PUBLICATIONS OF
THE UNIVERSITY OF EASTERN FINLAND

Dissertations in Health Sciences

SARI RÄISÄNEN

YOUNG SACCULAR INTRACRANIAL ANEURYSM PATIENTS AND DE NOVO ANEURYSM FORMATION

RISK FACTORS AND PHARMACEUTICAL TREATMENT STRATEGIES

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To be presented by permission of the Faculty of Health Sciences,
University of Eastern Finland for public examination in Kuopio University
Hospital Auditorium 1, Kuopio on June 14th, 2024, at 12 o'clock noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
No 833

Department of Neurosurgery, Institute of Clinical Medicine,
School of Medicine, Faculty of Health Sciences
University of Eastern Finland, Kuopio
2024

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PunaMusta Oy
Joensuu, 2024
Distributor: University of Eastern Finland
Kuopio Campus Library

ISBN: 978-952-61-5237-0 (print/nid.)
ISBN: 978-952-61-5238-7 (PDF)
ISSNL: 1798-5706
ISSN: 1798-5706
ISSN: 1798-5714 (PDF)

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Räisänen, Sari
Young saccular intracranial aneuryms patients and de novo aneurysm formation
Risk factors and pharmaceutical treatment strategies
Kuopio: University of Eastern Finland
Publications of the University of Eastern Finland
Dissertations in Health Sciences 833. 2024, 112 p.
ISBN: 978-952-61-5237 (print)
ISSNL: 1798-5706
ISSN: 1798-5706
ISBN: 978-952-61-5238-7 (PDF)
ISSN: 1798-5714 (PDF)

ABSTRACT

An intracranial aneurysm (IA) is usually a saccular outpouching of the cerebral artery wall, that mostly affects the branching sites of intracranial arteries. A rupture of the aneurysmal wall causes an aneurysmal subarachnoid hemorrhage (aSAH), a form of hemorrhagic stroke with high mortality affecting mostly the middle-aged population. 1-7 % of all the IAs are found in patients younger than 18 years old, and aneurysms are also rarely reported in young adults. The risk of IA formation is considered to be affected not only by multiple acquired risk factors, but also possibly some yet unknown genetic risk factors. The characteristics of young IA patients are incompletely known, and patients who developed IAs at a young age, may have a different pathobiology when compared to the middle-aged population. It is also possible that these patients need different thresholds for follow-up or interventions.

The pathobiology behind IA formation is not fully understood, but the inflammatory process, triggered by hemodynamic stress, is considered to play a crucial role in formation of saccular IAs (sIAs). Most of the forming aneurysms never rupture, but treatment options for aneurysms are invasive and may cause morbidity or even mortality. The best therapy

for preventing aneurysmal-related morbidity and mortality would be to prevent aneurysmal formation.

A de novo aneurysm is a new intracranial aneurysm forming in a different location in a patient, who has previously been diagnosed with sIA disease. De novo aneurysms offer a unique way to explore the risk factors affecting formation of sIAs during follow-up.

We investigated the characteristics of young sIA patients, the risk factors behind de novo aneurysm formation and the possibility of affecting de novo sIA formation by pharmaceutical interventions in patients collected from Kuopio intracranial aneurysm database. There were 4082 patients diagnosed with sIAs in Kuopio University Hospital between 1980-2014. Of these patients 613 (15%) were younger than 40 years old at diagnosis. We also collected a cohort of 1419 sIA patients, who had been diagnosed with angiographically verified de novo sIA or who had received an angiographic follow-up for at least 5 years.

The study showed significant differences between patients who develop sIA disease manifestations at a young age and sIA patients overall. The young sIA patients developed de novo aneurysms even after 20 years of follow-up, demonstrating the need for possibly life-long follow-up. Investigations also showed that smoking is a significant risk factor for de novo aneurysm formation, which is why patients should actively be instructed to stop smoking. These patients' blood pressure should also be regularly measured, and high blood pressure, if diagnosed, should be meticulously treated. Selective COX-2 inhibitors and other NSAIDs with anti-inflammatory effects, did not significantly affect the risk of de novo aneurysm formation in our study, although inflammation is considered to play a crucial role in a formation of sIAs. However, aspirin might have some beneficial effects on de novo aneurysm formation and merits further studies as a non-invasive treatment strategy for reducing sIA formation.

Keywords: Intracranial aneurysm, subarachnoid hemorrhage, young age, antihypertensive agents, anti-inflammatory medication, aspirin

Räisänen, Sari
Nuoret aivovaltimoaneurysmapotilaat ja de novo aneurysmien muodostuminen. Riskitekijät ja lääkkeelliset hoitokeinot
Kuopio: Itä-Suomen yliopisto
Publications of the University of Eastern Finland
Dissertations in Health Sciences 833. 2024, 112 s.
ISBN: 978-952-61-5237 (nid.)
ISSNL: 1798-5706
ISSN: 1798-5706
ISBN: 978-952-61-5238-7 (PDF)
ISSN: 1798-5714 (PDF)

TIIVISTELMÄ

Aivovaltimoaneurysma on useimmiten sakkulaarinen (sIA) eli säkkimäinen pullistuma, joka muodostuu aivovaltimoiden haaraumakohtiin. Aneurysman seinämän puhkeaminen aiheuttaa tappavan lukinkalvonalaisen verenvuodon (aSAV). Se on erityisesti työikäiseen väestöön kohdistuva sairaus, johon sairastuneiden potilaiden keski-ikä on noin 54 vuotta. Aivovaltimoaneurysmista 1-7 % esiintyy alle 18-vuotiailla, ja aneurysmat ovat harvinaisia myös nuorilla aikuisilla. Näin ollen ajatellaankin, että aneurysmien muodostumiseen vaikuttavat erityisesti hankitut riskitekijät, mutta todennäköisesti myös jotkin geneettiset vielä tarkemmin tuntemattomat tekijät. Nuorella iällä aneurysmatautia sairastavien potilaiden ilmiasu tunnetaan vielä huonosti, mutta todennäköisesti heidän sairautensa taustalla vaikuttaa erilainen patobiologia kuin keski-iällä sairastavilla, mistä johtuen nuorten potilaiden seuranta- sekä hoitokriteerien tulisi erota keski-ikäisten vastaavista.

Sitä, miten sIA muodostuu ei vielä täysin tiedetä. Hemodynaamisen stressin laukaiseman, itseään ruokkivan inflammaatioreaktion, ajatellaan olevan merkittävässä roolissa aneurysmien muodostumisprosessin taustalla. Suurin osa muodostuvista aneurysmista ei koskaan vuoda ja toisaalta käytössä olevat hoitomenetelmät ovat invasiivisiä, joihin liittyy riski komplikaatioista sekä kuolleisuudesta. Tehokkain keino ehkäistä

aneurysmiin liittyvää sairastuvuutta olisi estää niiden muodostuminen. De novo aneurysmalla tarkoitetaan uutta aneurysmaa, joka muodostuu sIA-potilaalle. De novo aneurysmat mahdollistavat uniikilla tavalla aneurysman muodostumiseen vaikuttavien tekijöiden tutkimisen potilaan seuranta-aikana.

Tämä väitöskirja koostuu neljästä osajulkaisusta, joissa tutkittiin nuoren iän vaikutusta aneurysmatautiin, riskitekijöitä de novo aneurysmien muodostumisen taustalla sekä lääkkeellisiä vaikuttamismahdollisuuksia de novo aneurysmien muodostumiseen Kuopion aivovaltimoaneurysmarekisterin potilailla. Vuosina 1980–2014 Kuopion yliopistollisessa sairaalassa todettiin sIA 4082 potilaalla. Heistä 613 (15 %) oli alle 40-vuotiaita. Osajulkaisuihin II-IV Kuopion aivovaltimoaneurysmarekisteristä poimittiin kohortti, joka sisälsi 1419 sIA-potilasta, joita oli seurattu vähintään 5 vuotta angiografisesti tai heillä oli todettu angiografisesti vahvistettu de novo aneurysma.

Tutkimus osoitti, että nuoret sIA-potilaat eroavat merkittävästi ilmiasultaan muista sIA-potilaista, ja sen lisäksi he ovat merkittävässä riskissä muodostaa de novo aneurysmia, jopa 20 vuoden kuluttua ensimmäisen aneurysman toteamisesta. Nuoria aneurysmapotilaita tulisi todennäköisesti seurata niin kauan, kun heidän aneurysmiensa arvioidaan olevan aktiivisen hoidon piirissä. Tutkimukset osoittivat myös, että nuoren iän lisäksi merkittävä riskitekijä de novo aneurysmien muodostumiselle on tupakointi, jonka lopettamiseen potilaita tulisi aktiivisesti ohjata. Lisäksi korkeaa verenpainetta tulisi aktiivisesti etsiä ja hoitaa näiltä potilailta. Vaikka inflammaation ajatellaan olevan merkittävässä roolissa aneurysmien synnyssä eivät koksibit tai muut non-steroidaaliset anti-inflammatoriset lääkkeet vaikuttaneet merkittävästi de novo aneurysmien muodostumisriskiin. Sen sijaan aspiriinin käytöllä saattaa olla suotuisia vaikutuksia de novo aneurysmien muodostumiseen, ja sen käyttöä aneurysmien muodostumisen ehkäisyssä tulisi tutkia jatkossa.

Avainsanat: aivovaltimoaneurysma, lukinkalvonalainen verenvuoto, nuori, anti-inflammatorinen lääke, verenpainelääkkeet

ACKNOWLEDGEMENTS

This thesis is based on investigations conducted in the Department of Neurosurgery of Kuopio University Hospital from 2011-2022.

This study was supported by the Finnish Medical Foundation, the Kuopio University Hospital, the Päivikki and Sakari Solhberg Foundation, the Pro Humanitate Foundation and the Academy of Finland. I also want to thank the Finnish Cultural Foundation for a personal grant that made it possible to finish this thesis.

I want to first express my sincere gratitude to my supervisors Professor Juhana Frösén and Adjunct Professor Antti Lindgren for patiently supporting me through this process over the years. I will also always be grateful to Professors Juha E. Jääskeläinen and Mikael von und zu Fraunberg for their kind support and guidance at the beginning of my first steps as a PhD student. I also want to thank my co-authors for their valuable comments and support.

I want to thank the reviewers of the thesis, Melissa Rahi and Sami Tetri, for their thorough and precise reviewing process and their valuable and constructive comments.

I am very honoured that Professor Angelika Sorteberg accepted the invitation to be my opponent for the public examination of my doctoral dissertation.

I want to thank my friends and colleagues in pediatrics with my whole heart for supporting and encouraging me to continue with this thesis even during the times, when I was about to give up. I also want to especially thank Professor Marjo Renko for always being so exhilaratingly enthusiastic about research and teaching and for explaining the basics of statistics better than anyone before. I am grateful to Adjunct Professor Marjo Metsäranta for enabling me to combine clinical work with finishing this thesis.

And of course, the greatest gratitude goes to my family. I want to thank my mom Maija from her support and especially her help with the final moments of finishing the lay out of this book. Jussi, the love of my life, thank

you for always being there for me and patiently supporting me through this time-consuming process. Especial thanks to little Eino, for keeping me up all those nights, since it has been the most effective time to write some articles.

Hollola, April 2024
Sari Räisänen

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Räisänen S, Frösen J, Kurki MI, Huttunen T, Huttunen J, Koivisto T, Helin K, von und zu Fraunberg M, Jääskeläinen JE, Lindgren AE. Impact of Young Age on the Presentation of Saccular Intracranial Aneurysms: Population-Based Analysis of 4082 Patients. Neurosurgery. 2018 Jun 1;82(6):815-823

II Lindgren AE, Räisänen S, Björkman J, Tattari H, Huttunen J, Huttunen T, Kurki MI, Frösen J, Koivisto T, Jääskeläinen JE, von und zu Fraunberg M. De Novo Aneurysm Formation in Carriers of Saccular Intracranial Aneurysm Disease in Eastern Finland. Stroke. 2016 May;47(5):1213-8.

III Räisänen S, Huttunen J, Huuskonen TJ, von und zu Fraunberg M, Koivisto T, Jääskeläinen JE, Frösen J, Lindgren A. Use of antihypertensive medication and formation of de novo intracranial aneurysms. Eur J Neurol. 2022 Sep;29(9):2708-2715.

IV Räisänen S, Huttunen J, Huuskonen TJ, von und zu Fraunberg M, Koivisto T, Jääskeläinen JE, Lindgren A, Frösen J. Risk factor management matters more than pharmaceutical cyclooxygenase-2 inhibition in the prevention of de novo intracranial aneurysms. Eur J Neurol. 2022 Sep;29(9):2734-2743.

CONTENTS

ABBREVIATIONS

AAA	Abdominal aortic aneurysm
ACA	Anterior cerebral artery
ACoA	Anterior communicating artery
ADPKD	Autosomal dominant polycystic kidney disease
ASA	Acetylic asid or aspirin
aSAH	Aneurysmal subarachnoid hemorrhage
CCB	Calcium channel blocker
CCL2	Chemokine ligand 2
CD68	Macrophage-specific antigen
COX	Cyclooxygenase
CT	Computed tomography
CTA	Computed tomography angiography
CCA	Common carotid artery
DSA	Digital subtraction angiography
eNOS	Nitric oxide synthase of endothelial cells
EP_2	Prostaglandin E receptor 2
HR	Hazard ratio
IA	Intracranial aneurysm
ICA	Internal carotid artery
ICAbif	Bifurcation of internal carotid artery
KUH	Kuopio University Hospital
MCA	Middle cerebral artery
MCP-1	Monocyte chemoattractant protein-1
MMP-2	Matrix metalloproteinase-2
MMP-9	Matrix metalloproteinase-9

MRA	Magnetic resonance angiography
NF- κB	Nuclear factor κB
nNOS	Neuronal nitric synthetase
NO	Nitric oxide
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PGE_2	Prostaglandin E2
RAS	Renin angiotensin system
RIA	Ruptured intracranial aneurysm
RCT	Randomized controlled trial
sIA	Saccular intracranial aneurysm
sIA-SAH	Subarachnoid hemorrhage from ruptured sIA
SAH	Subarachnoid hemorrhage
TNFα	Tumor necrosis factor alfa
UIA	Unruptured intracranial aneurysm
VSMC	Vascular smooth muscle cell
WSS	Wall shear stress

1 INTRODUCTION

Intracranial aneurysms (IA) are outpouchings of cerebral arteries caused by degenerative cerebrovascular disease of cerebral arteries (1,2). IAs come from different etiologies, of which the idiopathic saccular intracranial aneurysms (sIA) are the most common type in the general population (1,2). The wall of an aneurysm ruptures when it weakens, leading to an aneurysmal subarachnoid hemorrhage (aSAH), a hemorrhagic stroke with an average mortality rate of 30-40% (3). Additionally, 30% of aSAH survivors will have a severe neurological and/or neurocognitive deficit (3). The incidence of aSAH fortunatelly seem to be decreasing (4,5) and approximately only 30% of IAs rupture during a lifetime (6).

About 3% of people develop unruptured sIAs and the risk of having sIA disease increases with age (7). SIA disease is not congenital (8); rather, the risk factors for the disease are acquired such as smoking and hypertension (7,9). However, aneurysms are still found in patients younger than 18 years old (10,11).

Young sIA patients seem to differ from the general sIA population regarding the disease's phenotype, but also longer life-expectancy (10,12,13). Follow-up studies of young patients have shown new aneurysms forming in sIA patients in different location in relation to the initial aneurysm, and these so called de novo aneurysms, are more common in young patients. However, studies of young sIA patients and de novo aneurysms are very heterogeneous (14–16). It might be that formation and rupture of sIAs have a different pathobiology in patients developing disease manifestations at a young age compared to typical aneurysm patients.

Treatment modalities for sIA are invasive and come with the risk of morbidity and mortality (17), which is why the best way to affect the sIA disease would be to prevent sIA development. Non-invasive treatment options are also needed because more and more unruptured sIAs are diagnosed due to increased screening and most of the sIAs never rupture, as previously mentioned.

Studies of the pathophysiology of sIA disease have hypothesized that inflammation, triggered by hemodynamic stress, has a crucial role in sIA formation and progression (18). De novo aneurysms forming during follow-up offer a special way to investigate sIA formation.

This study focuses on characteristics of Eastern Finnish patients who develop sIAs at a young age and the risk factors for formation of de novo aneurysms. We also investigated whether de novo aneurysm formation can be affected by pharmaceutical treatment.

2 REVIEW OF THE LITERATURE

2.1 INTRACRANIAL ANEURYSMS

Intracranial aneurysms (IA) are acquired cerebrovascular malformations caused by a cerebrovascular disease that is characterized by local degerative changes in the cerebral artery wall (1,2,19). Intracranial aneurysms are classified based on many features, for example shape (saccular, fusiform), etiology (mycotic, traumatic, dissecting, idiopathic) and size.

