long-term follow-up are probably the cause of the higher rates of non-cardiac deaths. Given that the intervention (PCI) is not expected to increase long-term non-cardiac death (as compared fibrinolysis), the most relevant outcome to be interpreted is time to event. In fact, if the follow-up of the trial was prolonged long enough, one can anticipate that all cause death would be identical (100%), with significantly lower cardiac death and significantly higher non-cardiac death in the PCI arm. These facts reinforces the concept of measuring time-to-event in long-term follow-ups like the one here presented.

The DANAMI-2 very long-term follow-up data here presented[15] have been obtained thanks to fantastic Danish national registries where vital status, cause of death, re-hospitalizations for MI and even incidence of revascularizations can be obtained in virtually the entire population. This registry has been validated before for these purposes.[16] While the 30 days[12] and 3 years follow-up[14] was included in the study protocol as a pre-specified endpoint and adjudicated by an independent committee, the 16 years follow-up is only based on registries. While the quality of data in this very long-term follow-up is expected to be lower than in the previous cutoffs, this seems to have had little impact in the results here reported.

The most relevant questions to put this article into perspective are to what extent the results here reported represent today´s standards and how they will change our practice. DANAMI-2 trial enrolled patients from 1997 to 2001. Reperfusion regimes back then were significantly different from current standards.[1] Primary PCI technique has been significantly improved, but fibrinolysis strategy has changed conceptually to a bigger extent. Fibrinolytic agents, their administration protocol, and the concomitant antithrombotic regime (agents and treatment maintenance) have been improved. Patients undergoing fibrinolysis in the DANAMI-2 trial received accelerated t-PA (90 min infusion) and unfractionated heparin for 48 hours, while dual antiplatelet therapy was maintained for one month. Today´s recommended fibrinolysis regime includes tenecteplase (TNK) bolus plus enoxaparin and dual antiplatelet therapy for one year.[1] However, the old fibrinolysis regime might have had only a small clinical impact in the differences between treatment arms only in the very short-term. Something more relevant to interpret the long-term results of this study is the rate of post-fibrinolysis invasive angiography. In DANAMI-2, according to late 1990s standards, angiography was seldom performed. Patients with failed thrombolysis were conservatively managed, and planned angiography in patients with successful fibrinolysis was not considered. This management explains the excessive incidence of repeat revascularizations and re-MI rates, the main driver of the long-term clinical differences between treatment arms. Based on evidence from several RCTs and metaanalyses,[17, 18] current guidelines recommend an early (2-24 hours) routine angiography (plus PCI if indicated) in all patients.[1] The STREAM trial[19] is the most recent large RCT comparing transfer to PCI vs onsite fibrinolysis and applied current state-of-the-art management to fibrinolysis patients. In this trial, cardiac mortality at 1 year was similar for both treatment strategies (4.0% vs 4.1%),[20] showing that, today, any potential clinical benefit of timely transfer to PCI over fibrinolysis appear in the very early phase (bleeding events, microvascular obstruction, etc). Benefits of early angiography after successful fibrinolysis (pharmaco-invasive strategy) apply no only to intervention of the residual lesion in the infarct-related artery (IRA), but also to the potential intervention to non-IRA. Current myocardial revascularization guidelines recommend preventive PCI of non-IRA during hospital admission in STEMI patients.[21] This approach has been associated with a significant reduction in the rates of re-MI and future coronary revascularizations.[22] However, the benefits of angiography in identifying severe stenosis in non-IRA probably had no impact on the long-term results of DANAMI-2 since the protocol of the study considered a conservative approach to severe non-IRA stenosis in the PCI arm. Overall, the results presented in this study only represent the differences between PCI and stand-alone fibrinolysis, a strategy no longer recommended.

In summary, the 16 years follow-up of the DANAMI-2 trial represent a strong (indirect) argument to further reinforce current recommendations for performing an invasive approach early after successful fibrinolysis and treat all severe residual stenoses.[1]

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Disclosures

None.

