Material and Methods

Registries

Each resident in Denmark has a unique and permanent ten digit identification number which enables linkage of information from the Danish nation-wide registries on an individual level. Since 1978, all admissions to Danish hospitals are collected in the Danish National Patient Registry according to the International Classification Code (ICD) and the Nordic classification of surgical procedures (NCSP), respectively.\(^1\,^2\) All redeemed prescriptions since 1995 are enumerated in The Danish Registry of Medicinal Product Statistics (the Prescription Registry), according to the Anatomical Therapeutic Chemical (ATC) classification system. This registry holds specific information on prescription date, package size, amount of packages, and strength of the medication.\(^3\,^4\) Causes of death are registered in the National Causes of Death Registry and information on birth date, vital status, sex, annual income and migration is collected in the Central Person Registry.

Study population and outcomes

During 1995–2011, we obtained information on all patients with AAAs (ICD8 441 and ICD10 DI 714, 716, 719, 719A, 790), identified in the National Patient Registry. We validated the AAA codes in a sample of 100 patients randomly selected from 3 separate Danish hospitals and found an overall positive predictive value of 89%. Diagnoses were substantiated by imaging techniques including ultrasound and computer tomography in 90% of the cases. We applied a 60-day qualifying period starting at the day of the AAA diagnosis to avoid an anticipated high risk of AAA complications in temporal proximity of establishment of the AAAs diagnosis and to allow sufficient time for patients to claim their prescriptions from pharmacies. Only patients, who survived the qualifying period without undergoing surgery for AAA (including endovascular aortic repair) were included in the study. Patients undergoing surgery for AAA within the follow up period were censored at the time of the surgical intervention and patients permanently leaving the country were censored at the time of emigration. Also, patients with congestive heart failure (CHF) were censored at the time of CHF diagnosis to decrease the probability of confounding by indication with ACEI and ARB treatment. The cohort was followed until occurrence of a study outcome or for a maximum of 10 years. The primary outcome of the study was death from AAA (ICD8 441 and ICD10 DI71). Secondary outcomes were surgery for AAA (procedure codes KPCG, KPCP, KPCQ, KPDG, KPDN, KPDQ, KFCD and KPDC10), the composite of surgery for AAA or death from AAA, and all-cause death, respectively. We did not censor patients at time of surgery for AAA in our statistical modeling of all-cause death. The procedure codes for surgery for AAA have previously been validated in the Danish National Vascular Registry to have a reproducibility of 90-100%.\(^5\) The risk of surgery for AAA was defined as the probability of undergoing surgery for AAA within 10 years of diagnosis, the maximal time of follow up. Patients only contributed with one of the above-mentioned outcomes, whichever came first.