Saccular intracranial aneurysms (sIA) are sac-like outpouchings of an artery wall, often described also as berry aneurysms (1). Fusiform aneurysms are spindle-shaped dilations of the artery wall. They have a different underlying pathomechanism than saccular aneurysms and are rarer among the adult population than saccular aneurysms (2). Mycotic intracranial aneurysms are caused by a hematogenous spread of a septic infection, most often bacterial endocarditis, but they can also be caused by fungal or viral infections and can be either saccular or fusiform shaped (20). Fewer than 5 % of all the IAs are mycotic among all the IA patients (20). Traumatic intracranial aneurysms result from blunt or penetrating trauma and are rather rare since fewer than 1 % of all IAs are traumatic. Traumatic aneurysms are further categorized as true, false, or mixed (21). The arterial wall dissects without a preceding trauma in dissecting aneurysm and blood can leak between the vessel wall layers, causing fusiform dilation of the artery or a so-called pseudoaneurysm (19).

A weakened aneurysmal vessel wall may break eventually, causing an aneurysm to rupture. An sIA rupture leads to an aneurysmal subarachnoid hemorrhage (aSAH), a form of stroke with an average mortality rate of 30-40%. About 30% of survivors will have a severe neurological and/or neurocognitive deficit (3). Aneurysmal SAH mainly affects the middle-aged population (3); its incidence has previously been estimated to be approximately nine per 100 000 person-years (22), except for Finland and Japan where the incidence has been reported to be over twofold for

unknown reasons (22). It seems that the aSAH incidence is decreasing (4,5), fortunately, and most sIAs never rupture (6).

2.2 SACCULAR INTRACRANIAL ANEURYSM DISEASE IN YOUNG PATIENTS

The prevalence of saccular unruptured intracranial aneurysms (UIAs) is estimated to be approximately 3%, and increases with age (7). According to recent literature, 1-7% of all the aneurysm patients are found in patients younger than 18 years old (10,23–32). Based on autopsy studies, it has been concluded that aneurysms are not congenital but rather acquired lesions (8). However, aneurysms are still found, though extremely rarely, even in neonates (11).

Pediatric studies on IAs are variable, probably because of their rarity in this subgroup, and even the definition of a pediatric aneurysm patient is variable. The upper age limit of patients who are defined as pediatric in different cohorts differs between 15 and 20 years old. Most of the pediatric cohorts also include aneurysms of all etiologies, not only saccular ones. Only a few published case series exist that include only saccular pediatric aneurysms (23,33,34). Additionally, only a few population-based pediatric studies exist on intracranial aneurysms (10)(35). Therefore, the phenotype of patients developing sIAs at a young age has remained incompletely known.

The incidence of hemorrhagic stroke among the pediatric population was 1.4 / 100 000 person-years in a population-based study of 2.3 million children followed for 3.5 years (35). Aneurysm was diagnosed in 13% of these patients yielding an incidence of 0.18 /100 000 person-years for aneurysmal hemorrhagic stroke (35). Aneurysmal SAH is also rare in young adults. According to the literature, about 10-20% of all aneurysm patients are between 20-39 years old (36–39).

2.2.1 Acquired risk factors for intracranial aneurysms and young sIA patients

Acquired risk factors such as smoking that are generally connected to UIAs and aSAH (7,9) are usually not present in pediatric patients. Hypertension in childhood is relatively rare.

The first normal blood pressure distribution for children was published in the1970s according to measurements of healthy children (40). The upper limit for blood pressure was defined as blood pressure exceeding the 95th percentile age-related blood pressure curves. Hypertension in childhood is still diagnosed based on blood pressure levels exceeding the age-related 95th percentile, because there is still no data on blood pressure levels in childhood that associate with higher risk for adverse cardiovascular events (41). The prevalence of childhood hypertension has been estimated, within these limits, to be around 3%, and is increasing among overweight children (42,43). The secondary reasons for hypertension are more common than primary hypertension in young children, but the prevalence of primary hypertension is increasing especially among adolescents with overweight or obesity and a family history of hypertension (41). The reasons for secondary hypertension such as coarctation of the aorta, fibromuscular dysplasia, and autosomal dominant polycystic kidney disease (ADPKD) are also diseases connected to sIA disease (44). Elevated blood pressure in childhood and adolescence has been shown to associate with elevated blood pressure in adulthood (45). It has recently been shown that childhood cardiovascular risk factors, including systolic blood pressure and youth smoking, are associated with cardiovascular events and death from cardiovascular causes before the age of 60 (46).

It is plausible that these known acquired risk factors for aneurysm formation have also affected young adults for a shorter time than typical middle-aged aneurysm patients (7). It is remarkable, however, that there has been reports that smoking among pediatric IA patients (10) and young adults with sIA disease is much more common than in the general population (47). No studies exist on exposure to passive smoking or electronic cigarettes and the risk for sIA at a young age.

2.2.2 Characteristics of young sIA patients

Previous cohorts of pediatric sIA patients have shown that pediatric patients differ from the adult sIA patients in multiple ways, including their phenotype, among others. Some authors have suggested that pediatric intracranial aneurysm disease is distinct from adults (12,13,48).

Female gender is a known risk factor for sIA disease in the general population, but most pediatric patient cohorts have reported a male predominance (10,24,28,31,32). This has raised the question of whether some congenital factors affecting IA pathogenesis are more common in boys than in girls, and whether the influence of environmental factors changes the gender distribution as patients age (49). The clear predominance of the male gender disappears quite early, because roughly half of the young adult IA patient cohorts report male predominance (36,39) and half female predominance (38,50).

The location distribution of pediatric aneurysms is different than in adults. One of the most striking and coherently reported difference between adult and pediatric IA patients is that around 20-30% of pediatric aneurysms are at the internal carotid artery bifurcation (10) whereas only about 3-5% of the aneurysms are found at this location in adults (51). Aneurysms of the anterior cerebral artery (ACA) are not usually as common among pediatric IA patient as in adults, but variability exists between different pediatric cohorts. Posterior circulation aneurysms are also reported to be more common in pediatric patients than in adults (12,51); however, the reported portion varies from 0% to 60% (30,52).

Horiuchi et al. compared patients in their twenties and thirties and found differences in aneurysm locations and sizes similar to those seen in pediatric and adult IA patients (53). Patients in their study's cohort who were in their third decade had aneurysms more frequently in their ICA, and ACA aneurysm were rarely found. ACA aneurysms were most common in patients in their forties and in older IA patients. Patients in their forties had larger aneurysms more often than did younger patients (53). Kamitani et al (37) had similar results and hypothesised that presence of aneurysms in young adults and the sudden increase of ruptured aneurysms in patients

over 40 years old could indicate that aneurysms were already formed in childhood and adolescence and reach critical size, when patients are in their fifties (37).

The percentages of multiple aneurysms are reported with variability among young IA patients. Many cohorts (23,24,33) and a systematic review (54) of 573 children with 656 aneurysms have reported multiple aneurysms being rarer in pediatric patients than in the adult population. However, some cohorts also exist in which multiple aneurysms have been as common as in the adult population (16). Multiplicity has often been connected to other comorbidities (54).

Giant aneurysms (≥ 25mm) are also more commonly reported in pediatric cohorts, however, the percentage of giant lesions in different cohorts varies from 0-54% (31) between reports.

The variability of the pediatric cohorts also probably originates from the fact that atypical etiologies for adult IAs are more common in the pediatric population than in the adult population, and the patients with aneurysms with different etiologies are very often clustered together in the pediatric IA cohorts. The incidence of saccular aneurysms varies between 27-100% in pediatric aneurysm cohorts, and the incidence of fusiform aneurysm is between 6-59% (23,24). The incidence of aneurysm that is considered as mycotic varies between 3-14% and the incidence of traumatic aneurysms varies between 1.5-20% (24). The proportion of dissecting aneurysms was as high as 45% in a pediatric cohort reported by Lasjaunias et al. (26). Krings T. et al. likewise estimated the proportion of dissecting aneurysms to be about 50% from all the pediatric aneurysms and classical saccular aneurysms to be about 30% (55), while others also consider the saccular aneurysm without another known etiology to be as the most often reported aneurysm type in pediatric cohorts (56). It seems that the percentage of saccular aneurysms is most rare in toddlers and increases in school-age children. Saraf et. al reported that all the saccular aneurysms were in patients older than 10 years (49). Gross et al. reported a cohort of 33 pediatric aneurysm patients, of whom the patients aged 11-18 years were more likely to harbour saccular aneurysms than younger patients (8/14 versus 3/19) (57). Krings T. et al. similarly reported that

saccular aneurysms are rarely seen in children under the age of eight, but the incidence increases with age (55).

2.2.3 Familial disease

About 10% of sIA patients have a family background (58), meaning that these patients have at least two first-degree relatives with diagnosed sIA disease. The differences in patient and aneurysm characteristics have been described between patients with familial sIA disease and sporadic sIA patients, but the results are inconsistent. A meta-analysis of 16346 patients with 14225 IAs (59), reported that multiple IAs were found more often in familial patients (28.5%) than in sporadic patients (20 %) and familial patients more often had ruptured sIAs in their middle cerebral artery (MCA) (41 %). The aneurysms of patients with familial backgrounds seem to have ruptured at a younger age (46.5 yrs vs. 50.8 yrs), but it should be noted that there was considerable heterogeneity between the data in the included studies.

Familial background is rarely reported in pediatric patients in the literature, and familial aneurysms are even described as exceedingly rare among pediatric patients in one systematic review (54). Aeron G. et al. reported that familial IAs account for only 5 % of all the IAs in patients under 20 years old based on epidemiologic studies (60).

2.2.4 Clinical presentation and outcome of young IA patients

Most aneurysm in previous reports of pediatric aneurysm cohorts have been symptomatic and the rates of hemorrhagic presentation are high, up to 90% (10,61). However, the percentage of aSAH might be decreasing: A literature review of 1165 pediatric cases between 1939 and 2011 reported that 72% of patients under 18 years old presented with SAH (62). A smaller review of 573 children with 656 aneurysms from more recent literature between 2000-2015 reported that 55% presented with rupture and 30% with neurological symptom secondary to a mass effect (54). Some authors have divided their pediatric aneurysm cohort into different categories

based on aneurysm etiology (infections, post-traumatic, non-traumatic non-infectious saccular and non-traumatic, non-infectious fusiform) and learned that saccular non-traumatic, non-infectious aneurysms might be more prone to rupture than other aneurysms (26,63). Weir B. et al. studied the risk of rupture in sIAs categorized by size and patients age. They learned, as expected, that ruptured aneurysms were larger than unruptured, but they also reported that when patients were categorized by age, the percentage of ruptured aneurysms was highest (73%) in the group of patients who were 20-39 years old. The chance of patients presenting with a ruptured aneurysm decreased with increasing age (64), but it was also smaller (58%) in pediatric patients (≤19 years) than in patients in their twenties and thirties. A younger age has generally not been found to be a risk for rupture (65,66).

Incidentally found aneurysms in pediatric case reports have been rather rare (30,67) and it might be for this reason that many reports in the literature do not categorize patients' aneurysms into unruptured and ruptured when reporting patient outcomes (30,48,67). There is probably only one follow-up study of 60 incidentally found UIAs in patients younger than 18 years old (68). Of these aneurysms 72% were saccular with a mean size of 5mm (range 2-30mm). The follow-up time was 109 patient years, and during this time none of the IAs ruptured. Growth was seen in 8 (13%) aneurysms (4 saccular, 4 fusiform) and 6 aneurysms even decreased in size (68). Syndromic association was found in 43% of patients, with sickle cell disease the most common diagnosis (45%) (68).

Yasin et al. conducted a meta-analysis about treatment of pediatric IAs. The meta-analysis included 560 pediatric IA patients, of whom 473 (84.5%) had a favorable clinical outcome. Patients with unruptured IAs, as expected, had more favourable outcomes than patients with ruptured IAs (94.7% vs. 77.5%, $p < 0.001$). No statistically significant difference existed in long-term clinical outcomes between these treatment modalities in any subgroup when surgical treatment was compared to endovascular treatment (69). A systematic review of 135 studies published between 2000-2015 had similar results and reported good outcome in 85% patients aged 3 days-18 years and a mortality rate of 8% (54).

Alawi et al. collected a large sample of 1120 children from a national database between 1998 and 2009 and studied hospital mortality and complication rates between endovascular and surgical treatment (70). The mortality rate of the entire cohort was 2.41%, and the mortality rate was significantly higher among patients with ruptured aneurysms (6.99% vs. 0.94%, respectively, $p<0.0001$) when aSAH patients were compared with patients with unruptured aneurysms. Mortality was highest (5.3%) in children aged 1 year or younger and lowest (1.3%) in children 2-12 years old when children were categorized by age (70). In-hospital mortality was higher in surgically treated children than in endovascularly coiled children (6.09 vs 1.65%, respectively. OR 2.52, $p= 0.05$). This trend was also observed when patients were stratified by rupture status. The overall risk for complications was also higher (30.4% vs. 15.7%, respectively) and length of hospital stay was longer (median 11 vs. 3 days, respectively) in the surgical group than in the endovascularly treated group (70). This study's limitation is the lack of information about patients' clinical characteristics and aneurysm characteristics (70). A study from Eastern Finland showed that aSAH patients, who are in good condition at admission had a mortality rate of 3.5 % at 12 months regardless of old (71).

What is probably the only long-term outcome study found that, of 114 pediatric IA patients followed for nearly 25 years, 62% of the patients had a good outcome at discharge, 3% were dependent and 35% had died. 68% of the deaths were aneurysm related and 43% of deaths occurred during the first year after the IA diagnosis (10).

Koroknay-Pal et al. also reported that there is an almost 20% aneurysm related excess mortality among pediatric one-year SAH survivors 40 years after their diagnosis, especially among boys (72). This excess mortality was caused in many cases by de novo aneurysms, which are new intracranial aneurysms forming into an anatomically unrelated location with respect to the initially diagnosed aneurysm. The annual rate for de novo development was 1.6% in their cohort. However, some of the angiographies were up to 50 years old; hence, some of the "new" aneurysms might have already existed at initial admission (14). Amelot et al. reported long-term outcomes of 51 children ≤ 15 years old with mean follow-up time of 8.3 years. The

mortality rate was 19.6% and 68.6% children had favorable outcomes (73). The annual aneurysm recurrence rate was 2.6% whereas the recurrence rate was 0.6% in the Finnish cohort (72,73). The difference may be due to the Finnish study including older patients (mean age over 14 years) 98% of whom had their aneurysm treated surgically, whereas most of the aneurysms were treated endovascularly (84%) in Amelot et Aal.'s study (72,73). The annual rate of de novo aneurysm formation was also lower (0.7%) in Amelot et. Aal's study (73).

Earlier pediatric case series have also reported de novo aneurysm formation even with rather short follow-up times. Hetts. et al. reported that nine (8.4%) of the 83 young IA patients developed de novo aneurysms during an average follow-up time of 4.2 years (15) and Sanai et al. reported that 4 patients in their cohort of 32 pediatric patients, developed de novo aneurysms during a mean follow-up time of 5.7 years (48). In the study of Hetts et al. patients with fusiform aneurysms and patients with other comorbidities were more likely to develop de novo aneurysms and Sanai et al. had similar findings (15,48). Kakarla et al. reported nine de novo aneurysms in 3 patients in a cohort of 48 patients ≤ 18 years old (16). The mean follow-up time was 53 months and the annual risk for de novo formation was 7.8% (16). However, their study population might have been biased because most patients were admitted semi-electively. One of their patients developed a de novo aneurysm after 18 years of follow-up, which is why they highlight the need for long-term follow-up for young IA patients (16).

2.3 SACCULAR INTRACRANIAL ANEURYSM FORMATION

2.3.1 Hemodynamic stress and formation of intracranial aneurysms

Saccular intracranial aneurysms usually form at the branching sites of cerebral arteries, locations that are susceptible to flow induced mechanical stress (74). The wall shear stress (WSS) ergo viscous force vector that the blood stream exerts tangentially on the vessel wall, changes naturally throughout the cardiac cycle in both magnitude and direction (75).

Endothelial cells lining the vessel walls activate biological pathways and gene expression patterns to maintain circulatory homeostasis in response to WSS (76). Hemodynamic forces have also been shown to affect the morphology of endothelial cells (77). The role of endothelial cells has been studied vigorously and endothelial cell dysfunction has generally been shown to contribute to cardiovascular diseases (78,79). Animal models of intracranial aneurysms have also shown that the first changes in the formation of intracranial aneurysms are endothelial cell responses (80). For example, nitric oxide synthase expressed by endothelial cells (eNOS) produces nitric oxide (NO), a potent vasodilator that affects adjacent vascular smooth muscle cells (VSMC) as a reaction to wall shear stress. NO has also been found to have a role as an antioxidant and anti-inflammatory agent (81). Aoki et al. discovered that in an eNOS knockout mice model, eNOS defiency was compensated by functions of neuronal nitric synthetase (nNOS), produced mainly by neurons of media of the vessel wall. The incidence of IA formation remarkably increased, when the nNOS production was also compromised, suggesting that NOS enzymes have a role in preventing aneurysm formation probably by reducing the hemodynamic forces affecting artery walls (82). Now it is believed that this wall shear stress vector is the triggering factor leading to destructive changes in vessel wall seen in histopathological aneurysm studies, such as the loss of internal elastic lamina and medial thinning that eventually leads to aneurysm formation (18,83,84).

