**Standard operating procedures**

**15-year follow-up in the ADDITION-Europe Study**

# Danish Arm

The ADDITION study has demonstrated that early started and intensive cardio metabolic and anti-glycemic treatment potentially has a role in individuals with screen-detected type 2 diabetes. The effect of intensive treatment showed a non-significant 9% reduction of all-cause mortality and 11% reduction of the incidence rate of first CVD at 10-year follow-up in the ADDITON study.

The 15-year follow-up in the Danish arm of the ADDITION study is planned as a register based study, using the comprehensive Danish registers.

# Dutch Arm

For the Dutch arm data from Statistics Netherlands will be used.

## Primary endpoints:

The primary endpoint is a composite of first cardiovascular event, including

* + cardiovascular mortality,
  + cardiovascular morbidity (non-fatal myocardial infarction and non-fatal stroke)
  + revascularisation, and
  + non-traumatic amputation of extremities

Danish Arm

The National Patient Registry and *NOMESCO Classification of Surgical Procedures* will provide data on these endpoints using ICD-10 codes and operation codes, respectively (please see table 1).

Cardiovascular mortality will be identified as either a) information on diagnoses from the National Patient registry combined with information on subsequently death within 30 days of the cardiovascular event or b) information from the Cause of Death registry, in those situations where a person has died without primary admission to hospital. The Danish Cause of Death registry uses ICD-10 codes and we will search the same ICD-10 and operation procedure codes as for cardiovascular events (AMI and stroke in table 1) + the ICD-10 code for sudden cardiac death (I461).

# Dutch Arm

ICD-10 Death codes from the National Death registry from Statistics Netherlands combined with first events based on DBC codes (insurance declaration codes for diagnoses and treatments)

## Secondary endpoints:

The secondary outcomes are the individual components of the primary endpoint and all-cause mortality (see table 1)

## Date of event:

Danish Arm

The date of event will be defined as date of cardiovascular death or the date of first registration of a non-fatal event in the National Patient Registry. For the secondary end-points we will use the date of first registration for each of the non-fatal events and non-cardiovascular mortality and all-cause mortality (date of death in The Danish Cause of Death registry). Hence, an individual can be included in more than one secondary analysis e.g. if they first have a stroke and afterwards a AMI

# Dutch Arm

The date of event will be defined as date of cardiovascular death or the date of first registration of a non-fatal event in the National Cause of Death Registry. For the secondary end-points we will use the date of first registration for each of the non-fatal events and non-cardiovascular mortality and all-cause mortality (date of death in Dutch Cause of Death registry). Hence, an individual can be included in more than one secondary analysis e.g. if they first have a stroke and afterwards a AMI

## Mode of analysis Denmark:

The analysis of the Danish arm of the ADDITION study will take place at a locked server at Statistics Denmark. As the Danish authorities only accept extraction of non-personalised and aggregated data the analysis will be performed at this server. We will be able to deliver aggregated results of incidence rates, hazard ratios and variation of CVD and all-cause mortality for use in the ADDITION Europe 15-year meta-analysis.

## Mode of analysis The Netherlands:

The analysis of the Dutch arm of the ADDITION study will take place at a locked server at Statistics Netherlands. We will be able to deliver aggregated results of incidence rates, hazard ratios and variation of CVD and all-cause mortality for use in the ADDITION Europe 15-year meta-analysis.

## Recurrent events

We will not be able to identify dates of repeated events (e.g. date of a second or third AMI etc.) using the Danish registries.

## Analysis of 5-year and 10-year follow-up

In order to investigate the consequences of using register based identification of primary and secondary outcomes instead of expert-committee evaluation, we will repeat the examination of the 5 and 10-year incidence rates and rate ratios using the suggested coding algorithm in this protocol. We will use the same ICD-10 codes and coding algorithm as the suggestion for the 15-year follow-up. The end of follow-up will be 31.12.2009 and 31.12.2014 for 5-year follow-up and 10-year follow-up, respectively.

