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EDITORIAL

Sudden cardiac death in young patients with diabetes: a call to study additional causes beyond ischaemic heart disease

Hanno L. Tan[1,2]*, Laura H. van Dongen [1], and Dominic S. Zimmerman [1]

[1]Department of Cardiology, Heart Center, Academic Medical Center, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; and [2]Netherlands Heart Institute, Utrecht, The Netherlands

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This editorial refers to 'Sudden cardiac death among persons with diabetes aged 1-49 years: a 10-year nationwide study of 14 294 deaths in Denmark'†, by T.H. Lynge *et al.*, on page 2699.

Sudden cardiac death (SCD) accounts for 20% of natural deaths in Europe. SCD is most often caused by fatal cardiac arrhythmia and occurs across all patient categories. Diabetes is an important category, because it has a rising prevalence. Resolving the causes of increased SCD risk in diabetes has clear clinical relevance, particularly since diabetes is associated with an approximately two- to four-fold increased SCD risk after adjustments for cardiovascular risk factors.[1] The elevated prevalence of ischaemic heart disease (IHD) in diabetes, secondary to the accelerated development of atherosclerosis in diabetes, is usually regarded as the mechanism underlying this association, but emerging evidence suggests that it does not fully account for it, and that diabetes also increases SCD risk independently of IHD. It is expected that the role of non-IHD causes of SCD in diabetes is particularly large in young diabetes patients in whom manifest IHD is thought to not yet have developed fully. Systematic studies to explore this possibility have, however, so far been lacking. In this issue of the *European Heart Journal*, Lynge *et al.* have filled this knowledge gap by presenting data from a nationwide SCD registry in Denmark, supported by autopsy in a substantial proportion of diabetes patients (32%) and non-diabetes patients (57%).[2] In addition to focusing on young SCD victims with diabetes (aged 1–49 years), this study also focuses not only on patients with type 2 diabetes (T2DM), but also on patients with type 1 diabetes (T1DM); this is of added interest, given that cardiovascular disease complications and increased cardiovascular mortality in T1DM are increasingly recognized.[3] The key findings are: (i) SCD and non-SCD are the most common causes of death, with a similar prevalence; (ii) incidence rates of SCD are ∼10-fold higher in diabetes patients than in non-diabetes patients; (iii) elevated incidence rates occur both in T1DM patients (n = 71) and in T2DM patients (n = 47); (iv) the proportion of SCD patients with known cardiovascular disease in the diabetes group, while higher than in the non-diabetes group (15%), was still as low as 27%; (v) IHD was the most prevalent cause of SCD as confirmed by autopsy (47%); and (vi) the proportion of SCD cases that remained unexplained after autopsy [termed sudden arrhythmic death syndrome (SADS) by the authors] was similar in diabetes patients (26%) and non-diabetes patients (37%).

To learn what these findings teach us, we may consider a previous report by these authors using data from the same source population.[4] That paper reported on the characteristics and (autopsy-proven) causes of death of all SCD victims aged 1–35 years across Denmark. It reported that 13% (40 of 314) of SCDs were due to IHD and 43% (136 of 314) were due to SADS. These proportions are highly similar to the proportions in the 1–35 year age group in the present study (15% and 54%, respectively). Thus, with similar proportions of IHD in the diabetes and non-diabetes groups, but an ∼10-fold higher incidence rate of SCD in diabetes patients, the burden of severe IHD (of sufficient severity to be responsible for SCD) is indeed higher in diabetes, as generally assumed. Surprisingly, however, this also appears to apply to SADS. One possible conclusion is that diabetes confers SCD risk beyond the risk of IHD or SADS alone through as yet undiscovered factors (*Take home figure*). Diabetes patients in whom such factors are present may be sensitized to the