This flow-induced aneurysm formation theory is further supported by the findings from animal models showing that these similar histological changes and aneurysm formation at the bifurcation sites of cerebral arteries can be triggered by increasing the hemodynamic forces through ligation of the unilateral common carotid artery combined with induced systemic hypertension (85). Clinical findings that changed flow conditions, such as arteriovenous malformations (86), are also associated with cerebral aneurysm formation in the feeding arteries, can be considered to support this theory. Why someone's cerebral arteries are more vulnerable to hemodynamic forces than others is unknown. Anatomical variations might be one explanation (76).

Hemodynamic forces, in addition to aneurysm initiation, are thought to also play a critical role also in the growth and eventual rupture of intracranial aneurysms. However, the mechanisms behind these two events are not fully understood, and some controversy exists about the hemodynamic forces affecting these processes, since both high and low aneurysmal WSS have been separately linked to the growth and rupture of intracranial aneurysms in different analyses (87,88). This controversy might come from study limitations, but it has also led to thinking that the complex formation and evolution of aneurysms might have two different biologic pathways (89,90). However, hemodynamic conditions understandably change, when an aneurysm enlarges (91), and different neck types and neck stability influence the hemodynamic forces inside the aneurysm sac (92,93). These different flow conditions associate with histologic arterial wall changes such as inflammation and degeneration, that are especially connected to aneurysm ruptures (90).

The intracranial aneurysm risk locus has been linked to elevated systolic blood pressure (94) and many studies have linked hypertension as a risk factor for aneurysmal formation (95–98), growth and rupture (65). This could further support the hypothesis that hemodynamic stress is an important factor behind the pathogenesis of intracranial aneurysms.

2.3.2 Wall shear stress as a triggering factor for inflammation

Many histopathologic studies of intracranial aneurysms have demonstrated that inflammatory cells, especially macrophages colonize the sIA wall. This has led to further investigations of inflammation as a one pathomechanism of sIA disease (99,100). A hypothetic link between hemodynamic forces and inflammation has been found in animal models. Jamous et al. investigated the formation of IAs in rats induced with intracranial aneurysms by systolic hypertension and ligation of the common carotid artery (CCA) (101). Their findings support the hypothesis that endothelial injury demonstrated by partial loss of eNOS expression, is one of the first steps in the process of IA formation. The endothelial injury was followed by formation of an inflammatory zone positive for a

macrophage-specific antigen (CD68) and progression of this inflammatory reaction led to proteolytic destruction of the vessel wall (101). Koseki et al. also investigated early events of IA formation in a rat model and learned that mechanical stretch induces activation of fibroblasts in adventitia of vessels and these fibroblasts produced chemokine ligand 2 (CCL2), which is also referred to as a monocyte chemoattractant protein-1 (MCP-1), a significant chemoattractant for monocytes and macrophages (102). Koseki et al. demonstrated that the invasion of macrophages from blood flow to adventitia, requires changes in the structure of internal elastic lamina. The authors suggested that these critical changes are induced by high WSS due to increased blood flow and systemic blood pressure at the early stage of aneurysm formation (102). It has been shown that IA walls, especially endothelial cells, have upregulated expression of MCP-1 already at early phase of IA development, further supporting the role of inflammation in a process of IA formation (103) and animal models of MCP-1 knockout mice or mice with macrophage depletion have further confirmed the critical role of macrophages in the formation of IAs (103,104).

Many other cytokines and inflammatory mediators have also been studied. Nuclear factor-κB (NF-κB) is a family of transcriptional factors, that mediate different immune and inflammatory reactions and is linked to various inflammatory diseases (105). Aoki et al. demonstrated that NF-κB activation is increased in the arterial wall of IA not only in an animal model, but also in human aneurysm samples (106). They investigated the importance of NF-κB activation with different knockout mice models and discovered that since the NF-κB upregulates MCP-1 gene-expression, among others, macrophage recruitment into the aneurysmal wall was reduced by inhibition of the NF-κB pathway. They also showed that the incidence of aneurysmal changes, for example disruption of internal elastic lamina and size of aneurysm, can be influenced by affecting the NF-κB pathway (106). Interestingly, NF-κB was activated in a site where aneurysms eventually formed before any histological findings of an aneurysm could be seen (106). Once activated, NF-κB activation has been observed to spread during the aneurysm formation process from the luminal side and the adventitia of the arterial wall to neighbouring areas and eventually to

the whole artery wall with increasing intensity (107). Immunofluorescence analysis showed that NF-κB activation occurred in endothelial cells, smooth muscle cells of media and macrophages in adventitia (107). Aoki et al. also showed that prostaglandin E2 – prostaglandin E receptor signalling (PGE_2-EP_2) is activated by hemodynamic stress in the endothelium, and it further activates NF-κB at an early state of aneurysm formation, proposing a further link between two recognized mechanisms behind aneurysm formation, hemodynamic forces, and inflammation (108). PGE_2 is synthetized from arachidonic acid by cyclooxygenase (COX) and PGE synthase (PGES) enzymes. Cyclooxygenase has two isoforms, cyclooxygenace 1 (COX-1), and cyclooxygenace 2 (COX 2). COX-2 expression has been known to increase in response to hemodynamic stress and Aoki et al. showed that hemodynamic shear stress induced COX-2 expression in the endothelial cells of aneurysm (108). Once activated, COX-2-PGE_2-EP_2 – NF-κB signalling amplifies and sustains the inflammatory process through a positive feedback loop, in which more and more macrophages are recruited, and expression of MCP-1 and COX-2 consequently increases (18,108). The observations that human IAs have also increased expression of COX-2 unlike other regions of cerebral arteries, further support the hypothesis that COX-2-PGE_2-EP_2 – NF-κB signalling is also important for aneurysm formation in humans (108,109).

2.3.3 Other mediators of vessel wall remodelling related to aneurysm formation

Tumor necrosis factor alfa (TNF-α) is a known proinflammatory cytokine that among other things activates inflammatory cells to produce other inflammatory mediators. Ruptured human cerebral aneurysms has been found to have increased expression of TNF-α when compared to samples collected from temporal arteries (110). Based on animal models it has been suggested that TNF-α is involved in aneurysm formation by inducing a phenotypic change of vascular smooth muscle cells (VSMC) (111) from the contractile type into the synthetic type of cells, which produce pro-inflammatory factors like MCP-1 and matrix metalloproteinase-9 (MMP-9) (111,112). This phenotypic chance in the smooth muscle cells is a

degenerative change in the tunica media and one the critical changes in the IA wall during aneurysm formation. The critical role of TNF-α in an aneurysm formation and its further evolution has been verified in knockout mice models and mice treated with TNF-α inhibitor, which both showed decreased formation of IA in comparison to sham mice model (113).

Matrix metalloproteinases (MMPs) are a group of enzymes, that degrade various proteins of the extracellular matrix of a vessel wall and have a role in vascular remodelling. MMPs regulate the growth and proliferation of vascular smooth muscle cells (114). Samples of human cerebral aneurysms have shown increased expression of MMPs, especially MMP-2 and MMP-9 when compared to normal cerebral arteries (115) . It has been proposed that these enzymes weaken the extracellular matrix of vessel walls (116) ultimately leading to a weakened aneurysmal wall.

The Renin Angiotensin System (RAS) plays a crucial role in many vascular diseases, including abdominal aortic aneurysms (AAAs), among others (117). Besides its importance in blood pressure regulation, the RAS is involved in inflammatory responses and remodelling of vasculature with a key mediator being angiotensin II and its receptors (118,119). Among others, RAS signalling has been shown to activate the transcriptional activity of NF-κB (120). However, the expression of the angiotensin II receptor seems to be downregulated in human IAs and animal models (121,122).

2.3.4 Oral bacteria and intracranial aneurysms

In addition to the previously described mycotic aneurysms, bacterial DNA of oral origin has also been found from samples of unruptured and ruptured sIAs statistically significantly more than from control samples (123). A Finnish observational study found that the prevalence of periodontitis was 1.4 times higher in sIA patients than among the general Finnish population and prevalence of severe periodontitis was almost two times higher (124). Periodontitis was found to associate with IAs and aSAH independently of other known risk factors (124). In another Finnish

study, 90 sIA patients had a routine teeth investigation before sIA surgery. These patients were observed to have periodontitis more often than the Finnish population (125). Earlier periodontitis has also been linked to cardiovascular diaseases and endothelial dysfunction, which can be affected by periodontal treatment (126). This has led to the hypothesis that oral infections have a role in IA diasease (127). Several possible mechanisms have been described through which periodontitis can induce NF-κB activation in the cerebral artery and aneurysm wall (127).

2.3.5 Known risk factors for sIA formation

Hypertension, as mentioned earlier, seems to be a risk factor for IA formation (95–98). Vlak et al., among others, studied risk factors for IA formation in a cohort of 206 UIA patients in a case-control study. Current smoking, hypertension, and a family history of stroke other than aSAH were independent risk factors, and the joint risk of smoking and hypertension was very high (OR 8.3, 95% CI, 4.5–15.2) (98). A Mendelian randomization study also suggests that smoking and high blood pressure are significant risk factors for IAs together with insomnia (97).

Kang et al. investigated risk factors for UIA formation in patients who had a magnetic resonance angiography (MRA) as a part of their health examination and compared them with patients without UIAs and with patients who had an MRA at their clinic because of a headache (128). Of the 18954 patients who underwent an MRA examination, 367 (1.93%) had a UIA. Independent risk factors for UIAs were older age, female gender, hypertension, and smoking. Coronary artery disease was negatively associated with UIAs (128). However, the findings about atherosclerotic diseases and hypercholesterolemia have been controversial: Some studies have found that hypercholesterolemia might decrease the risk for UIA (98), but some other studies have listed it as a risk factor for UIA (96). Kang et al. also found that the risk factors they identified for UIAs varied between different locations (128).

The additive risk from family background has been hard to investigate because many UIAs are found based on family screening and due to this

study, the populations are biased (98). A sporadic exposure to IA disease through both parents did not increase the offspring's risk for sIA disease in Finnish study of IA families, but exposure to sIA disease through the parents of whom one carried the familial sIA disease and the other carried the sporadic sIA disease, increased their offspring's risk for sIA disease (129). A specific gene that strongly associates with IA formation has not yet been found.

2.4 DE NOVO SACCULAR INTRACRANIAL ANEURYSMS

2.4.1 Incidence of de novo aneurysms

De novo aneurysm is a new intracranial aneurysm forming in an sIA patient into an anatomically unrelated location in relation to the patient's initial aneurysm. The risk for de novo aneurysm formation has been reported in different sIA patient cohorts with a quite large range, from 0.1% to 4.15% per year (130–133). However, there is also variability among these cohorts regarding cohort sizes, follow-up times and patient inclusion criteria (only aSAH patiens vs UIA patients vs mixed). A recent meta-analysis involving 14968 aneurysm patients, found that the overall incidence of de novo aneurysm formation was 2% during a mean follow-up time of 8.3 years and the incidence density among all the patients was 0.3 % per patient-year (134). There was no statistically significant difference in rates of de novo aneurysm formation when comparing patients with ruptured and unruptured aneurysms at their initial aneurysm diagnosis (134).

2.4.2 Risk factors for de novo formation

The literature is quite consistent in reporting that smoking is a significant risk factor for de novo aneurysm formation (131,133–137). Other risk factors most often connected to de novo aneurysm formation are hypertension (131,137), family background (131), female gender (133), multiplicity at initial sIA diagnosis (131,132) and younger age at initial

diagnosis (137). A multivariate analysis that included 6389 sIA patients with a focus on risk factors for de novo aneurysm formation found that the risk factors were female sex (OR 1.82, 95% Cl 1.30-2.56), age under 40 years (OR 2.96, 95% Cl 1.76-4.96), smoking history (OR 2.05, 95% Cl 1.81-4.12), multiplicity at initial diagnosis (OR 2.58, 95% Cl 1.12-3.91) and internal carotid artery as initial location (OR 2.58, 95% Cl 1.43-4.68) (135).

2.4.3 Risk of hemorrhage from de novo sIA

Kemp WJ 3rd et al., investigated the risk of hemorrhage from de novo aneurysms in a cohort of 37 de novo sIA patients (133). The five-year cumulative risk of hemorrhage of small de novo aneurysms was 14.5%, which is generally higher than in small aneurysms (44,65,133). A meta-analysis involving 6389 de novo sIA patients similarly reported the incidence of SAH from a ruptured de novo aneurysm being as high as 50 /100 000 (135). These findings suggest that de novo aneurysms cause significant risk for morbidity and mortality for IA patients. A meta-analysis of nearly 15 000 aneurysm patients found no ruptures of de novo aneurysms earlier than 10 years after the initial diagnosis (134).

2.5 RISK FACTORS FOR SACCULAR INTRACRANIAL ANEURYSM RUPTURE

Fortunately, most sIAs never rupture. A lifelong rupture risk study of unruptured aneurysms reported that about 30% of the aneurysms of working-aged patients ruptured (6). A meta-analysis that included nine prospective UIA studies with a total follow-up of 33 923 patient-years reported that the one-year annual risk for UIA rupture was estimated as 0.81% (138). Another meta-analysis of 8382 patients reported that the mean observed one-year rupture risk was 1.4% with an overall five-year rupture risk of 3.4% (65).

2.5.1 Aneurysm characteristics and rupture risk

Findings from a large international study of 4060 sIA patients with unruptured aneurysms (ISUIA) suggest that the risk of rupture in short term follow-up is very low for unruptured aneurysms smaller than 7mm and located in anterior circulation in patients without an aSAH history, whereas larger aneurysms in the posterior circulation are more likely to rupture even after only five years of follow-up (44). A large Japanese study of 6697 unruptured aneurysms similarly showed that aneurysms sized 7 mm or larger were associated with a significantly increased risk of rupture. However, the aneurysms located in an anterior or posterior communicating artery were prone to rupture even at size smaller than 7 mm in their cohort (139). Observational studies have shown that IAs smaller than 7 mm and located in an anterior communication artery (AcoA) and also in a distal anterior cerebral artery present with a rupture risk similar to posterior circulation aneurysms (64,140). In a meta-analysis of 4705 sIA patients with 6556 UIAs performed by Wermer et al. showed that statistically significant risk factors for rupture were size > 5 mm, location in posterior circulation and symptomatic aneurysms (66). A Japanese prospective cohort study of 2897 UIAs, reported that 70 % of ruptured IAs were smaller than 7 mm of their size, and IAs ≥ 5 mm were associated with a significantly increased risk of rupture when compared with smaller IAs (141). The outcome after rupture was poor in patients with larger aneurysms (141). Nevertheless, a Japanese study with 529 unruptured sIAs reported that small UIAs (< 5 mm) were assocated with a risk of rupture when there was a history of SAH (142), which is aligned with findings of a large ISUIA study (44). Another Japanese prospective multicenter study, sUAVE, also found that the annual rupture rate of small (< 5 mm) UIAs is low, 0.54 %. The risk was not increased by the patients earlier SAH history, but a multiplicity of sIAs increased the annual rupture risk to 0.95 % (143).

It has been proposed, in order to explain the observed discrepancy between follow-up studies and observational studies on the association of aneurysm size with rupture risk, that at least a subpopulation of small IAs is more unstable than others and so more prone to rupture (144). One sign

of instability is an IA's growth. A study of 258 asymptomatic UIAs, reported that 18 % of IAs grew. The observed rupture risk was 12- fold higher in growing aneurysms in this study (145). Most of the followed aneurysms were < 7 mm in size at the initial diagnosis (145). Van der Kamp et al. studied the absolute risk of rupture of an intracranial aneurysm within those aneurysms that grew during follow-up. The one-year rupture risk of an IA ranged from 2% to 10% in this prediction model that included site, size and shape of an aneurysm (146). It might also be, that IAs behave differently in different locations. sIAs increased in size with increasing age, in Finnish population-based cohort study of 4074 sIA patients, but an association of size and age could not be seen in all sIA locations, and it varied between different locations and between patients with multiple aneurysms and solitary aneurysms (147). Risk factors for growth have also been studied; overall the risk factors for UIA growth seem to be mainly the same as risk factors for rupture (148).

One sign of instability and risk of rupture can be an aneurysm's irregular shape (139,148,149), even irrespective of the aneurysm's size (147). Support for this observational finding can be seen in the findings of an electrocardiography-gated 3D-computed tomography angiography (4D-CTA) study that shows that UIAs with detected pulsation change in shape during follow-up (150) and from another 4D-CTA study showing that small ruptured intracranial aneurysms (RIAs) more often have irregular pulsation (151).

