Prior myocardial infarction in the young: predisposes to a high relative risk but low absolute risk of a sudden cardiac death

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Aims
The study reports the relative and absolute risk of sudden cardiac death (SCD) in patients <36 years with prior myocardial infarction (MI).

Methods and results
Through review of death certificates, we identified all SCDs in Danes aged 18–35 years between 1 January 2000 until 31st December 2006. We then used the unique Danish civil registration number, which enabled us to follow all Danes in national registries, in the same period. Through the National Patient Registry we identified those with a prior myocardial infarction [implantable cardioverter defibrillator (ICD)-8: 410, ICD-10: I21 and I22] and incidence rates for SCD were estimated for survivors of MI and for individuals who had not yet suffered an MI, respectively. We estimated the relative risk of SCD and all-cause mortality by using extended Cox regression models. The 1 862 431 Danes aged between 18 and 35 years were followed in 9 388 453 person-years between 2000 and 2006. There were 7434 deaths of which 387 (5.2%) were SCDs. Myocardial infarction was diagnosed in 1234 patients, of those 10 died of SCD. Prior MI increased the incidence rate of SCD from 4.1 to 305.0 per 100 000 person-years [95% confidence interval (CI): 164.1–567.0]. Myocardial infarction was correlated with SCD and all-cause mortality, with a hazard ratio (HR) of 55.5 (95% CI: 29.5–104.4), P < 0.0001 and HR 8.3 (95% CI: 6.0–11.3), P < 0.0001, respectively.

Conclusion
We report that prior MI at a young age significantly increases SCD incidence from 4.1 to 305.0 per 100 000 person-years. Myocardial infarction is furthermore correlated with SCD and all-cause mortality with HR of 55.5 and 8.3, respectively.

Keywords
Sudden cardiac death • Myocardial infarction • Risk

Introduction
Loss of young family members due to a sudden cardiac death (SCD) is always a tragic event. In the past decades, studies have reported varying incidences and underlying causes of these deaths.1–7 In Danes below 36 years of age, ischaemic heart disease (IHD) remains the most common cardiac cause of SCD, although most cases are unexplained after autopsy.8 During the acute phase of myocardial infarction (MI), SCD is typically the result of acute ischaemia which provokes lethal ventricular arrhythmias. Later, the origin of arrhythmias evolves as a consequence of the structural remodelling of the left ventricle. Increasing mass and scars may cause re-entry circuits which eventually may lead to arrhythmias and SCD.9

In patients with prior MI and heart failure, the New York Heart Association class and the left ventricular ejection fraction (EF) are powerful predictors of SCD.10 In these patients at high risk, multiple clinical trials have demonstrated the effectiveness of the implantable cardioverter defibrillator (ICD) in reducing mortality.11–13 Nevertheless, although IHD markedly increases the
risk of SCD, most patients suffering from SCD do not prior to their death fulfill criteria for prophylactic ICD implantation, and even with aggressive therapy, mortality remains high accounting for 50% in elderly patients.9,14–17 This is a major problem when designing preventive strategies and several other risk factors and tests have therefore been investigated.18–20

We have previously identified the highest possible incidence of SCD in the young in Denmark between 2000 and 2006 using both autopsied and non-autopsied cases.8 To our knowledge, no study has investigated prior MI as a risk factor of SCD in patients <36 years. By using the unique Danish registries we followed all Danes aged 18–36 years. We identified those diagnosed with prior MI and calculated their absolute and relative risk of later dying of SCD.

Methods

Danish registries and death certificates

All Danish citizens have a unique and personal civil registration number (CRN) which can be linked to national registries on an individual level. The Danish National Patient Registry (NPR) contains information on all in- and outpatient activities in Denmark since 1978. Diagnoses are coded according to the corresponding International Classification of Diseases, the 8th revision (ICD-8) until 1993 and since 1994 the 10th revision (ICD-10) has been used. In the Cause of Death Registry (CDR), all primary and contributing causes of death are recorded. In this way, all non-sudden cardiac causes of death were obtained and categorized. Data in the CDR are based on the death certificates that are always issued when death occurs inside the Danish borders.