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| --- | --- | --- |
|  | Denmark | The Netherlands |
| Endpoints: | Definition  Note: For the international NOMESCO classification the "K" before all the codes are not included e.g. KFNA in Denmark is FNA in the international classification. The link for the SKS codebook is at the end of this table |  |
| Ischaemic heart disease | *ICD10 codes – all sub-numbers included:*  I21-24 (I21: acute myocardial infarction, I23: complications after acute myocardial infarction, I24: other acute ischaemic heart disease)  and  *NOMESCO Classification of Surgical Procedures*  KFNA-KFNG (Coronary bypass or Percutan coronary intervention (PCI))  %KFNG20 & %KFNG22 (removal of foreign object) | *Mortality: Dutch death registry:*  *ICD10 codes – all sub-numbers included:*  I21-24 (I21: acute myocardial infarction, I23: complications after acute myocardial infarction, I24: other acute ischaemic heart disease)   |  |  |  | | --- | --- | --- | |  | | | |  |  |  |   *Morbidity: first episode from Vektis datafiles (financial care registry) DBC codes:*  *0320-02-00-0204, Cardiologie, ST elevatie hartinfarct*  *0320-02-00-0205, Cardiologie, Non ST elevatie hartinfarct*  *0320-08-00-0801, Cardiologie, Follow-up na acuut coronair syndroom*  *0320-08-00-0802,Cardiologie , Follow-up na PTCA en/of CABG en/of ablatie* |
| Stroke | *ICD10 codes – all sub-numbers included:*  I61 (cerebral bleeding),  I62: Other nontraumatic intracranial haemorrhage  I63 (cerebrovascular infarct),  I64: Stroke, not specified as haemorrhage or infarction  *NOMESCO Classification of Surgical Procedures*  KAAL10 (thrombolysis)  KAAL11 (thrombektomia)  KPAQ 10 (Insertion of stent into brachiocephalic trunk )  KPAQ 20 (Insertion of stent into common carotid artery)  KPAQ 21 (Insertion of stent into internal carotid artery) | *Dutch death registry*  *-Stroke I61-69*    *Excluded from the non-fatal stroke endpoint:*  *Subdural hemorrhage I62 Cerebral aneurysm I67.1*  *Cerebral arteritis I68.2*  *Moyamoya I67.5*  *Morbidity: first episode from Vektis datafiles (financial care registry) DBC codes:*  *0330-11-00-1102, Neurologie, Intracerebrale bloeding*  *0330-11-00-111, Neurologie, Onbloedige beroerte*  *0330-11-00-1199, Neurologie, Overige cerebrovasculaire aandoeningen* |
| Invasive peripheral vascular revascularisation | *NOMESCO Classification of Surgical Procedures*  *Head and neck*  KPAE10 and KPAE25 (thrombechtomy from truncus brachiocephalicus and a. carotis communis)  KPAF10, KPAF20, KPAF21, KPAF22 (thromboendarterectomy from truncus brachiocephalicus and a. carotis communis, a. carotis interna, a. carotis externa)  KPAH10, KPAH20, KPAH21 (Bypass to truncus brachiocephalicus and a. carotis communis, a. carotis interna)  Lower extremities – all sub-numbers included  KPEE (Thrombechtomy from a. femoralis)  KPEF (Thromboendarterectomy from a. femoralis  KPEH (bypass from a. femoralis)  KPEP (percutan angioplastic on a. femoralis)  KPEQ (endoproteste in a. femoralis  KPFE (Thrombechtomy from a. poplitea)  KPFH (bypass from a. poplitea)  KPFP (percutan angioplastic on a. poplitea)  KPFQ (endoproteste in a. poplitea | *Morbidity: first episode from Vektis datafiles (financial care registry) DBC codes:*  0313 - Interne geneeskunde 124 - Atherosclerose extremiteiten/perifeer vaatlijden  0303 - Chirurgie (Heelkunde) 439 - Overige perifere vaatziekten |
| Amputation  Non traumatic | *NOMESCO Classification of Surgical Procedures*  KNFQ09 (Exarticulation at hip or thigh)  KNFQ19 (amputation at thigh)  KNFQ99 (other amputation at hip or thigh)  KNGQ09 (exarticulation at knee)  KNGQ19 (amputation at knee or lower level)  KNGQ99 (other amputation at knee or lower level)  KNHQ09 (exarticulation at ankle or foot level)  KNHQ19 (amputation at ankle or foot level)  KNHQ99 (other amputation at ankle or foot level ) | *Morbidity: first episode from Vektis datafiles (financial care registry) DBC codes:*  *0303 - Chirurgie (Heelkunde) 432 – Operatie Diabetische voet (diabetes n.n.o.)* |
| Cardiovascular death | Death within 30 days after an ischaemic heart disease or stroke as defined above in the table  or  Death reason is cardiovascular according to the death register (using the same ICD-10 codes as mentioned above) + I461 (sudden cardiac death), without a prior admission to the hospital 30 days before death. | See above  Maybe include sudden death?   |  |  | | --- | --- | | Sudden death and death within 24h of symptom onset | R96.0-96.1 |   Death all causes will be registered |
| All-cause mortality | Defined by information from The Danish Civil Registration system | Death all causes from Dutch death registry |
| The coding is derived by the ICD-10 codes and by the Danish Operation-registry ( *NOMESCO Classification of Surgical Procedures* ):  ICD-10: <https://icd.who.int/browse10/2016/en#/Z80-Z99> SKS codebook: https://norden.diva-portal.org/smash/get/diva2:970547/FULLTEXT01.pdf SKS-browser: <http://medinfo.dk/sks/brows.php> | | DBC coding: <https://www.opendisdata.nl/msz/zorgproduct/099699071>  SN registry data, among others death registry and Vektis:  <https://www.cbs.nl/en-gb/onze-diensten/customised-services-microdata/microdata-conducting-your-own-research/microdata-catalogue> |