Vessel wall imaging has also been used to investigate aneurysm wall enhancement, which has been proposed as a biomarker of aneurysm wall inflammation and later aneurysmal growth and rupture. A meta-analysis of 505 UIAs, that were imaged with high-resolution vessel wall imaging showed, that enhancement of the vessel wall was statistically significantly associated with aneurysmal instability (152), but more studies are needed in the future to evaluate the role of wall enhancement as a risk factor for rupture (138).

2.5.2 Patient characteristics and rupture risk

Hypertension (9,148), female gender, smoking (9,148,153), excessive alcohol intake (9), multiplicity and previous SAH (44,142) have been suggested as risk factors for rupture based mainly on observational studies.

Female gender is probably one of the most often reported risk factors for SAH. A large nationwide prospective cohort study of 950 000 adults was conducted in Sweden based on 21 population-based cohorts collected over 50 years. The incidence rate of aSAH was 9/100 000 person years in men and 13.8 / 100 000 person years in women (154). Female gender was similarly a major risk factor for aSAH in large prospective population-based cohort studies conducted in Finland (155) and Norway (156). The findings are in line with previous large reports (9) and the same finding has also been confirmed in studies comparing ruptured sIA patients with unruptured sIA patients (6).

Hypertension is also considered a major risk factor for rupture (9). However, observations about hypertension are not as straightforward as for the gender-associated risk. High blood pressure was associated in the same Swedish study with a higher risk of SAH in both genders when compared with the general population (154) and similarly in previously mentioned Norwegian (156) and Finnish (155) prospective population-based studies. However, hypertension has not always been a risk factor for rupture in case control studies with unruptured sIA patients as a control group (6,96). This has raised a question regarding, whether hypertension is more of a risk for formation than of rupture. However, at the same time association of systemic blood pressure and a risk for unruptured aneurysm have not been found in some large prospective population-based studies (157).

Another consistently reported risk factor for aSAH is smoking (6,97,158). Smoking increased the risk for aSAH in both genders in previously mentioned large Swedish study, but the risk was much higher in smoking females than in smoking men (RR 2.24, 95% CI 1.95–2.57 in women and RR

1.62 Cl 1.47–1.79 in men) (154). Smoking seems to be also a risk factor for IA growth (145,159).

It seems that different combinations of these observed risk factors are predictive of increased risk for rupture (6,65,160). The combination of hypertension and smoking have been especially highlighted as a strong risk factor for aSAH (6,98,160). Smoking is also a risk factor for periodontitis, which has recently been found to be associated with IA and aSAH (124). It might be, that smoking increases the risk of sIA disease through periodontitis (124,127).

Nahed et al. especially investigated ruptured aneurysms that were 7 mm or smaller in a retrospective case-control study of 100 aSAH patients and learned that hypertension significantly increased the rupture risk (161). Additionally, a posterior location increased the rupture risk and there was a trend towards an inverse correlation between age and risk of rupture after adjustment of location and hypertension (161). Authors speculate that small sample size may have affected that other risk factors like smoking or family history were not statistically significant risk factors for rupture (161). However, their findings could support the hypothesis that small aneurysms have a subpopulation that is more prone to rupture than others (144).

Some other studies besides Nahed et al. have also raised a relatively young age as a risk factor for rupture (143,161,162). A Japanese prospective multicenter study raised patients younger than 50 years old with hypertension and multiple aneurysms as a subgroup of patients with a high risk for aSAH. However, many large studies have reported older age as a risk factor for rupture (65,66).

Familial sIA disease might increase the risk of rupture to some extent. Broderick J. et al.'s study found a rupture risk as much as 17 times higher in patients with family history for IA disease when compared to unruptured sIA patients from the International Study of unruptured aneurysms (163). The cohorts' aneurysms were matched for size and distribution, but the patients were recruited from different populations and familial patients also had diagnosed hypertension and were smokers (163). Mensing L. et al., found a threefold increased risk of rupture, which was not statistically significant, when they compared 62 familial IA patients with 412 sporadic

IA patients (164). Bor A.S.E et al. identified 5282 aSAH patients from their Swedish registry and collected five controls for each patient (165). They also retrieved all first-degree relatives for patients and their controls (n= 130 272) and checked whether these controls had been diagnosed with aSAH. They discovered that risk of aSAH was slightly increased (OR 2.15; 95% Cl 1.77-2.59) if a person had one affected first-degree relative, and the risk was clearly increased (OR 51.0; 95% Cl 8.56-1117) in case of two or more affected first-degree relatives. Risk was not influenced by individuals' gender, age, or type of kinship (165). However, there are also several studies in which family background has not been associated with increased risk for aSAH (149), (139,141). Interestingly, current smoking might increase the risk for aSAH significantly in patients with a family background, when compared to patients with family background without smoking or even with patients who are former smokers (166).

Use of stimulating agents like cocaine, caffeine and nicotine have also been associated with risk for aneurysmal SAH (158) as well as excessive alcohol consumption (162,167).

2.5.3 Risk scores that combine multiple risk factors for IA growth and rupture

As mentioned before, different combinations of risk factors seems to affect the overall risk; thus predicting rupture risk is difficult. A PHASES score is a risk score for rupture, that was developed based on a large review and pooled analysis of individual patient data from six prospective cohort studies of natural history of UIAs (65). It is noteworthy that some of the included data were collected already during the 1950s-1970s. Based on this analysis, population (Japanese, Finnish or other), hypertension, age, aneurysm size, earlier SAH and site of an aneurysm location (=PHASES) were found to be the factors with the largest prognostic information for rupture risk. Somewhat surprisingly, smoking, the patients' gender or the presence of multiple aneurysms did not have an important effect on rupture risk (65). Many studies since have reported that the PHASES score underestimates the rupture risk (164,168–171), so it can be questioned

whether the PHASES score can be applied to estimating the rupture risk of IA patients in every population.

The ELAPSS score (earlier SAH, location of the aneurysm, age > 60 years (per 5 years), population, size of the IA and shape of the IA) was developed to predict IAs growth (172). The study included 1507 patients with 1909 UIAs from 10 different cohorts from Europe, Canada, and Japan. An aneurysm was considered to have grown if the size was increased ≥ 1 mm or its configuration changed from regular to irregular. Risk for growth was increased in Japanese and Finnish patients. Most of the risk factors are the same as for an aneurysm rupture. Data on smoking and family history could not be included. IA growth was detected in almost half of the aneurysms in this pooled cohort. Writers speculate that this substantiates that growth is a good marker for rupture (172). The ELAPSS score was compared with PHASES, and it seems that ELAPSS is a more accurate measure for growth (173). Brinjikji W. et al.'s study confirms the results of the ELAPSS study; however, the significance of a smoking history is highlighted as a risk factor that is not included in the scoring system (173).

The unruptured intracranial aneurysm treatment score (UIATS) model was developed based on the Delphi consensus process to help clinicians involved in decision making treat individual patients based on the recommendations of 69 specialists (174). It has been criticized as not being sensitive enough to detect aneurysms that are in risk of rupture (175–177).

2.6 TREATMENT STRATEGIES

2.6.1 Invasive treatment

Invasive management of an unruptured or ruptured aneurysm includes surgical clipping or endovascular procedures; both include severe risks (17).

The decision to treat or not to treat UIAs needs to be made considering the risk of rupture, risk of treatment complications, the patients' life-expectancy and anxiety level. A systematic review and meta-analysis were done to investigate the complication risks and case-fatality rate in both

endovascular and neurosurgical preventive treatments of UIAs (178). the pooled complication risk was somewhat higher in a surgical group (8.34%) than in an endovascularly treated group (4.96%), but these results cannot be compared because the included studies were nonrandomized (178). However, there are not yet any randomized controlled trials (RCT) of preventive treatment of UIAs. Based on the preliminary results of ongoing RCT comparing microsurgical and endovascular treatment of UIAs, the risk of preventive treatment of UIA is about 4% in both treatment modalities (179). A multicenter cohort study of three continents was conducted to develop risk scores to assess complication risks related to microsurgical and endovascular treatment modalities in preventive treatment of UIAs (180). The absolute complication risk in that study ranged from 3-33 % in endovascular treatment and from 5-50 % in microsurgical treatment (180).

Ruptured IAs (RIAs) need to be treated because of the risk of rebleeding and an associated high mortality rate (181). Based on randomized trials of aSAH patients (182–184) and systematic review (185), for aSAH patients who are in good condition at admission and whose IA is considered suitable to both endovascular coiling and neurosurgical clipping, endovascular coiling is associated with a better outcome. However, there are no trials that include aSAH patients with a poor clinical condition.

2.6.2 Non-invasive treatment strategies

The need for non-invasive treatment modalities for UIA has emerged with the ability to balance between rupture risk and treatment-associated risks. Many studies have focused on preventing rupture of UIAs, only a few focus on prevention of UIA formation or suppression of IA progression.

2.6.3 Antihypertensive medication

A cross-sectional study by Shimizu et al., examined candidate drugs based on findings of human and animal studies as prevention for IA rupture. This study included 310 patients with RIAs and 610 patients with UIAs, whose drug therapy data were available, respectively. They learned

that statins, calcium channel blockers and angiotensin II blockers had inverse associations with rupture (186). A dose-response was found for rosuvastatin, pitavastatin, benidipine, cilnidipine, amlodipine, valsartan, azilsartan, candesartan, and olmesartan (186).

A Chinese study of 392 hypertensive UIA patients investigated usage of calcium channel blockers (CCBs) and aneurysm instability. They hypothesized based on animal model findings (187), that CCBs could stabilize UIAs by affecting endothelial dysfunction and vascular inflammation in addition to their antihypertensive effects (188). Their analysis showed that CCB users had a lower risk for UIA growth and rupture than non-CCB users (188).

Renin-angiotensin-aldosterone system (RAAS), mentioned earlier, plays a crucial role in many vascular diseases and is also an inflammatory cascade. However, in a rat model of IA, angiotensin II -receptors were not up-regulated and treatment with angiotensin receptor blockers did not inhibit aneurysm formation (121). However, a large Chinese multicenter study of 3044 hypertensive patients with sIAs, reported that RAAS inhibitors were significantly associated with decreased rupture risk when compared with other antihypertensive medications even if a patient's hypertension was uncontrolled. They did not study UIA growth (189). One explanation can be the finding from another animal study which showed that despite the fact that the angiotensin-converting enzyme (ACE) is not induced in aneurysm walls, the affected ACE inhibitor imidapril stills IA formation by suppressing MMP-9 activity (190).

Statins also have known anti-inflammatory effects (191). Aoki et al. demonstrated in an animal model that pitavastatin could inhibit NF-κB activity and IA formation (192). The same investigators previously discovered that simvastatin affected IA progression in a rat model by inhibiting inflammatory reactions (193). However, a study conducted by Tada et al., revealed that pravastatin had unexpected dose-related effects on IAs in estrogen-deficient rats. Low doses of pravastatin reduced endothelial damage and IA formation whereas higher doses promoted IA formation of IAs and even induced rupture (194). A Japanese retrospective

case-control study observed statin usage in 117 aSAH patients and 304 UIA patients. Statin usage was significantly more common in UIA patients (26 %) than in patients with RIA (9.4 %), and use of statins was inversely associated with IA rupture (195). Most patients had normal to high levels of cholesterol and control patients especially had high cholesterol levels, which is why the authors speculate that it is possible that high cholesterol levels associate inversely with IA rupture (195).

2.6.4 Non-steroidal anti-inflammatory medication

Non-steroidal anti-inflammatory medications have especially raised interest as a treatment option for UIAs because they are already widely used and they decrease inflammation by inhibiting the COX-2-PGE2-EP2-NF-κB signalling pathway. However, knowledge of these drugs adverse effects has also increased; after the selective COX-2 -inhibitor rofecoxib was shown to increase the incidence of acute coronary syndrome, the safety of traditional NSAIDs has also been questioned (196,197). Studies have indeed shown that traditional NSAIDs especially increase the risk of cardiovascular events in patients with a prior myocardial infarct (197,198) and they have also been associated with stroke (197,199). The previously mentioned cross-sectional study showed that, non-aspirin non-steroidal anti-inflammatory drugs (NANSAIDs) had, in fact, a positive association with IA rupture (OR, 3.24; 95% CI 1.71–6.13); thus the investigators propose careful use of NANSAIDS among patients with an unruptured intracranial aneurysm (186). A meta-analysis of 25 studies was conducted to assess the association between aSAH and drug use (200). Use of NANSAID and glucocorticoids was also positively associated with aSAH in this meta-analysis (200). However, a previous meta-analysis of 10 studies did not find as clear an association (201). One notable aspect in treatment with NSAIDs is, that NSAIDs induce hypertension even in patients using antihypertensive medication (202,203).

2.6.5 Aspirin

Aspirin (ASA or acetylic asid) is a characteristic NSAID, that has cardioprotective effects through inhibition of thromboxane, when used in lower doses and anti-inflammatory effects through inhibition of the COX-pathway at least when used in higher doses. However, evidence exists that inflammatory effects are also seeing with lower doses (204).

Based on animal and human studies, aspirin has been considered one of the most promising agents for prevention of UIA growth and rupture (200,205,206). Hasan et al. investigated aspirin treatment in a case -control study by selecting individuals from the ISUIA study cohort (205). Patients who used aspirin three times in a week or more had a decreased risk for aSAH when compared with patients who did not use aspirin (OR 0.27, p=0.03) (205). A multicenter case-control study of 2234 sIA patients was conducted to investigate differences between UIA and RIA patients. Aspirin use was significantly less frequent among patients with ruptured aneurysms than patients with unruptured aneurysm even after adjusting for confounding factors (OR 0.28, 95% Cl 0.69-0.84) (207). A propensity-score weighted, large case-control study of 4701 IA patients diagnosed with ruptured and unruptured sIAs showed that aspirin users had a lower risk for aSAH and that the risk was dose dependent so that patients using a high aspirin dose had significantly decreased their risk for IA rupture (208). However, they also observed that aspirin was associated with an increased risk of re-bleeding (208). A meta-analysis evaluating the association between aspirin and aSAH, reported that a decreased use of aspirin was a risk for aSAH (OR 0.68, 95% Cl 0.48-0.96) (209). However, there was significant heterogeneity between the included studies. The same meta-analysis also found that the frequency of aspirin use is similar between those with SAH and those without in a general population. The authors speculate that this difference might be affected by the prevalence of aneurysms (209).

The safety of aspirin use has also been studied in IA patients. Carcía-Rodríguez et al. investigated the association of antithrombotic drugs with a risk for hemorrhagic stroke in the general population. They found that

aspirin use did not increase the risk of intracerebral hemorrhage when compared to no therapy, but aspirin use might decrease the risk for aSAH in long-term use (> 3 years) (210). Weng et al. studied the safety of aspirin use in patients who were diagnosed with ischemic cerebrovascular disease and small (< 7 mm) UIAs (211). Of 1866 UIA patients in this study, 643 of them received aspirin continuously. The incidence rate for rupture (IRR) in patients who used aspirin was 0.06 / 100 person-years when IRR was 0.39 / 100 person-years in a group of patients who did not use aspirin continuously (211). A aspirin use was associated with a lower risk for rupture (HR 0.11, 95 % Cl 0.01-0.86) in a multivariate analysis, and uncontrolled hypertension (HR 16.66, 95 % Cl 2.10-132.09) and aneurysm size 5- <7 mm (HR 7.45, 95 % Cl 2.15-25.79) were associated with an increased risk for rupture. In total aspirin use was interpreted as being safe, because it did not affect the incidence of hemorrhagic stroke and aspirin use was associated with a decreased rate of UIA growth in a secondary analysis (HR 0.29, 95 % Cl 0.11-0.77) (211).

Aspirin is now being studied as one medical treatment strategy for UIAs in a multicenter randomized trial (PROTECT-U) (212).

2.6.6 Other potential medical treatments

Antidiabetec agents also have anti-inflammatory effects and can have potential as a future treament for UIAs. A dipeptidyl peptidase-4 inhibitor, anagliptin was shown to decrease aneurysm growth in a rat model through inhibition of macrophage infiltration and activation (213). Another diabetes medication, metformin affected IA formation and rupture among others by inhibiting the phenotypic switch of VSMCs in an animal model (214).

TNF-α inhibitors, in addition to the aforementioned treatments, are also promising agents based on animal models in which TNF-α knockout mice and mice treated with TNF-α inhibitor had significantly lower incidences of aneurysm formation and rupture (113).

3 AIMS OF THE STUDY

1. To study the phenotype of patients who develop sIA(s) at a young age in order to focus screening, therapy and follow-up efforts on relevant patients
2. To study the incidence, phenotype and risk factors for de novo sIA formation in sIA patients, with special emphasis on young patients with more time for de novo aneurysm to develop
3. To study the possibility of affecting de novo sIA formation by pharmaceutical management strategies

4 SUBJECTS AND METHODS

4.1 CATCHMENT POPULATION OF KUOPIO UNIVERSITY HOSPITAL

Kuopio University Hospital (KUH) has provided neurosurgical services, full-time acute and elective, for it's defined KUH catchment are in Eastern Finland during the study period. The area remained the same during this time, but the population has decreased from 823 674 to 816 405.