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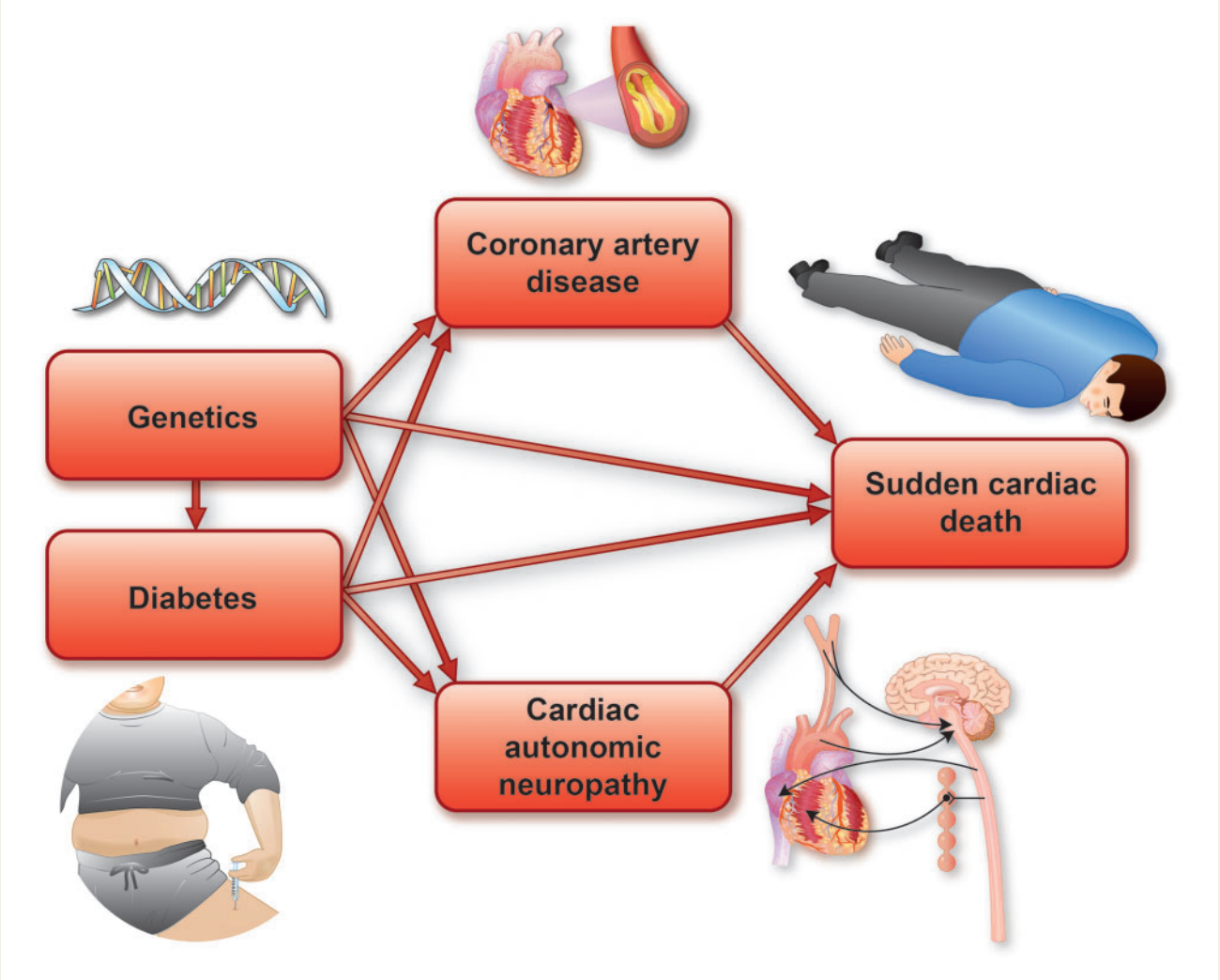
* Corresponding author. Department of Cardiology, Academic Medical Center, Amsterdam University Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: +31 20 5663264, Email: h.l.tan@amc.nl



Take home figure Possible pathways of which diabetes confers sudden cardiac death risk, additional to ischaemic heart disease or sudden arrhythmic death syndrome.

pro-arrhythmic effects of the pathomechanisms that underlie IHD and SADS. Future research efforts should aim to discover these factors.