The Danish death certificates can only be issued by a medical doctor. In cases where citizens or patients are found dead and/or the death is sudden and unexpected, medico-legal external examinations are mandatory by law. These thorough examinations are performed by 34 certified medical doctors together with the police, and information from these examinations can be found in the supplemental information field on the Danish death certificate. If no mode of death is secured by the medico-legal external examination a forensic autopsy is to be performed. Owing to this great level of detail, the Danish death certificates are highly suitable to identify SCDs in Denmark.8

Study population and sudden cardiac death

All Danes aged 18–35 years were followed through Danish registries. Individuals were observed from the day they turned 18 years or from 1 January 2000, whichever came last, until the day the individual turned 36 years or until 31 December 2006, whichever came first.

Our group has, through review of all death certificates and autopsy reports, identified all SCDs in this period (2000–2006), as previously described in detail by Winkel et al.8 Briefly, in that study we estimated the highest possible incidence of SCD by using both autopsied and non-autopsied cases. An SCD was in autopsied cases defined as ‘the sudden, natural unexpected death of unknown, or cardiac cause; in unwitnessed cases as a person last seen alive and functioning normally <24 h before being found dead and in witnessed cases as an acute change in cardiovascular status with the time to death being <1 h’. Based on the circumstances related to the death, the same criteria were used in the non-autopsied cases and a previous medical history was not an exclusion criterion, but was taken into account in every single case.

We use these previously defined cases from both autopsied and non-autopsied SCDs to calculate the incidences and relative risks in this study. Not all SCDs were autopsied, and we therefore preferred to use the term possible SCD (SCDpos).

Myocardial infarction, cardiovascular comorbidities, and study endpoint

We used the Danish NPR and searched our study population for patients with a discharge diagnosis of MI (ICD-8: 410 and ICD-10: I21 and I22). These ICD diagnoses have previously been validated with a positive predictive value of 92% and a sensitivity of 91% by Madsen et al.21 We excluded all deaths occurring in 2 weeks after an MI, thereby eliminating those dying from acute heart failure following MI. All SCDpos were furthermore characterized through the NPR with regard to cardiovascular comorbidities. Our study endpoint was defined as SCDpos or death from any other cause.

Hospital records and the general practitioner

For all SCDpos we were able to identify all previous hospital contacts through the NPR. We then retrieved all records when available to describe circumstances surrounding the related time, especially to the MI and later death. Finally, we contacted the general practitioners (GP) and retrieved their records to further describe comorbidities, dispositions, family history and medications, etc.

Statistical methods

Clinical features and endpoints of the analysis were assessed with the use of the Stata software package (StataCorp, Collage Station, TX, version 12.0). Incidence rates for SCDpos were estimated for survivors of MI and for individuals who had not yet suffered an MI, respectively. We estimated the relative risk of SCDpos and all-cause mortality by using extended Cox regression models. In the Cox model, MI was treated as a time-dependent Heaviside
function, age was the underlying time-scale, and in the SCD_{pos} model, individuals were censored in case of non-SCD. Individuals with MI at baseline were allowed to enter the analysis. Relevant model assumptions were found to be valid. Owing to the relatively low number of SCD_{pos} among MI survivors, adjustment for potential confounders was not possible. We considered a two-sided \( P < 0.05 \) to be statistically significant. The study was approved by the local ethics committee (KF 01 272484), The Danish Data Protection Agency (2005-41-5237), and the Danish National Board of Health (7-505-29-58/1-5).

**Results**

In the seven-year study period 1,862,431 Danes aged between 18 and 36 years were followed in 9,388,453 person-years. Each individual was followed for a median of 6.4 years (IQR 3.1–7.0). There were 7,434 deaths of which 387 (5.2\%) were SCD_{pos}. Myocardial infarction was diagnosed in 1,234 patients, of those 434 patients (34\%) had been diagnosed before entering the study period. The remaining 760 patients were diagnosed in between 2000 and 2006. Of 1,234 patients with prior MI, 86 died of non-SCD (Figure 1) and 10 died of SCD_{pos}. Prior MI significantly increased the incidence rate of SCD_{pos} from 4.1 to 305.0 per 100,000 person-years (95\% CI: 164.1–567.0) (Table 1). Myocardial infarction was correlated with SCD_{pos} and all-cause mortality, with a hazard ratio (HR) of 55.5 (95\% CI: 29.5–104.4), \( P < 0.0001 \) and HR 8.3 (95\% CI: 6.0–11.3) \( P < 0.0001 \), respectively (Table 2).