4.2 KUOPIO INTRACRANIAL ANEURYSM DATABASE

All patients with SAH, verified by head CT / MRI scans or spinal tap if needed, have been acutely admitted to the KUH for diagnostic angiography, if they are not moribund or very aged. Patients diagnosed with UIAs in CT or MRI scans have had diagnostic angiography in KUH, unless excluded from treatment due to very advanced age or serious pre-existing medical conditions. sIA diagnosis was made by four-vessel DSA, magnetic resonance angiography (MRA) or computed tomography angiography (CTA).

A new aneurysm identified during follow-up in vascular imaging (CTA, MRA or DSA) was specified as a de novo sIA. Most index sIAs have been treated microsurgically. All sIAs that were seen in the operative field in these cases were clipped if technically possible. Small aneurysms that were not diagnosed in preoperative angiography, were found in rare cases during the operation. We did not consider these de novo aneurysms, but these aneurysms were added to our database.

Patients were entered into the Kuopio Intracranial Aneurysm database after the existence of an aneurysm was verified by angiography. The database includes all the sIA patients diagnosed in the catchment area since 1977. The database is retrospective until 1989 and from 1990 onward data has been collected prospectively. Database is run by a conscientious research nurse, who interviews all new cases of sIA and aSAH and also collects detailed information from hospital stays, follow-up visits and family histories of sIA disease.

4.3 STUDY POPULATIONS

4.3.1 Publication I

The inclusion criteria for the study population were

1. citizen of Finland and resident of the KUH catchment area at the time of first diagnosis of sIA disease between January 1, 1980 and October 28, 2014
2. admission alive to the KUH and verification of sIA(s) by angiography
3. Fusiform aneurysms and saccular aneurysms with mycotic or traumatic etiology excluded

The final study population included 4082 sIA patients who were further stratified into four subgroups according to age at admission (Fig. 1).

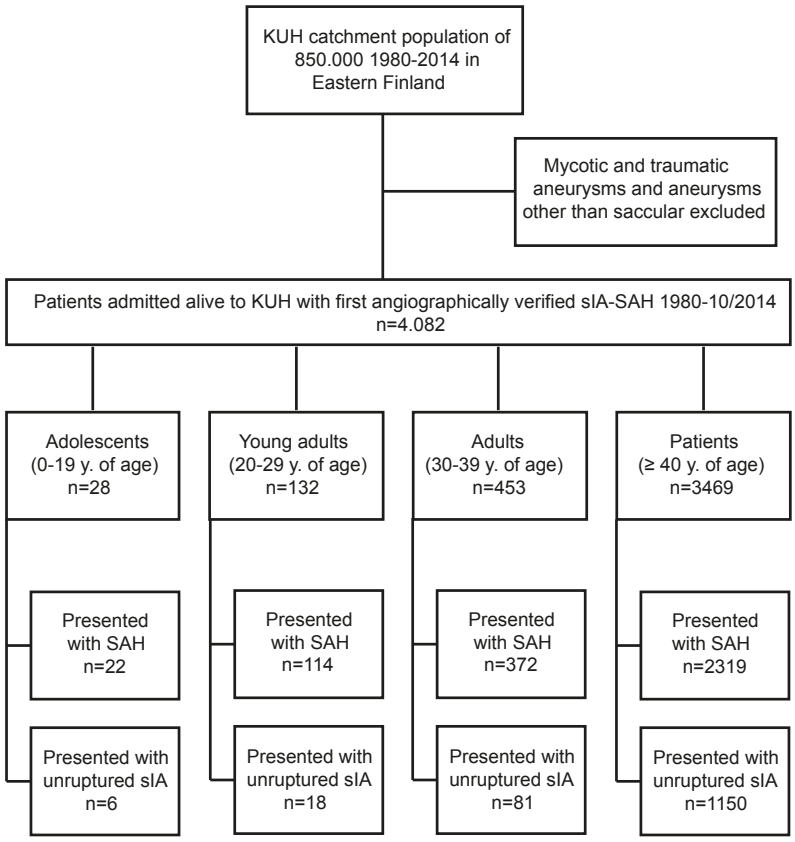

Figure 1. Flowchart of the final study population of publication I. Räisänen et al. 2018. Neurosurgery. Reprinted by permission from Wolters Kluwer.

4.3.2 Publications II-IV

The basic study population was same in the publications II-IV. The cohort comprised 1419 sIA patients fulfilling the following criteria:

1. a citizen of Finland and resident of the KUH catchment area at the first diagnosis of sIA disease between January 1, 1975, and December 31, 2014
2. angiographically verified de novo aneurysm during the follow up, available for re-review OR
3. at least 5 years of de novo negative angiographic (CTA, MRA or DSA) follow up after the first sIA diagnosis (Fig. 2).

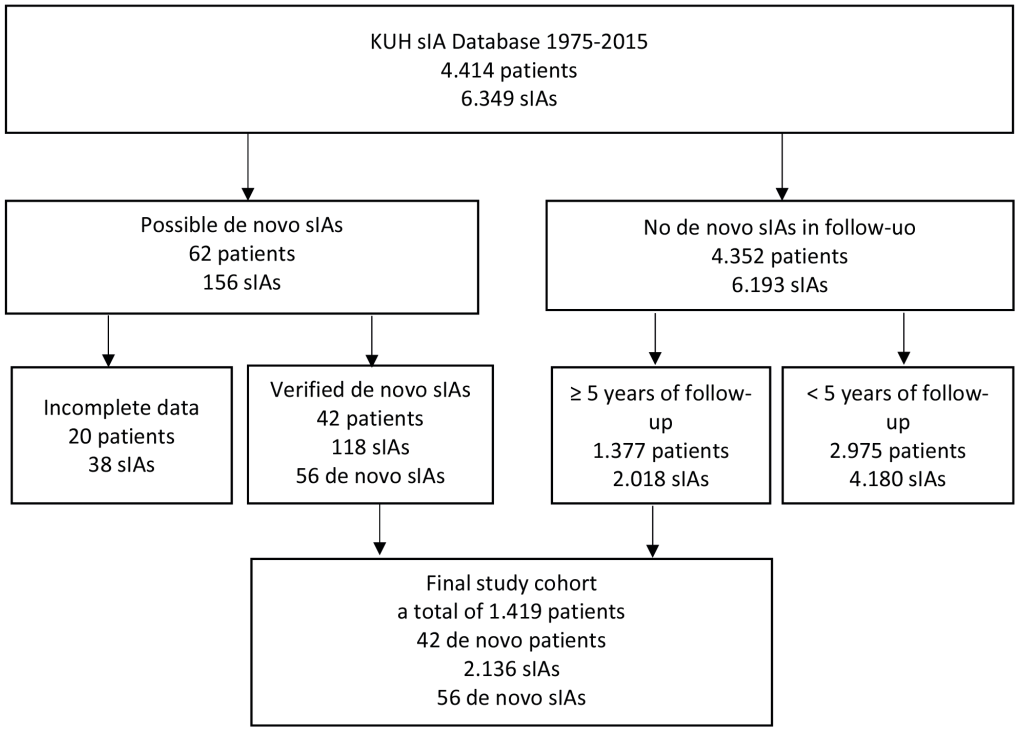

Figure 2. Final study population of publications II-IV. Lindgren AE, Räisänen S. et al. 2016. Stroke. Reprinted by permission from Wolters Kluwer.

Publication IV also had a second study cohort comprising 117 patients who had experienced least one sIA that had been treated with stenting or stent assisted embolization. These patients had follow-up since the first case was treated on July 29, 1992, until February 16, 2017. Twenty-six of these patients were already included in the basic study population.

4.4 REGISTRY OF PRESCRIBED DRUG PURCHASES

All prescribed drug purchases at any Finnish pharmacy are included in a nationwide registry maintained by The Social Insurance Institution of Finland. Medications on the registry are identified by their Anatomic Therapeutic Chemical (ATC) codes and all the medications that are available in Finland by prescription are included in the registry.

Data from the registry of prescribed medications were combined with the Kuopio sIA database and information about patients' drug purchases including date of first purchase, date of last purchase and the total number of purchases obtained from the registry from January 1, 1995, to December 31, 2014.

4.4.1 Use of antihypertensive medications

Date of first purchase, date of last purchase and the total number of purchases were collected from the registry of prescribed drug purchases for the following antihypertensive medications (per ATC-code): C02 (antihypertensives), C03 (diuretics; thiazides), C04 (peripheral vasodilators), C07 (beta blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the renin-angiotensin system). This information about patients' use of antihypertensive medications was combined with clinical data with personal identification codes.

Based on the collected information, the patients were regarded using antihypertensive medication regularly, if the following criteria were fulfilled (215):

1. Patients had at least 12 months of antihypertensive medication use
2. Patients purchased at least 80% of packages required for 12 months regular usage
3. Antihypertensive medication was started at least 6 months before the angiographic diagnosis of de novo sIA.

Patient who had antihypertensive medication but did not fulfill the first two of the above-mentioned criteria were considered to use antihypertensive medication irregularly.

4.4.2 Use of anti-inflammatory medication

Patients' use of nonsteroidal anti-inflammatory medications was investigated in study nro IV. The information on usage of nonsteroidal anti-inflammatory medications was collected from the registry of prescribed drug purchases (per ATC-code). This included information on date of first purchase, date of last purchase and the total number of purchases which were connected to the patients' clinical data with personal identification codes. Patients were regarded as using nonsteroidal anti-inflammatory medication if there was at least one purchase by prescription. The following medications were included in the study: indomethacin (M01AB01), diclofenac (M01AB05), etodolac (M01AB08), ketorolac (M01AB15), aseclofenac (M01AB16), indomethacin combinations (M01AB51), diclofenac combinations (M01AB55), piroxicam (M01AC01), tenoxicam (M01Ac02), meloxicam (M01AC06), ibuprofen (M01AE03), tiaprofenic acid (M01AE11), dexibuprofen (M01AE14), ibuprofen combinations (M01AE51), naproxen and esomeprazole (M01AE52), mefenamic acid (M01AG01), tolfenamic acid (M01AG02), celecoxib (M01AH01), rofecoxib (M01AH02), valdecoxib (M01AH03), etoricoxib (M01AH05), nabumetone (M01AX01), nimesulide (M01AX17), acetylsalicylic acid (B01AC06). From these medications, ASA, ibuprofen, and naproxen, are also available without prescription in Finland.

4.5 THE REGISTER FOR HEALTH CARE (HILMO)

ASA is also sold without prescription in Finland, so we could not identify all the ASA users from The Registry of Prescribed Drugs. We therefore looked for indications of ASA use in the Register for Health Care (HILMO). Register for Health Care (HILMO) is a registry managed by the Finnish Institution

for Health and Welfare; it includes all hospital diagnoses (ICD-10) covering all secondary and tertiary referral hospitals in Finland. By combining the Register of Health Care and the register of prescribed drugs with our database, we gathered patients who were regarded as using ASA if the following criteria were fulfilled (Fig. 3):

1. Diagnosis of
    a. ischemic cardiac event
    b. ischemic stroke
    c. transient ischemic attack
    d. occlusion / stenosis of precerebral / cerebral arteries or
    e. atherosclerosis of extremities
2. Diagnoses listed in 1) made before de novo sIA diagnosis
3. No use of other antiplatelet or anticoagulant medications only sold by prescription in Finland

4.6 VARIABLES

4.6.1 Diagnosis of hypertension

We had no data on patients blood pressure measurements. Data on a hypertension diagnosis are based on personal interviews performed by our research nurse.

4.6.2 Smoking history

Information on patients' smoking history is based on personal interviews performed by our research nurse or markings on the medical records of any medical speciality. This information might vary between different time points. Studies II-IV classified patients who had at least smoked once to have a positive smoking history to ensure that those who smoked intermittenly were classified as smokers and that only those who have never smoked were correctly classified as non-smokers.

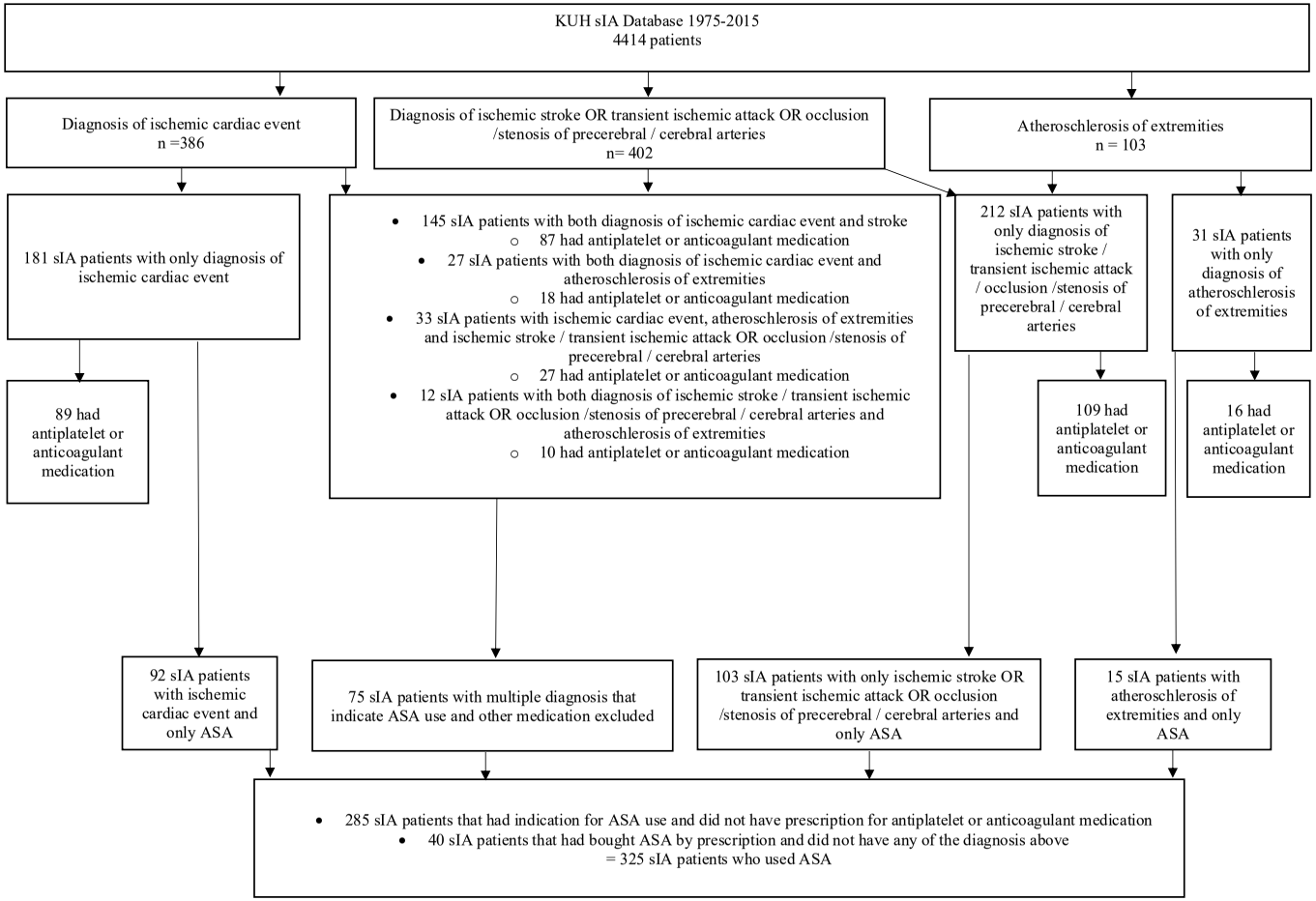

Figure 3. Flowchart showing selection of patients who were considered to use aspirin according to hospital diagnoses and prescription purchases in publication IV. Räisänen et al. 2022. European Journal of Neurology. Reprinted by permission from John Wiley and Sons.

4.7 STATISTICAL ANALYSIS

Discrete variables were expressed in proportions and continuous variables in medians and ranges. The subgroups were compared using the Chi-square test, Fisher exact test, Kruskal–Wallis test or independent samples t-test when appropriate. Multivariable Cox regression analysis was used to analyze de novo sIA formation with the following variables: sex, age at presentation of sIA disease, smoking history, hypertension, family history for sIAs, antihypertensive medication use and usage of different anti-inflammatory medications. The date from the imaging study confirming the first de novo sIA formation were used in the time-to-event variable calculation in Cox regression and Kaplan–Meier estimate. Kaplan–Meier curves were plotted to visualize the effect of different risk factors on de novo sIA formation. P-values less than .05 were considered significant. SPSS statistical software (SPSS Inc, IBM, Armonk, New York) was used.