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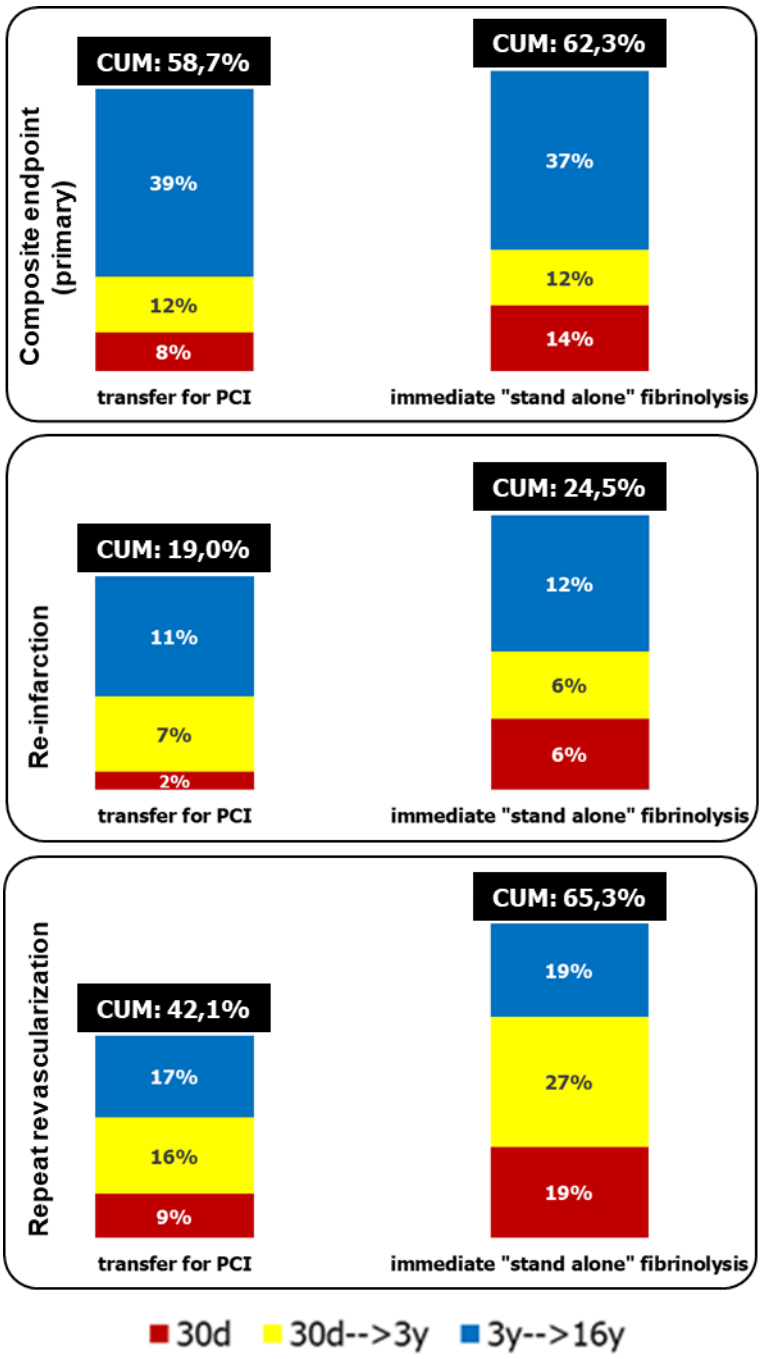
FIGURE. Cumulative and time-period incidence of major endpoints in DANAMI-2.



Data calculated (not actual) from DANAMI-2 publications, thus percentages are a proxy to actual numbers to illustrate the trajectories in the incidence of endpoints. As noted in text, primary endpoint differences are mainly driven by the excess in re-infarction rates in the fibrinolysis arm at 30 days. Conversely, the rate of revascularizations is lower in the PCI arm at every follow-up. The latter explains to a big extent the reduced incidence of cardiac death at 16 years follow-up. CUM: cumulative.