The mean age at time of SCD_{pos} was 31 years [standard deviation (SD) ± 2.7; range 26–34]. All patients except two were men and mean time from MI to death was 2.9 years (SD ± 3.0; range 58 days–11 years and 5 months). Known dispositions to IHD were active smoking (\( n = 8 \)), family history of IHD (\( n = 5 \)), hypercholesterolemia (\( n = 3 \)), and hypertension (\( n = 2 \)).

The 10 SCD_{pos} had previously, primarily been diagnosed with an ST-elevation-myocardial infarction (STEMI) treated with either thrombolysis or percutaneous transluminal coronary angioplasty. Ejection fraction after MI was estimated by echocardiography. All deaths happened at home or in public places except for one in-hospital death. Almost all patients died while awake and in four cases death occurred under physical activity/exercise. Of the seven witnessed deaths, six had bystander heart and lung resuscitation, five of those with documented malignant arrhythmias treated with defibrillation, although all unsuccessfully (Table 3).

To describe comorbidity all ICD-8/10 diagnoses from the NPR along with medications are presented. Two patients had known insulin-dependent diabetes mellitus, one had epilepsy diagnosed before MI and finally one patient had a congenital heart disease. The remaining six patients had no other comorbidities than MI prior to their death (Table 4).

Surprisingly, none of these 10 deaths were autopsied and only 3 patients had a medico-legal external examination performed.

**Discussion**

In this nationwide study we followed all Danes aged 18–36 years for a 7-year period through registries, from 2000 to 2006. We identified 1,862,431 persons and followed them for 9,388,453 person-years with an incidence of SCD_{pos} of 4.1 per 100,000 person-years. Despite the young age of our study population, 1,234 patients had an MI discharge diagnosis in the NPR and of those, 474 (38\%), were diagnosed before 1 January 2000. Prior MI significantly increased the incidence rate of SCD_{pos} from 4.1 to 305.0 per 100,000 person-years.

This study is not the first to describe an association between IHD and SCD, although previously studies to our knowledge all have been conducted on much older populations. Thus, in patients with IHD there has been reported a 2.8- to 5.3-fold...
increase in risk of SCD, women and men with prior MI have been associated with a 4- to 10-fold higher risk of SCD, respectively. We reported an HR of 55.5 for SCDpos after MI and hence, MI seems to have a much higher impact in the young compared with older populations.

Although we find an HR of 55.5, the absolute risk of av SCDpos still remains low. It is noteworthy, though, that this study does not address all deaths related to MI and IHD. We only included patients if MI was diagnosed more than 2 weeks before death thereby excluding all those dying from acute heart failure following MI. In fact, IHD is the most common cardiac cause of SCD in young Danes, although most cases are unexplained. Of 314 previously reported cases of SCD in 2000–2006 in persons aged 1–35 years, 40 SCD cases were caused by IHD, and of those 39 were aged between 18 and 36 years. None of these specific patients had a history of prior MI.

The shortest interval between MI and SCD pos was almost 2 months and the mean time from MI to death was 2.9 years. It is well-known that in older populations, mortality rates are highest in the first 30 days after MI, and from here gradually decreases over time. Therefore it seems that survival patterns might look different in the young, and it could be speculated that with a longer follow-up period, even more patients would die of SCDpos following MI.

Improvements in primary and secondary prevention have, in the past 30 years, caused a decline in mortality due to IHD, but SCD mortality has declined to a lesser extent. Hence, new prevention strategies that will reduce SCD mortality are today a major challenge to reduce the overall mortality. Once overt IHD has been established traditionally risk factors for IHD are not specific for prediction of SCD with the exception of diabetes, kidney disease, and smoking. The current best-known predictor is heart failure with reduced EF, but most patients do not have a documented EF < 35% prior to their death and this may especially be a problem in the young. We found only two individuals fulfilling these criteria and they were both physically active at the time of death, which may indicate that they did not suffer from severe heart failure at all.

Furthermore, it is obvious that even though we report a high relative risk, the absolute risk is low and implantation of ICD-units in all young patients with MI in general is not an option, and better stratifications tools are therefore needed.

Sudden and unexpected deaths are by Danish laws required to have medico-legal external examinations together with the police, but only three persons were examined. It is remarkable and problematic that none of these patients were autopsied considering that 6 of 10 patients had no other known comorbidities than prior MI. Because none of these patients were autopsied we could not tell for sure if all patients died of SCD, hence we used the term SCDpos. Nevertheless, all patients had a prior MI, and because we had access to their death certificate, registry entries, and records from both hospitals and GPs we indeed believe that they definitely died of SCD, although not documented by autopsy.