4.8 ETHICS

Digital subtraction angiography (DSA) is used in sIA follow-up. It is an invasive imaging technique with the possibility of complications, which is why we should know which patients need to be followed, for how long and how intensively. Current treatment methods also come with a risk, and we should know which patient should be treated and when. Nevertheless, the burden that comes with living each day with a severe chronic disease and repetitive controls should also not be underestimated. This study provided more information about the above mentioned questions and was therefore considered ethically justified.

The study was approved by the Ethics Committee of the Kuopio University Hospital. Data fusion from the national registries was performed with the permission of the Finnish Institute for Health and Welfare. Patients signed a consent before their data were included in the Kuopio sIA database. This was a retrospective study and no patients were contacted during the study.

5 RESULTS

5.1 CHARACTERISTICS OF YOUNG EASTERN FINNISH SIA PATIENTS

Between 1980 and October 2014, 613 (15 %) sIA patients out of a total of 4082 sIA patients were diagnosed as having sIA diasease at an age younger than 40 years. 508 of these patients had aSAH and 105 patients were carriers of an unruptured sIA. These 613 patients were further divided into three age groups: 0-19 years (n= 28, 0.7 %), 20-29 years (n= 132, 3.2 %) and 30-39 years (n=453, 11 %) (Fig. 1). sIA-SAH was rare in patients younger than 20 years and increased with age (Fig. 4). In total there were 299 unruptured sIAs in patients under 40 years old. 145 of these unruptured sIAs were found because of SAH from another sIA, 109 as an incidental finding and 45 by screening sIA families.

Patients under 40 years old presenting with sIA-SAH more often had a family background unrelated to APDKP (19-30%) than did patients 40 years old or older (13%). Among patients diagnosed with unruptured sIA, family background was similarly twice as common in patients 20-29 years old (39%) and in patients 30-39 years old (47%) when compared to older unruptured sIA patients (21%) (Table 1).

The number of multiple aneurysms did not differ according to age among sIA-SAH patients; interestingly, however, patients diagnosed with unruptured sIAs at an age younger than 40 years more often had multiple sIAs than coeval sIA-SAH patients (34/ 105, 32% vs 98/508, 19%). Of these patients with multiple sIAs and an sIA-disease diagnosis at an age younger than 40 years, 32% had a positive family history.

Table 1. Characteristics of 613 young sIA patients compared with 3469 sIA patients ≥ 40 years old. Räisänen et al. 2018. Neurosurgery. Reprinted by permission from Wolters Kluwer.

	Patients with unruptured sIA at first diagnosis					**Patients with first sIA-SAH on admission**				
	0-19 years n= 6	**20-29 years n= 18**	**30-39 years n= 81**	**≥ 40 years n=1150**	**p-value**	**0-19 years n= 22**	**20-29 years n= 114**	**30-39 years n=372**	**≥40 years n= 2319**	**p-value**
	N (%)	**N (%)**	**N (%)**	**N (%)**		**N (%)**	**N (%)**	**N (%)**	**N (%)**	
Family history for sIAs	1 (17%)	7 (39%)	38 (47%)	238 (21%)	0.000*	5 (23%)	34 (30%)	71 (19%)	302 (13%)	0.000*
APCKD	-	-	2 (3%)	16 (1%)	0.687	-	3 (3%)	8 (2%)	16 (1%)	0.005*
Patients with multiple sIAs	3/6 (50%)	4/18 (22%)	27/81 (33%)	313/1150 (27%)	0.256	5/22 (23%)	15/114 (13%)	78/372 (21%)	503/2319 (22%)	0.255
Gender (females)	4 (67%)	11 (61%)	41 (51%)	662 (58%)	0.411	11 (50%)	53 (47%)	140 (38%)	1333 (58%)	0.000*
Male to Female Ratio	1:2	1:1.6	1:1	1:1.4		1:1	1.2:1	1.7:1	1:1.4	
History of smoking					0.000*					0.007*
Current	2 (33%)	10 (56%)	50 (62%)	323 (28%)		4 (18)	38 (33%)	102 (27%)	495 (21%)	
Former		1 (6%)	8 (10%)	123 (11%)		-	6 (5%)	17 (5%)	129 (6%)	
Hypertension	-	-	17 (21%)	481 (43%)	0.000*	1 (5%)	8 (7%)	58 (16%)	791 (35%)	0.000*

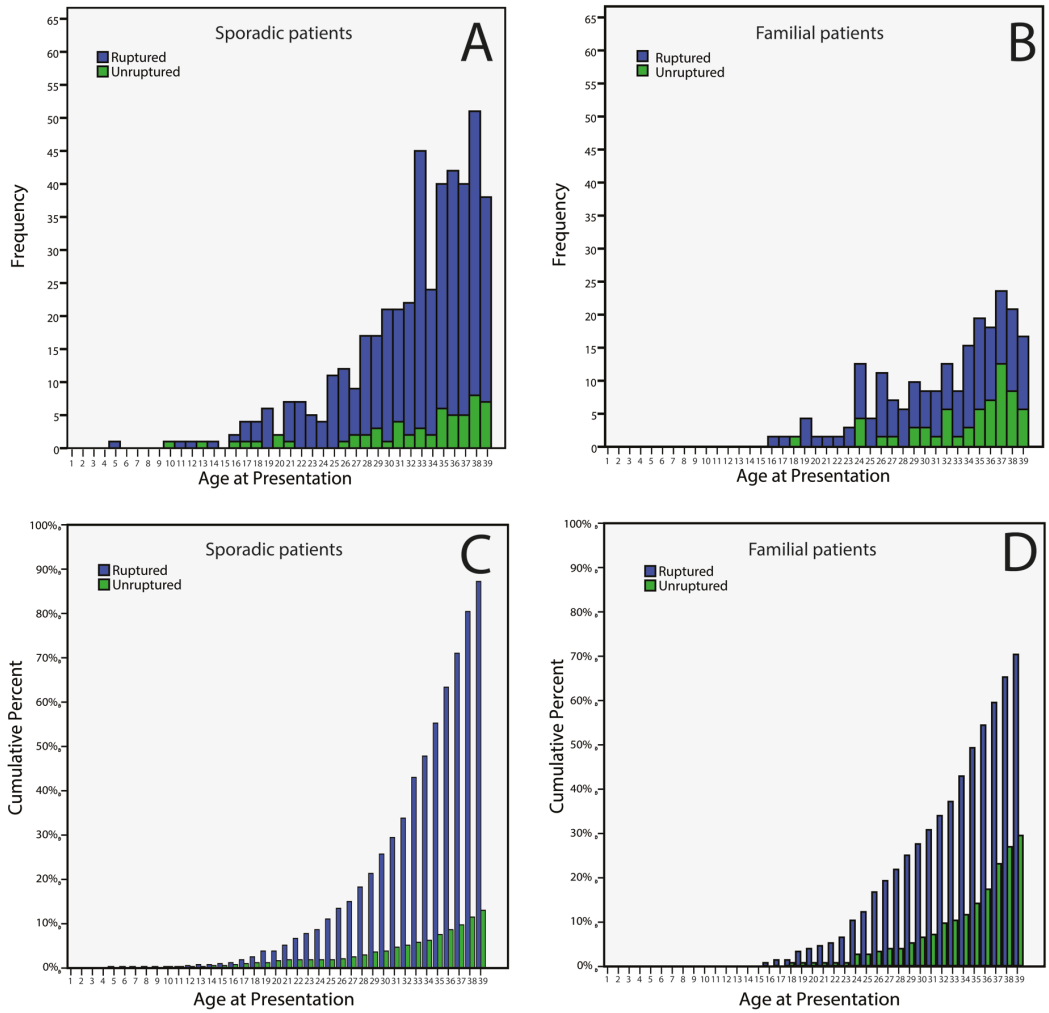

Figure 4. Number of patients diagnosed with aSAH or unruptured sIA at an age younger than 40 years old, shown separately for sporadic sIA patients (A) and for patients with a family history (B). Cumulative percentage of diagnosed sIAs in sporadic patients (C) and patients with family history (D). Räisänen et al. 2018. Neurosurgery. Reprinted by permission from Wolters Kluwer.

5.1.1 Risk factors for sIA formation in young sIA patients differ from older sIA patients

As mentioned before, family background for sIA was clearly more common among patients diagnosed with unruptured sIAs at young age than in older (≥ 40 yr) unruptured sIA patients (Table 1). Of the other known risk factors for sIA disease, smoking history was very common among young patients diagnosed with unruptured sIAs (68%), more so than among older (≥ 40 yr) unruptured sIA patients (39%) (Table 1). However, diagnosed hypertension was not reported among patients younger than 30 years old and was two times less common among young, unruptured sIA patients (21%) than among patients ≥ 40 years old (43%) (Table 1).

Family history (13/22) was associated with de novo sIA formation in young sIA patients (P = 0.001) and smoking history (13/22) showed a trend towards association with de novo sIA formation (P = 0.072) in a univariate analysis, whereas hypertension (3/22) was not associated with de novo sIA formation in this series (P = 1.000).

A Cox regression analysis that included gender, age at presentation of sIA disease, family history, hypertension, and known smoking history, showed that family history (hazard ratio [HR] 3.1, 95% confidence interval [CI] 1.3-7.7), smoking history (HR 2.8, 95% CI 1.2-7.0), and age at presentation (HR 0.91 per year, 95% CI 0.85-0.98) were independent significant risk factors for de novo sIA formation.

5.1.2 Risk factors for sIA rupture in young sIA patients differ from older sIA patients

Smoking, a significant risk factor for aSAH, was more common among patients with a ruptured sIA at ages 20-39 years than among patients ≥ 40 years old with aSAH. Hypertension, another known risk factor for aSAH, was, however, clearly less common among young aSAH patients when compared to older patients (≥ 40 years).

We also analyzed rupture risk by calculating PHASES scores (age omitted) and learned that patients who had suffered aSAH at an age < 20 years or at ages 20-29 years had significantly lower PHASES scores

($p < 0.001$) than patients ≥ 40 years old. The PHASES scores of patients 30-39 years old did not significantly differ from those of older patients.

Gender distribution of aSAH patients at ages 20-39 years old showed a male predominance (male to female ratio 1.2:1–1.7:1), which was not seen in coeval patients with unruptured aneurysms. AcoA aneurysms accounted for 36 % of the ruptured aneurysms in this age group of aSAH patients, but they were less common in females, which can explain the male predominance, at least to some extent. Among unruptured siA patients aged 30-39 years, Acom location was underrepresented suggesting the high rupture risk of sIAs at this location. The most common locations of ruptured sIAs in patients aged 20-39 years old were their anterior communicating artery (AComA) and middle cerebral artery bifurcation (MCAbif), whereas the internal carotid artery bifurcation (ICAbif) was the most common site of ruptured sIAs (44 %) in the youngest sIA-SAH patients (< 20 years old).

The median size of ruptured sIAs increased from 6 mm to 8 mm with age. In patients younger than 20 years old, 57 % of sIAs were smaller than 7 mm, 44 % in age group 20-29 years old and 33 % in age group 30-39 years old. Among patients under age 40, the surface of ruptured sIAs was irregular in most aneurysms, but in degreasing proportion with increasing age, that is, 95 %, 94 % and 90 %, respectively.

5.2 DE NOVO SIA FORMATION

5.2.1 De novo formation in young Eastern Finnish sIA patients

De novo sIA was diagnosed in 4 % (22/613) of the sIA patients younger than 40 years old. Most (13/22) of these young patients were 30-39 years old at the initial sIA diagnosis. When comparing de novo formation between age groups, the percentage of patients diagnosed with de novo aneurysm decreased with increasing age: 14 % (4/28) in patients 19 years or younger, 4 % (5/132) of the sIA patients 20-29 years old, 3 % (13/453) of sIA patients 30-39 years of age and 0,6 % (20/3469) of patients 40 years old or older had developed denovo sIAs during follow-up. Median time to de novo

sIA diagnosis was 11.8 years after the initial sIA diagnosis and none were diagnosed after 3 years of follow-up. 9 % of the diagnosed de novo sIAs had been found after 5 years of follow-up, 27 % after 10 years of follow-up, 59 % after 15 years of follow-up, and 82 % after 20 years of follow-up. It is remarkable, that 18 % of the de novo sIAs were found more than 20 years from their initial diagnosis. Of the patients who were alive at 12 months after their initial sIA diagnosis, 67 % (n=18) of the patients under 20 years old, 53 % (n = 70) of 20 to 29 years old, 48 % (n = 191) of 30 to 39 years old and 38 % (n = 1130) of patients ≥40 years old had undergone angiographic follow-up ≥5 years.

5.2.2 Incidence of de novo sIAs in a cohort of 1419 Eastern Finnish sIA patients

We further investigated the incidence of de novo sIAs in a cohort of 1419 sIA patients (1107 ruptured, 312 unruptured) with their first sIA diagnosis between 1975 -2014. These patients had at least one follow-up angiography between 1975 and October 2015, with a median follow-up time from the first diagnosis to the last angiography of 11.0 years (18 526 patients-years). At this time 56 de novo sIAs were angiographically diagnosed in 42 sIA patients, yielding a 0.3 % overall cumulative discovery rate for de novo sIAs per patient year and the overall discovery rate for de novo patients was 0.23 % per patient years. The median time from the initial sIA diagnosis to the de novo diagnosis was 11.7 years (range 0.7-30 years) (Table 2). The cumulative incidence was found to decrease with increasing age at the initial sIA diagnosis: 2.2 % for patients aged <20 years; 0.46 % for those aged 21 to 40 years; 0.19 % for those aged 41 to 60 years; and 0.02 % for >60 years. Nine (20 %) de novo sIAs ruptured with the median time from the initial sIA diagnosis to rupture being 10.3 years.

The incidence of aSAH from a ruptured de novo aneurysm was higher than the incidence of aSAH in the general population, 50 / 100 000 vs. 4-7/ 100 000, respectively.

5.2.3 Characteristics of de novo sIAs patients

The 42 de novo sIA patients differed significantly from the rest of the 1377 sIA patients without de novo diagnosis in 4 aspects when patient characteristics at the initial sIA diagnosis were compared: de novo sIA patients were younger at their initial diagnosis (median 39 years versus 51 years), more often had a smoking history (60 % versus 27 %) and a positive family history (30 % versus 17 %), and the site distributions of primary sIA(s) were different (Table 2). The prevalence of a hypertension diagnosis was equal (31 % versus 33 %) (Table 2). 11 (26 %) de novo sIA patients had multiple de novo sIAs (Table 2).

5.2.4 Characteristics of de novo sIAs

The median size of the nine ruptured sIAs was 7.5 mm and there was not feature that would distinguish them from the 1066 ruptured primary sIAs, nor did the 47 unruptured de novo sIAs differ from the primary unruptured sIAs.

5.3 RISK FACTORS FOR DE NOVO SIA FORMATION

Positive smoking history (HR, 5.61), age at the first sIA diagnosis (HR, 0.96 per year), and the anterior cerebral artery location of the primary sIA (HR, 0.19) were independently associated with de novo sIA formation in the multivariate Cox regression analysis. The hazard ratio decreased by age at the first sIA diagnosis as follows: HR, 27.4 for <20 years; HR, 8.63 for 20 to 40 years; HR, 5.32 (not significant) for 41 to 60 years; and with >60 years as a reference. A positive family history and a primarily unruptured sIA disease were not independent risk factors for de novo sIA formation (Fig. 5, Table 3).

Table 2. Characteristics of the study cohort of 1419 sIA patients. Lindgren AE, Räisänen S. et al. 2016. Stroke. Reprinted by permission from Wolters Kluwer.