To do so, one strategy is to focus on factors that remain undetected at autopsy (and lead to the diagnosis SADS). Diabetes-induced cardiac autonomic neuropathy (CAN) could be such a factor. CAN leads to an imbalance of sympathetic and parasympathetic control of the cardiac ion channels that control cardiac electrophysiology, thereby facilitating the occurrence of cardiac arrhythmia. Accordingly, CAN is associated with an increased mortality rate in diabetes.[5] While diabetic neuropathy, including CAN, has traditionally been viewed as a long-term complication of diabetes, recent evidence indicates that it may already occur at the time of the diagnosis of diabetes, and even in pre-diabetics.[6] In the patients studied by Lynge *et al.*, CAN may thus have already been present, although the median time from the diagnosis of diabetes was 13.9 years among the T1DM patients studied, and a mere 3.9 years among the T2DM patients. CAN is thought to result from a combination of microvascular disease of the vasa nervorum and neuronal oxidative stress.[7] Hyperglycaemia-induced metabolic changes may induce direct neuronal damage.[7] Accordingly, a predictor of CAN is a high level of glycated haemoglobin (HbA_{1C}), an indicator of chronically elevated blood glucose levels. Similarly, high HbA_{1C} levels are associated with increased SCD risk both in individuals with manifest diabetes[8] and in those without.[9] In addition, an inherited vulnerability to develop CAN is possible, but genetic research on CAN is scarce. A number of genes have been linked to CAN, based on their involvement in autonomic dysfunction in T1DM patients and in animal models.[10] Genetic variants associated with risk of CAN in T2DM patients have been found in the genes *TCF7L2*, *TNF-α*, and *CHT1*. Moreover, polymorphisms involved in CAN and other types of diabetic neuropathy were found in *ACE*, *AKR1B1*, *APOE*, *MTHFR*, *NOS3*, and *VEGF*. Still, twin studies showed contradictory results with regards to effect size introduced by genetic and environmental factors on CAN risk.

Clearly, further research on the genetic association between CAN, SCD, and diabetes is warranted. Other genetic studies have focused on factors involved in the development of IHD in DM. A genome-wide association study in T1DM patients discovered three loci for IHD (*CDK1*, *FAM189A2*, and *PKD1*).[11] Additionally, genetic variants at the *ANKS1A*, *COL4A2*, and *APOE* loci related to IHD were found, with a possible stronger effect size in T1DM than in the general population. Also, genetic variants for functionally related pathways (carbohydrate metabolism and glycan degradation) are enriched in both T2DM and cardiovascular disease, but there is limited evidence for locus overlap between T2DM and cardiovascular disease. Of interest, in a genome-wide association study into atherosclerosis risk, a variant in *HNF1A*, which could be predictive for development of T2DM,[13] reached genome-wide significance.[14] That study also found that a polymorphism in *SH2B3* may have a role in the progression of coronary plaque formation, while *SH2B3* is associated with T1DM. Finally, variants in genes involved in SADS should be investigated. Such genes typically encode the major or ancillary subunits of cardiac ion channels, i.e. causative genes for inherited arrhythmia syndromes such as long QT syndrome (*KCNQ1, KCNH2*, *KCNE1*, *KCNE2*, and *SCN5A*), Brugada syndrome (*SCN5A*), or catecholaminergic polymorphic ventricular tachycardia (*RYR2*). SADS-associated inherited vulnerability may increase SCD risk in the presence of acquired conditions such as IHD.[14] In T1DM and T2DM patients, unstable cardiac repolarization, a well-established mechanisms underlying SCD, may be the mechanistic link. For instance, since both hyperinsulinism and hypoglycaemia are associated with QT prolongation, it is conceivable that T1DM and T2DM patients who carry variants in repolarization-controlling genes are particularly susceptible to SCD. Surprisingly, however, the repolarization-controlling *KCNE1* gene also plays a role in atherosclerosis, as confirned in mouse studies.[15] Clearly, genetic studies are crucial to uncover relevant pathways that have so far remained unsuspected.

In summary, the study of Lynge *et al.* provides a strong and dearly needed boost for the notion that increased SCD risk in diabetes is not solely mediated by IHD and that additional factors are also involved. Future research efforts to discover such factors must retain a broad scope. For instance, a search for genetic variation and increased vulnerability for SCD in diabetes should, at a minumum, look at genes and pathways involved in control of both the autonomic nervous system and/or cardiac ion channels, and the development of IHD. It is hoped that these studies eventually increase our ability to recognize diabetes patients with elevated SCD risk, allowing for the design of preventive strategies.

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