In conclusion we found 1234 patients previously diagnosed with MI aged 18–35 years, of which 10 patients died of SCDpos. Although seemingly few deaths were found, the incidence of...
<table>
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<tr>
<th>Patient number</th>
<th>ICD-8/10</th>
<th>Date</th>
<th>Description</th>
<th>Medication before death</th>
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<td>1</td>
<td>E10.9</td>
<td>20-01-95</td>
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<td>Mixtard, Acetylsalicylic acid, Metoprolol, Verapamil</td>
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<td>E15.9</td>
<td>07-10-98</td>
<td>Hypoglycaemic coma</td>
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<td>01-06-95</td>
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<td>Defectus congenitus septi ventriculorum</td>
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<td>18-11-88</td>
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<td>13-02-95</td>
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<td>10-08-99</td>
<td>Acute myocardial infarction, unspecified</td>
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<td>5</td>
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SCDpos increased significantly from 4.1 to 305.0 per 100,000 persons-years in patients diagnosed with prior MI. We furthermore report that in a young population, MI indeed increases risk of SCDpos and all-cause with HR of 55.5 and 8.3, respectively. In a young population, MI indeed increases risk of SCDpos and all-cause with HR of 55.5 and 8.3, respectively. In the future, studies should evaluate the long-term consequences of MI in a young age, and focus on improving the preventive strategies, so that we will reduce the burden of SCD in not only the young but also in general.

**Study strengths and limitations**

The main strength of this study was that it was performed on nationwide data from a thorough review of death certificates of all deaths between 1 January 2000 and 31 December 2006. The Danish death certificates are unique and suitable to identify SCDs. It is, though, a limitation that they were identified in a retrospective design. It was fairly easy to extract data on whether or not a death was witnessed and if seen alive <24 h before, but in some cases more precise time limits were difficult to assess (<1 h). If in doubt the cases were discarded. Furthermore, it is a major limitation that none of our cases were autopsied thereby securing the SCD diagnosis, but they all fulfilled previously defined criteria for SCD. Myocardial infarction diagnoses were retrieved through nationwide registries which have previously been validated with a positive predictive value of 92% and a sensitivity of 91%. Owing to relatively few numbers of SCD after MI, the study had insufficient statistical power to adjust for confounders. Furthermore, we cannot exclude that an arrhythmic event may have occurred in these 10 patients without being directly associated with the primary MI. We allowed patients to enter the analysis if MI were diagnosed before 1 January 2000, thereby introducing some survivor bias. Nevertheless, to meet such problems with bias and confounding, a prospective design would necessitate an enormous cohort due to the few MIs and SCDs in this young population and this is currently the best that can be done.

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**Conflict of interest:** none declared.

**Author contributions**

BJørke Rigsby: drafting of manuscript, statistics, data collection, data analysis, and review of death certificates.

Jonas Bille Nielsen: statistics, drafting of manuscript.

Reza Jabbari: critical revision of manuscript and data analysis.

Stig Haunse: fundraising and critical revision of manuscript.

Anders Gaarsdal Holst: study design, statistics, review of death certificates.

Bo Gregers Winkel: review of death certificates, critical revision manuscript, and study design.

Jacob Tfelt-Hansen: review of death certificates, critical revision manuscript, and study design.

**References**


Defibrillation testing can reveal ‘concealed’ lead fracture

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Summary version
A 68-year-old patient with ischemic cardiomyopathy was admitted for a single-chamber implantable cardioverter-defibrillator (ICD) generator replacement after normal battery depletion. He was implanted in 2001 with a dual-coil lead (Sprint Quattro, Medtronic) and a Medtronic Gem 7227 device in secondary prevention. After connection of the new generator (Protecta XT VR, Medtronic), shock impedances of the ICD lead measured with subthreshold test pulses were normal (see figure). After defibrillation testing (DT), shock impedances were abnormal (>200 Ω). A screw problem was excluded, and a new defibrillation lead (Sprint Quattro Secure S6935, Medtronic) was implanted with normal shock impedance (71 Ω) and successful DT. This case highlights the importance of DT to identify ‘concealed’ high-energy lead dysfunction, especially in old leads.

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The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/defibrillation-testing-concealed-lead-fracture.pdf