	No de novo sIAs n=1377 (97%)	**Verified de novo sIA n=42 (3%)**	**Log-rank p values**
Females	693 (50%)	21 (50%)	ns
Median age at presentation	51	39	
Age group at primary presentation			<0.000
-20	15 (1%)	5 (12%)	
20-40	273 (20%)	15 (37%)	
40-60	739 (54%)	20 (50%)	
>60	352 (25%)	1 (3%)	
Presentation as ruptured	1078 (78%)	29 (69%)	<0.000
Median follow-up time after sIA diagnosis (range)	10.9 (5-37)	14.8 (1.7-33)	
Median time to de novo diagnosis		11.7 (0.74-30)	
Familial disease	24 (17%)	12 (30%)	<0.000
Ruptured	1068 (78%)	26 (65%)	
Ruptured de novo sIA	0	9 (20%)	
Multiple de novo sIAS	0	11 (26%)	
Multiple sIAs on first presentation	403 (29%)	17 (41%)	0.030
Hypertension	425 (31%)	14 (33%)	ns
Smoking	371 (27%)	25 (60%)	<0.000
Location of primary sIA			<0.000
ICA	129 (9%)	10 (24%)	
MCA	500 (36%)	22 (53%)	
ACA	474 (34%)	4 (10%)	
VA	24 (2%)	0	
BA	64 (5%)	1 (2%)	
PICA	185 (14%)	5 (12%)	
others	1 (0%)	0	
Primary sIA treatment			
Surgical	1083 (79%)	27 (64%)	
Endovascular	164 (12%)	3 (7%)	
Conservative	130 (9%)	12 (29%)	

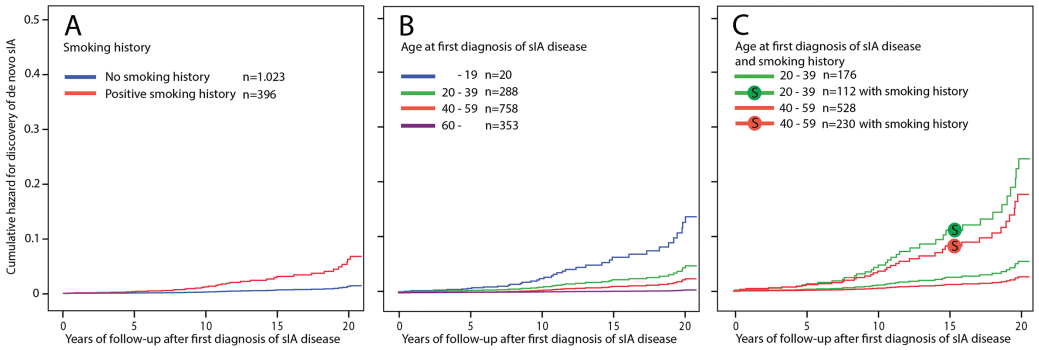

Figure 5. Cox regression hazard curves for the risk factors of de novo sIA formation: A, history of smoking, B, age at first diagnosis of sIA disease and C, combined smoking history and age groups 20-39 years and 40-59 years old. "Years of follow-up" represents the time between the first diagnosis of sIA disease and the first diagnosed de novo sIA or the latest available follow-up angiography. Lindgren AE, Räisänen S. et al. 2016. Stroke. Reprinted by permission from Wolters Kluwer.

Table 3. Multivariate COX regression analysis of risk factors for de novo sIA formation. Lindgren AE, Räisänen S. et al. 2016. Stroke. Reprinted by permission from Wolters Kluwer.

	HR	**95% CI**	**P Values**
Family history for sIAs	0.98	0.48-1.98	0.965
History of smoking	5.61	2.86-11.1	0.000
Age at presentation			
-20	27.4	2.90-258	0.004
20-39	8.63	1.12-66.5	0.39
40-59	5.32	0.71-1.12	0.105
60+	Reference	Reference	Reference
Primary sIA at ACA	0.19	0.05-0.66	0.008

5.4 IMPACT OF ANTIHYPERTENSIVE MEDICATIONS ON DE NOVO SIA FORMATION

The use of antihypertensive medication was more common in a group of patients who did not have de novo aneurysms than in patients who developed de novo sIAs (821/1377, 60 % vs. 20/42, 48 %). However, the use of antihypertensive medication did not significantly affect the de novo aneurysm formation in a multivariate analysis.

5.4.1 Risk factor profile of de novo sIA patients with and without antihypertensive medication

Of the total of 1419 sIA patients, 453 sIA patients did not use antihypertensive medication and 10 were diagnosed with de novo sIA. These patients could be classified as a group of sIA patients without hypertension as an etiology of sIA formation. The 10 de novo sIA patients without antihypertensive medication were younger (31 y.) than other patients (51 y.) at the initial diagnosis but also at time of de novo diagnosis, and more often had family history of sIA disease (40 % vs. 17 %, respectively) (Table 4). Many of them also smoked (50 % vs 25 %, respectively), but smoking was even more common among those de novo sIA patients who also used antihypertensive medication (Table 4).

The remaining 966 sIA patients in our cohort had used antihypertensive medication, but 125 patients used the medication irregularly according to our classification. Twelve of these 125 sIA patients developed de novo sIA during follow-up (Table 4).

The use of regular antihypertensive medications did not significantly reduce de novo sIA formation (HR 1.60, 95 % Cl 0.84-3.06) in the multivariate Cox regression analysis that included age at primary diagnosis, gender, family background, presentation with multiple sIAs at initial sIA diagnosis, smoking history and regular antihypertensive medication. Age at the initial sIA diagnosis (HR 0.95, 95 % Cl 0.93-0.98) and smoking history (HR 5.53, 95 % Cl 2.77-11.05) were the only significant risk factors for de novo sIA formation.

We learned when we further investigated the use of antihypertensive agents with different multivariate COX regression models that regular use

Table 4. Use of antihypertensive medication and risk factors for de novo sIA formation. Räisänen et al. 2022. European Journal of Neurology. Reprinted by permission from John Wiley and Sons.

	De novo patient					
	Yes n = 42			**No n = 1377**		
	Antihypetensive medication			**Antihypertensive medication**		
	Regular n =20	**Irregular n=12**	**No n=10**	**Regular n=821**	**Irregular n=113**	**No n=443**
Median age at primary presentation	44 (17-73)	36 (22-57)	31 (14-51)	52 (16-83)	50 (13-80)	51 (5-79)
Median age at de novo diagnosis	55 (26-81)	50 (32-63)	43 (31-65)			
Median time to de novo diagnosis (years)	12 (0.7-30)	10 (4-28)	14 (5-29)			
Positive family history	3 (15%)	6 (50%)	4 (40%)	144 (18%)	20 (18%)	76 (17%)
Positive smoking history	15 (75%)	5 (42%)	5 (50%)	218 (27%)	41 (36%)	112 (25%)
Positive family and smoking history						
Yes	3 (15%)	2 (17%)	3 (30%)	50 (6%)	11 (10%)	31 (7%)
Neither	5 (25%)	3 (25%)	4 (40%)	508 (62%)	63 (56%)	286 (65%)
Presenting with multiple sIAs	9 (45%)	5 (42%)	3 (30%)	251 (31%)	24 (21%)	128 (29%)
Diagnosis of hypertension	12 (60%)	3 (25%)	0	379 (46%)	25 (22%)	27 (6%)

of the inhibitors of renin-angiotensin system did not reduce formation of de novo aneurysms (HR 1.47, 95 % CI 0.76-2.84) and also that there was no difference in de novo aneurysm formation between usage of inhibitors of renin-angiotensin system (HR 0.57, 95 % CI 0.28-1.15) and other antihypertensive agents (HR 0.55, 95 % CI 0.21-1.42) (Fig 6). However, in a model that included regular or irregular use of antihypertensive medication, irregular use of prescribed antihypertensive medication was found to increase the risk of de novo sIA formation (HR 3.84, 95 % CI 1.59-9.29) (Fig 6).

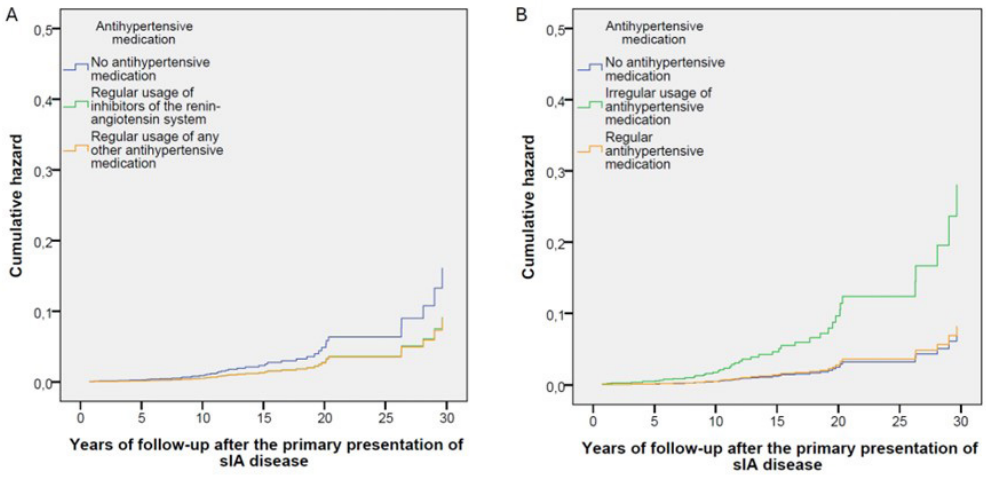

Figure 6. Cox regression hazard curves showing that antihypertensive medication did not significantly affect the risk for de novo aneurysms formation and that there was no significant difference between different antihypertensive medications (A). However, irregular use of antihypertensive medication was associated with the risk of de novo aneurysm formation (B). “Years of follow-up” represents the time between the first diagnosis of sIA disease and the first diagnosed de novo sIA or the latest available follow-up angiography. Räisänen et al. 2022. European Journal of Neurology. Reprinted by permission from John Wiley and Sons.

5.5 EFFECT OF PHARMACEUTICAL CYCLOOXYGENASE-2 INHIBITION ON DE NOVO SIA FORMATION

5.5.1 Effect of COX-2 inhibition on de novo sIA formation

The percentage of de novo patients was the same among patients who used selective COX-2 inhibitors and those who did not (3 % vs. 3 %) (Table 5) and the incidence rate of de novo sIAs was even higher in a group that used COX-2 inhibitors than in a group that did not, 0.58 % per patient-year (8 de novo patients during 1364 person-years with COX-2 inhibitor use) vs. 0.24 % per patient-year (34 de novo patients during 14429 person-years of follow up after initial sIA diagnosis).

The de novo patients, as in previous analyses and also in this univariate analysis, were younger at the primary presentation of sIA disease in both subgroups (p = 0.000) (Table 5), and smoking among de novo patients was common, but it was significantly more common only among patients who did not use COX-2 inhibitors (p= 0.000) (Table 5). In a Cox regression -multivariate analysis, age at the primary sIA diagnosis (HR 0.95, 95 % Cl 0.92-0.97), smoking history (HR 4.98, 95% Cl 2.49-9.95) and irregular use of antihypertensive medication (HR 3.86, 95% Cl 1.61-9.30) were significant risk factors for de novo sIA formation and use of selective COX-2 inhibition did not have a significant effect on de novo sIA formation (HR 0.63, 95 % Cl 0.29-1.39) (Fig. 7).

5.5.2 Usage of NSAIDs and de novo sIA formation

Usage of NSAIDs did not have a decreasing effect on de novo aneurysm formation; rather, the percentage of de novo patients (3 % vs 2 %) (Table 5) and the incidence ratio per patient-year (0.34 %, 34 de novo patients during 9934 patient-years with use of NSAIDs vs. 0.19 %, 8 de novo patients during 4314 patient-years of follow-up after initial diagnosis of sIA disease) were slightly higher among the patients who used NSAIDs than those who did not.

Age at the primary sIA diagnosis (HR 0.95, 95 % Cl 0.92-0.97), smoking history (HR 4.87, 95 % Cl 2.44-9.69) and irregular use of antihypertensive

Table 5. Characteristics of 1419 sIA patients and use of selective COX-2 inhibitors. Räisänen et al. 2022. European Journal of Neurology. Reprinted by permission from John Wiley and Sons.

	Use of COX 2 -inhibition			
	Yes n=319		**No n= 1100**	
	De novo patient		**De novo patient**	
	Yes n = 8 (3 %)	**No n = 311 (97 %)**	**Yes n = 34 (3 %)**	**No n = 1066 (97 %)**
Median age at primary presentation	38 (14-49) **	51 (15-82)	41 (17-73) **	52 (5-83)
Median age at de novo diagnosis	43 (31-68)		53 (26-81)	
Median time to de novo diagnosis (years)	14.3 (3.1-26.3)		11.1 (0.74-30)	
Positive family history	3 (38%)	71 (23%)	10 (29%)	169 (16%)
Positive smoking history	5 (63%)	99 (32%)	20 (59%) **	272 (26%)
Positive family and smoking history				
Yes	3 (38%)	30 (10%)	5 (15%)	62 (6%)
Neither	3 (38%)	170 (55%)	9 (27%)	687 (64%)
Presenting with multiple sIAs	4 (50%)	96 (31%)	13 (38%)	307 (29%)
Antihypertensive medication				
Regular	3 (38%)	204 (66%)	17 (50%)	617 (58%)
Irregular	0	40 (13%)	12 (35%)	73 (7%)

	Use of NSAIDs			
	Yes n= 1079		**No n=340**	
	De novo patient		**De novo patient**	
	Yes n = 34 (3 %)	**No n = 1045 (97 %)**	**Yes n = 8 (2 %)**	**No n= 332 (98 %)**
Median age at primary presentation	42 (14-59) **	50 (11–83)	28 (22-73) **	54 (5-80)
Median age at de novo diagnosis	55 (26-81)		44 (32-75)	
Median time to de novo diagnosis (years)	12.02 (0.74-29.6)		10.3 (1.6-28.1)	
Positive family history	10 (29%)	194 (19 %)	3 (38%)	46 (14%)
Positive smoking history	21 (62%) **	326 (31 %)	4 (50%) *	45 (14%)
Positive family and smoking history				
Yes	7 (21%)	80 (8%)	1 (12.5%)	12 (4%)
Neither	10 (29%)	604 (58%)	2 (25%)	253 (76%)
Presenting with multiple sIAs	13 (38%)	307 (29 %)	4 (50%)	96 (29%)
Antihypertensive medication				
Regular	18 (53%)	701 (67%)	2 (25%)	120 (36%)
Irregular	6 (18%)	100 (10%)	6 (75%)	13 (4%)

	Use of ASA			
	Yes n = 325		**No n=1094**	
	De novo patient		**De novo patient**	
	Yes n = 3 (1 %)	**No n = 322 (99 %)**	**Yes n = 39 (4 %)**	**No n=1055 (96 %)**
Median age at primary presentation	45 (44-49)	56 (23-80)	38 (14-73) **	50 (5-83)
Median age at de novo diagnosis	68 (50-73)		51 (26-81)	
Median time to de novo diagnosis (years)	18.6 (5.4-29.6)		11.5 (0.74-29.0)	
Positive family history	2 (67%) *	35 (11%)	11 (28%)	205 (19%)
Positive smoking history	2 (67%)	55 (17%)	23 (59%) *	316 (30%)
Positive family and smoking history				
Yes	2 (67%)	10 (3%)	6 (15%)	82 (8%)
Neither	1 (33%)	242 (75%)	11 (28%)	615 (58%)
Presenting with multiple sIAs	1 (33%)	93 (29%)	16 (41%)	310 (29%)
Antihypertensive medication				
Regular	2 (67%)	206 (64%)	18 (46%)	615 (58%)
Irregular	1 (33%)	11 (3,4%)	11 (28%)	102 (10%)

medication (HR 3.88, 95 % Cl 1.60-9.42) were significant risk factors for de novo sIA formation, in a Cox regression -multivariate analysis, and use of NSAIDs did not have a significant effect on de novo sIA formation (HR 1.11, 95% Cl 0.50-2.45) (Fig 7).