Concomitant medication, comorbidity and socioeconomics

Administration of ACEIs (ACT C09A), ARBs (C09B) and other medications were determined by prescription redemptions from the Danish pharmacies. The Danish Prescription Registry does not supply information on daily dosage or duration of treatment; therefore, we estimated an average daily dosage on the basis of up to four consecutive prescriptions. To avoid prediction on the future, calculations were exclusively based on previous prescription claims. By applying knowledge of the minimum, maximum, and ‘default’ (standard) treatment dose for each tablet strength of the specific drug of interest, we calculated whether the drug quantity dispensed to each individual was sufficient to allow for uninterrupted treatment between one prescription and the next. If this was not achievable, the treatment period was taken to be terminated at the
last day of treatment that was calculated from the on-going collection of consecutive prescriptions. If at a later point in time a new prescription was redeemed, a new treatment period was, by definition, initiated and the same scheme for determination of treatment periods was subsequently applied, so that several treatment periods were calculated for each individual patient. This method for determination of whether or not a drug was available to an individual at a particular time during follow-up has been used and validated by our group previously.\(^6\)\(^,\)\(^7\) To increase the sensitivity of the diagnostic codes, prescriptions of glucose-lowering drugs (A10), and loop diuretics (C03C) were used as proxies for diabetes and CHF, respectively.\(^8\)\(^,\)\(^9\) Similarly, we defined hypertension by treatment with two or more antihypertensive drugs within a period of three months, or any hospital admission with a hypertension diagnosis (ICD 8: 400-404; ICD10: DI10-15).\(^5\) Because the severity of hypertension is thought to play a role for AAA growth and rupture, and because the Danish registries lack blood pressure data, patients were classified in three hypertension severity groups by use of the surrogate of number of antihypertensive drugs (including ACEIs, ARBs, centrally acting adrenergic agents, beta blockers, calcium channel blockers and diuretics), i.e., those receiving ≤1 (group A), 2 (group B), and ≥3 (group C) drugs, respectively.\(^10\) Furthermore, we gathered information on the following comorbidities which previously have been linked to an increased risk of AAA rupture: chronic obstructive pulmonary disease/emphysema (ICD 8: 491, 492; ICD 10: DJ42-44), chronic kidney disease (ICD 8: 403-4, 581-84; ICD 10: DN02-08, DN11-12, DN14, DN18-19, DN26, DN158-159, DN160, DN162-164, DN168, DQ612-613, DQ615, DQ619, DE102, DE112, DE132, DE142, DI120, DM300, DM313, DM319, DM321B), ischemic heart disease (ICD8: 410-414; ICD 10: DI20-DI25), peripheral artery disease (ICD 8: 440; IDC 10: DI702-709) and carotid artery stenosis (ICD 10: DI652).\(^10\)\(^-\)\(^17\) We also divided the study population into high and low socioeconomic class based on the individual average annual gross income throughout the 5-year period prior to inclusion.

**Statistics**

Crude incidence rates (IRs) for each study outcome per 100 person-years were calculated for patients treated with ACEIs or ARBs. Differences in baseline characteristics were tested with Student’s t-test and Chi-square test for continuous and categorical covariates, respectively. Adherence to a given drug was calculated as the sum of on-treatment years for the total study population divided by the number of treated patients. Cox proportional hazard models were used to model survival and other endpoints. Each observation was split at the occurrence of any change in covariates (including [on- or off-] treatment status with ACEIs, ARBs and the other reported drugs) and after each year. Thus all covariates were considered in a time-dependent fashion and patient time ‘at risk’ with or without ACEIs and ARBs (and with respect to the other reported covariates) was fragmented into periods with different risk. Analyses were adjusted for age, sex, calendar year, socioeconomic class, diabetes, hypertension severity (group A, B, and C), chronic obstructive pulmonary disease, chronic kidney disease, ischemic heart disease, peripheral artery disease and carotid artery stenosis.\(^18\)

To examine if study outcomes were influenced by premature termination of treatment due to advanced age or comorbidity, results were tested in sensitivity analyses adjusted for treatment status at baseline or 60 days before an event. As the main analysis of death from AAA was censored at the time of surgery for AAA, we also examined this endpoint in a model not censored for AAA surgery as well as in a subgroup of patients who underwent surgery for AAA during follow-up. To further examine the role of confounding, we included a sensitivity analysis that did not censor for patients diagnosed with CHF. In addition, risk of death from AAA was tested for two other frequently used antihypertensive agents, i.e., beta-blockers and calcium channel blockers, by applying the exact same statistical model as used in the main analysis. To assess the impact of blood pressure control on our results, the primary endpoint was tested in a model not adjusted for hypertension severity group. We further investigated outcomes for 17 pre-specified subpopulations dependent on sex, age >
or ≤ 70 years, socioeconomic class, hypertension severity (groups A, B, and C), and presence of diabetes, chronic obstructive pulmonary disease, ischemic heart disease and peripheral artery disease, respectively. The proportional hazard assumption, linearity of continuous variables and absence of interaction between variables were fulfilled if not otherwise specified. A two-sided P value of 0.05 or less was considered significant. Analyses and data management were performed in SAS version 9.2 (SAS Institute Inc. Cary, North Carolina).