5.5.3 Usage of ASA and de novo sIA formation

The percentage of de novo sIAs was clearly smaller in the group who used ASA (1.1 % vs. 3.6 %) when comparing patients who used ASA

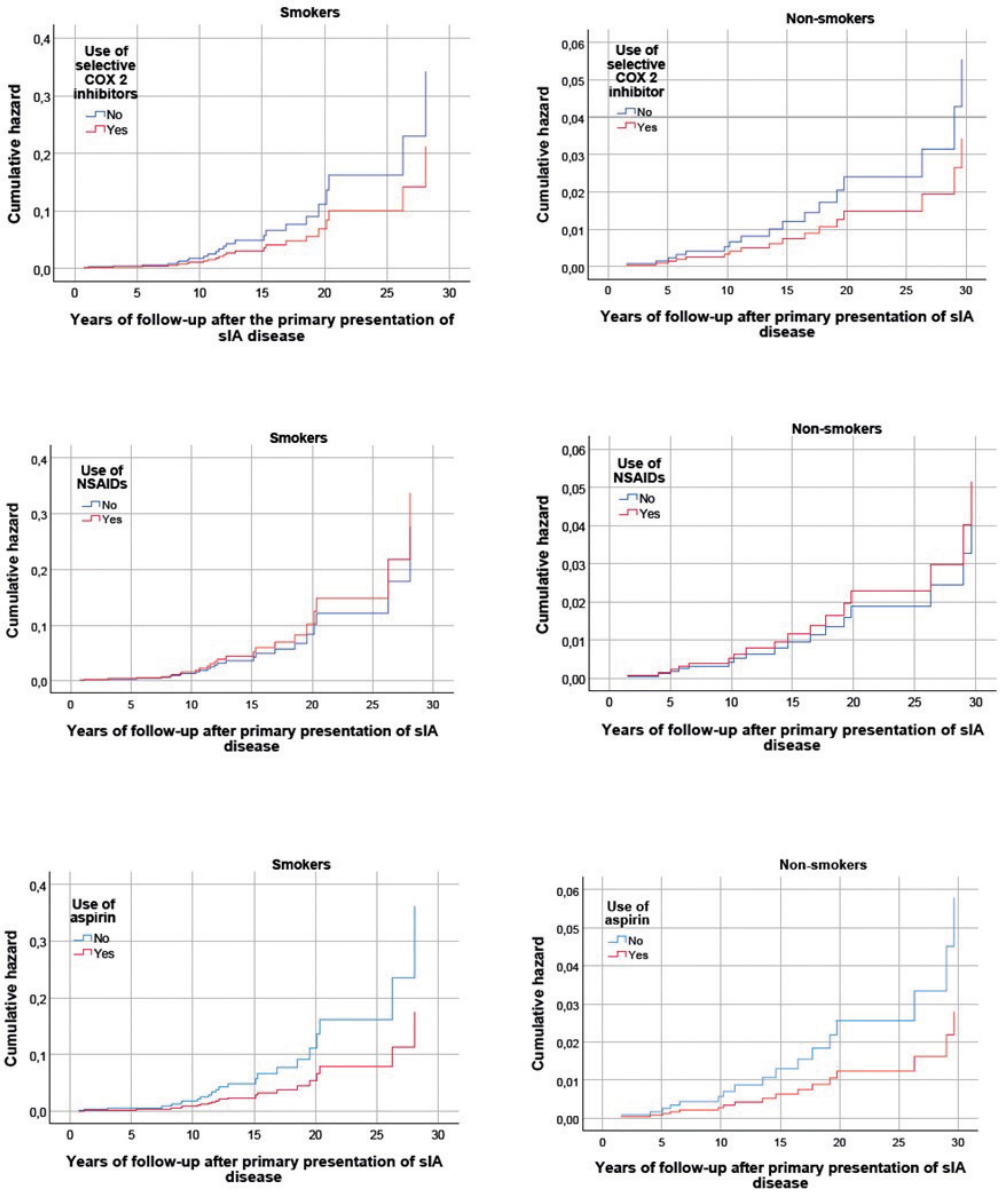

Figure 7. Cox regression hazard curves showing association of de novo aneurysm formation and usage of selective COX2 inhibitors, NSAIDs and aspirin among smokers and non-smoker, respectively. Räisänen et al. 2022. European Journal of Neurology. Reprinted by permission from John Wiley and Sons.

by prescription or had indication for ASA use because of concomitant diagnosis with patients who did not use ASA, as was well the incidence ratio of 0.10 % per patient year (3 de novo patients during 2919 patient years after diagnosis of concomitant disease or first purchase of ASA by prescription) vs 0.28 % per patient-years (39 de novo patients during 13862 patient-years of follow-up after initial diagnosis), respectively (Table 5).

However, in a Cox regression -multivariate analysis, the use of ASA had no significant effect on de novo sIA formation (HR 0.49, 95 % Cl 0.15–1.66), although it seemed to have a trend of reducing the risk for de novo sIA even when comparing smokers and non-smokers. As previously mentioned, age at the primary sIA diagnosis (HR 0.95, 95 % Cl 0.92–0.98), smoking history (HR 4.77, 95 % Cl 2.40-9.47) and irregular use of antihypertensive medication (HR 3.69, 95 % Cl 1.53-8.93) were also significant risk factors for de novo sIA formation in this multivariate model (Fig. 7).

5.5.4 Cohort of 117 sIA patients treated with stenting or stent-assisted embolization

A cohort of 117 sIA patients has used ASA since one of them had sIA treated with stenting or stent-assisted embolization. These patients included four patients with a de novo sIA diagnosis, but only one (0.9 %) of them was diagnosed with de novo sIA after stenting or stent-assisted embolizations. Patients in this cohort were followed, overall, for 287 patient years, with a mean follow-up time of 2.5 years (range 0-12 years); consequently, the incidence ratio for de novo sIA patients in this cohort was 0.35 %. Those de novo patients who had a de novo diagnosis before stenting had a median follow-up time of 2.3 years (0.45-10.7 years) without a new aneurysm formation. Multivariate analysis was not possible due to a lack of statistical power.

6 DISCUSSION

6.1 THE MAIN FINDINGS

We studied the phenotype of 613 sIA patients under age 40 in order to focus treatment and follow-up measures for relevant patients. We also studied 1419 sIA patients, who were selected based on their angiographic follow-up from the 4414 sIA patients treated at our institute during the study period. The focus was on finding the risk factors affecting de novo sIA formation and possible future pharmaceutical treatment options for patients at risk of developing de novo sIAs.

6.1.1 Risk factors for sIA formation are different in young sIA patients

Smoking among young sIA patients was remarkably common and a risk factor for sIA formation, highlighting the importance of smoking as a risk factor for sIA formation in general. However, hypertension did not seem to be a significant risk factor in our cohort of young sIA patients, although we did not have the exact blood pressures of these patients; rather, that diagnosis was based on interviews by our research nurse or on medical record markings. Consequently, it is possible that at least some of these patients had undiagnosed hypertension.

Family background was more common among young sIA patients, most clearly in groups of 20–39 year-old sIA patients, than among sIA patients overall. This might be a consequence of active screening of sIA patients' family members, yet it shows that family background may be a more important risk factor in young sIA patients, when compared to older sIA patients. Formation of multiple aneurysms also seemed to associate with family background in young sIA patients, supporting the interpretation that family background predisposes to sIA formation. It is remarkable that, although the number of sIA diagnoses increased after age 30, a significant proportion of sIAs were already diagnosed at the age of 20-30 years old, suggesting that MRA screening should be started at the age of 20-30 years old, when screening is indicated overall (Fig. 4).

The overall risk for de novo formation in young patients was 4 %, as in the prior population-based study of pediatric sIA patients (14). Smoking, family background and young age were significant risk factors for de novo sIA formation in young patients in Cox regression -multivariate analysis.

6.1.2 Active treatment and even lifelong follow-up are suggested for young sIA patients

The young SAH-sIA patients in our cohort often had small sIAs and a low cumulative risk factor burden (PHASES) (65) apart from smoking, which was very common. This suggests that either the subpopulation of sIAs in young patients is more prone to rupture or PHASES scoring does not include all the considerable risk factors for aSAH at a young age. Our findings – the youngest sIA patients most frequently had irregularly shaped sIAs, that irregularity decreased with increasing age and the divergent site distribution (51), especially the high rate of ICA bifurcation sIAs in youngest sIA patients – could support the interpretation that an unstable sIA wall is associated with young age at diasease onset. These findings together with the longer life-expectancy of young sIA patients, justify a more active approach to treatment of their aneurysms and follow-up.

Current guidelines do not offer recommendations for the frequency of follow-up or for how long young sIA patients should be followed (138). De novo sIAs were found even after 20 years of follow-up, in our cohort of young sIA patients, indicating the need for follow-up as long as the patient is considered to benefit from active treatment.

6.1.3 Active antismoking measures are critical

Smoking was a significant risk factor for de novo sIA formation in all our multivariate analyses. Young sIA patients were very active smokers and at an increased risk for developing de novo aneurysms later in life when compared to our older sIA patients. These findings, together with the hypothesis that at least a subgroup of young sIA patients have sIAs more prone to rupture, highlight the importance of active antismoking meassures when treating sIA patients.

6.1.4 Meticulous treatment of hypertension

About 2-3% of children and adolescents have hypertension, which is often unrecognized (42). Children with hypertension are also usually hypertensive as adults and have an increased risk of developing cardiovascular diseases later in life (42). Hypertension was not a significant risk factor for sIA formation, in our cohort of 613 young sIA patients, but we did not have exact blood pressure levels, and the hypertension diagnosis was mainly based on interviews. However, based on observational studies of general sIA patients, hypertension is considered a risk factor for sIA formation (95–98) and its ability to affect sIA formation is explained through its possible increasing effect on WSS. Nevertheless, there is hardly any evidence that antihypertensive medication would reduce sIA formation in humans. Many antihypertensive medications would, theoretically, be ideal treatments against aneurysm formation and stabilization of unruptured sIA since they have a potential to affect the hemodynamic factors and the inflammation triggered by WSS (120,190).

We investigated the effects of antihypertensive medication on aneurysm formation in a study cohort of 1419 sIA patients including 42 de novo patients. Regular antihypertensive medication was not associated with de novo aneurysm formation in our study. However, we did not have the patients' exact blood pressure measurements and we estimated that 80% adherence to antihypertensive medication would have been sufficient treatment. In the literature, 80% adherence to hypertensive medication is often defined as good adherence, even though this cut-off point is set based on any evidence of the efficacy of the medication used (215). Interestingly, irregular use of antihypertensive medication was significantly associated with a risk of developing de novo aneurysms. It might be that patients who are using antihypertensive medication have some other relevant risk factors for de novo aneurysm formation than hypertension, that overpower the effect of antihypertensive treatment. For example, especially many of those who developed de novo aneurysms and used antihypertensive medications were also smokers (75%). That is why we concluded that when irregular antihypertensive medication stands out as a significant risk factor for de novo aneurysm formation, it indicates that

sIA patients' blood pressure should be followed, and high blood pressure should be treated meticulously. An sIA patient who has an antihypertensive medication, should be monitored to ensure that patient uses the medication correctly.

6.1.5 Treatment strategies for inflammation

Use of selective COX-2 inhibition did not significantly reduce the rate of de novo aneurysm formation in our study of 1419 sIA patients. Significant factors affecting the risk of de novo aneurysm formation were smoking, effective treatment of hypertension and patient characteristics that suggest a propensity to form aneurysms such as young age at the first sIA diagnosis.

Non-selective COX -inhibitors also have the potential to inhibit, COX-2-PGE_2-EP_2 – NF-κB signalling, so we investigated the effect of these medications on de novo sIA formation. Use of NSAIDs did not have any effect on de novo sIA formation in our cohort, but low-dose ASA (100 mg/day) seem to have some effect on reducing the de novo sIA formation. Patients are using ASA without prescription in Finland, so we had to look for indications of ASA use to find those patients who are using ASA regularly. Of course, this approach is susceptible to multiple sources of bias. Therefore, we gathered another cohort of sIA patients, who were using ASA regularly after one of their sIAs had been treated with stent placement. This validation cohort had also significantly lower de novo formation rate than our study population overall. Based on these two patient cohorts we concluded that regular use of ASA might have some effect on reducing de novo sIA formation.

Aspirin is considered to mainly have antiplatelet effects when used in low doses. However, there have been studies showing, that aspirin in low-dose usage also has anti-inflammatory effects in humans (204) and Hassan et al.'s study demonstrated that even a lower dose (81 mg) than used in Finland has an effect on an sIA wall (216).

Previous studies have mainly focused on reducing sIA growth and rupture (205,207,208), which probably are separate processes from

the formation of sIAs, so findings from these studies cannot be directly used when making conclusions about aspirins effects on sIA formation. However, our findings suggest that aspirin should also be further investigated for the purpose of reducing de novo aneurysm formation.

Regarding safety issue considerations, aspirin is already used as a cardioprotective medication, so it does not share the same concerns connected to use of other NSAIDs and aspirin does not significantly influence the effectiveness of antihypertensive medications (203).

6.2 STRENGTHS AND LIMITATIONS

Finland is divided into five university hospitals, which enables forming cohorts that are unselected and minimally biased. Stable populations and detailed population statistics ensure that only a few patients are lost to follow-up. We studied only angiographically verified sIAs and did not include other forms of IAs in our study.

The timing of the patients' follow-up angiographies has been determined on an individual basis instead of a follow-up protocol in our cohorts. This may have affected our results, especially the estimation of when young patients are likely to form de novo sIAs. However, our results demonstrate a need for a predetermined follow-up protocol for young sIA patients.

Finnish ethnicity is a suspected risk factor for aSAH (65), so our results may not be appliable to all populations. It may be, that the onset of sIA disease, rupture and de novo formation happen at different ages in different populations. However, we demonstrated significant differences in young sIA patients when compared to sIA patients overall.

Antihypertensive medications, selective COX -2 inhibitors or other NSAIDs had no significant effect on formation of de novo sIAs, but because the incidence of de novo sIAs is low overall, our study cohort might be limited in statistical power, despite its relatively large sample size. Coxibs are sold in Finland only by prescription, so we can be certain that we have identified all the selective COX- 2 inhibitor users. However, we cannot be

sure how regularly they were used. Some NSAIDs are also sold in Finland without a prescription, so we cannot be sure if some of the patients considered as non-users had been using these. We can assume, that those patients who were using NSAIDs with a prescription, were also probably using NSAIDs without a prescription. We also had data on purchased packages per patients, so we concluded that if NSAIDs other than ASA would have had any dose response on de novo sIA formation, we would have seen it in an analysis and at least as a trend.

Patients in our cohort were using aspirin as a treatment for vascular disease, thus many of them were probably also users of statins. We did not separate statin users, so it is possible that statins had some effect on our results. However, statins have been shown to even increase sIA formation dose dependently in animal models (194), so we cannot be certain if the use of statins has indeed diminished the effects of ASA in our cohort. It is possible that some other medication that we were not taking into account, had some similar effect on our results. Conversely, it is also possible that patients could have had some condition predisposing them to sIA formation, which nullified the benefit of using COX-inhibitors.

It should also be noted that because of the registry-based nature of our studies, the follow-up times for cohorts using coxibs, NSAIDs and ASA were not equal, and our validation cohort clearly had a shorter median follow-up time (2.3 years) than the median de novo diagnosis time (11.7 years) was in our study cohort.

6.3 FUTURE PERSPECTIVES

The phenotype and disease process of young sIA patients should be further clarified in the future in different patient cohorts with the same aneurysm etiology in order to find those patients, who are already at risk of forming aneurysms at a young age and to focus on their follow-up measures.

Smoking is a significant risk factor behind sIA disease, and our findings suggest that young sIA patients especially those with a history of smoking are at an increased risk of developing de novo aneurysms. It would be

essential in the future to establish the mechanisms through which smoking affects aneurysm formation and rupture, as well as whether the use of electronic cigarettes carry the same risk as smoking.

Young sIA patients are at high risk of developing new sIAs in a long perspective. They need treatment strategies to prevent new aneurysm formation in addition to a need for non-invasive treatment modalities for already formed unruptured sIAs. In addition to the meticulous treatment of known risk factors, aspirin seems to be a promising agent and should also be investigated as a preventive strategy for decreasing new aneurysm formation. However, as our knowledge increases in the future, other possible agents that also target the inflammation process in the artery wall of aneurysms should be investigated.

It would be essential to distinguish those aneurysms that are unstable and need to be treated not only for an individual's perspective but also as a part of improving the efficacy and sustainability of our health care system. Understanding the pathobiology and inflammation process in the aneurysmal wall also could help us to develop new imaging techniques to differentiate the unstable aneurysms from stable ones.

7 CONCLUSIONS

1. Young sIA patients are at an increased risk of developing de novo sIAs; they should have angiographic follow-ups for as long as their sIA's preventive treatment is considered.
2. Young sIA patients should be highly encouraged to stop smoking and their blood pressure should be meticulously followed; if diagnosed, high blood pressure should be actively treated.
3. Non-invasive treatment strategies, such as aspirin, should be further investigated in the future to prevent de novo aneurysm formation.

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ORIGINAL PUBLICATIONS (I – IV)

I

Impact of young age on the presentation of saccular intracranial aneurysms: Population-based analysis of 4082 patients

Sari Räisänen, Juhana Frösén, Mitja Kurki, Terhi Huttunen, Jukka Huttunen, Timo Koivisto, Katariina Helin, Mikael von und zu Fraunberg, Juha E. Jääskeläinen and Antti E. Lindgren

NEUROSURGERY, JUN 1;82(6):815-823, 2018

II

De novo aneurysm formation in carriers of saccular intracranial aneurysm disease in Eastern Finland

Antti E. Lindgren, Sari Räisänen, Joel Björkman, Hanna Tattari, Jukka Huttunen, Terhi Huttunen, Mitja I. Kurki, Juhana Frösén, Timo Koivisto, Juha E. Jääskeläinen and Mikael von und zu Fraunberg

Stroke, May;47(5):1213-8, 2016

III

Use of antihypertensive medication and formation of de novo intracranial aneurysms

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European Journal of Neurology Sep;29(9):2708-2715, 2022

IV

Risk factor management matters more than pharmaceutical cyclooxygenase-2 inhibition in the prevention of de novo intracranial aneurysms

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European Journal of Neurology, Sep;29(9):2734-2743, 2022

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An intracranial aneurysm (IA) is a disease of cerebral arteries. A rupture of IA causes a subarachnoid hemorrhage, a form of stroke with high mortality affecting mostly the middle-aged population. IAs are, however, also found from children and young adults, who are in an increased risk of developing new, so called de novo aneurysms. This thesis focuses on characteristics of young Eastern Finnish IA patients, the risk factors for formation of de novo IAs and pharmaceutical treatment strategies.

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EASTERN FINLAND

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**PUBLICATIONS OF
THE UNIVERSITY OF EASTERN FINLAND**
Dissertations in Health Sciences

ISBN 978-952-61-5237-0
ISSN 1798-5706