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Expand the Success of Screening to Reduce Aortic Aneurysm Mortality - Progress Interpretation and New Fronts

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Running Title: Modernizing Aneurysm Screening to Save Lives

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Abstract

Aortic aneurysm is a leading cause of death across the world. Many victicms carry it without knowing. Ruputre of aortic aneurysms leads to devastating sudden death. This brings trauma to families and our society. Based upon sound results out of several cohort studies, US Preventative Services Task Force (USPST) crafted the 1st nationwide abdominal aorta aneurysm (AAA) screening program in 2005. It was renewed and expanded in each of the subsequent revisions in 2014 and 2019. UK and Sweden estalished their own programs as well. Since then, a significant decline in AAA prevalence and mortality is observed. Two decades into the practice, the state of the art on diagonstics, surgical approaches, and pharmacological options have drastically changed. Patients previously ineligible for treatment or inconclusive on diagnostics now have valid options. The screening program is on the verge for a bold expansion. In this review, we summarized the chroncles leading to the inception of the screening programs, progress interpretation after implementation including gains, gaps and controversies, advents of new technologies and approaches, new fronts facing us, as well as priorities to be addressed in future phases. Particularly, screening asssys with a clinically tested biomarker, tetrahydrobiopterin (H_4B), enables unpresended accessibility, consistency and throughput to accommodate the needs of a larger population. Furthermore, patients with AAAs at size below the eligibility threhold for surgical intervention (e.g., < 5.5 cm) can be treated with novel oral medications. Confronting factors such as changing demographics and COVID-19 aftermath are putting up new challenges. Nevertheless, running a program at this scale demands both unwavering commitment and agile fine-tuning. Technical innovation will be an indispensable chapter of its continued success. The burden of aortic aneurysm-led sudden death is too heavy for any family and the society to bear; it is time to step up our resolve with additional capacities as discussed in the present review.

Keywords

Abdominal aortic aneurysm, biomarker, cost-effectiveness, diagnostics, EVAR, mortality, preventative medicine, screening, smoking, surveillance, thoracic aortic aneurysm, ultrasonography, USPST.

Introduction

Aortic aneurysm is the second most common disease affecting the aorta after atherosclerosis, being devastatingly lethal (1, 2). It is responsible for 150,000 to 200,000 deaths each year across the globe (2). Reportedly, abdominal aortic aneurysm (AAA) is three- or four-times more prevalent than thoracic aortic aneurysm (TAA) and co-existence of AAA and TAA is not uncommon (3). An estimated over one million people in the US suffer from AAA (2, 4). The annual death toll of AAA in the US is 17,800 (2), among the leading causes of death for people aged over 55 as well as the whole population (1). In a UK analysis of 1,000 sudden death cases, consecutively and personally performed necropsies by Dr. O'Sullivan between 1988 and 1995 at St. Richards hospital (5), ruptured aortic aneurysm ranked top 5 as causal reasons for death.

Importantly, the prevalence and mortality rate of aortic aneurysms are known to be underestimated. Without proper screening, studies indicate that approximately 30% to 40% of AAA patients are not diagnosed (6), missing vital windows of therapy to prevent lethal rupture. Postmortem identification of AAA is riddled with challenges as well. Examples of misidentification include aging related death, sudden death with unknown reasons, and myocardial complications (7). Becuase of this, the Multicentre Aneurysm Screening Study (MASS) (8) found it necessary to set up a work group to review coronor's reports, necropsy reports, and doctor's notes to correct mislabelling. An accurate assessment of the actual global burden of aortic aneurysms, might only become possible when a reliable screening program is widely adopted, as we here emphasize in this review to promote rather than to cut back according to recent debates.

Several risk factors of aortic aneurysms have been reported. According to analyses of the Aneurysm Detection and Management (ADAM) study (9), male gender, age, smoking, hypertension, hyperlipidemia, Caucasian ethnicity, and family history are considered estalished risk factors for increased susceptibility to aneurysm development. On the other hand, more exercise and cessation of smoking could mitigate the risk. Thus, except for ethnicity or family history, there are many aspects

to work on to reduce risks for developing aortic aneurysms. These risk factors reported by US Veteran Affairs investigators (9) have been confirmed by clinicians and scientists across the globe (10, 11). Genetic factors also have a significant impact. For example, patients with Marfan syndrome face exponentially elevated vulnerability towards aortic aneurysms of both TAA and AAA (predominantly TAA). Greater height, coronary artery disease, cerebrovascular disease, and atherosclerosis accompany aneurysm formation in Marfan patients (10). As the screening program expands in the future, additional risk factors would be unveiled and considered for screening recruiting and clinical management of the disease.

An unprepared AAA rupture would kill up to 90%-95% of the victims and many of them couldn't have the opportunity to reach hospitals alive (8). Together, it combined into a formidable 65-85% motablity rate. Many victims exhibited no distinctive symptoms before rupture; hence, AAA gained the reputation as 'a silent killer'. Besides size and location, the risk of aneurysm rupture is also associated with the speed of their expansion, changes in aortic wall stress, female gender, tobacco use, recent surgery history and certain medication regiments. Dr. Albert Einstein was diagnosed with AAA via an exploratory laparotomy procedure in 1948. Although surgical options were primitive at the time by today's standard, diagnosis and intervention gave five more productive years to the iconic and influential scientist. Since then, many innovations within the last decade have revolutionized the potential clinically adaptable diagnostics and therapeutics for AAA.

Along the aorta, the infrarenal segment is most susceptible to develop aneurysm (i.e., AAA) (3), which is readily observable with ultrasound (12). The widely accepted threshold for a positive diagnosis is a localized enlargement with a diameter greater than 3 cm or 1.5 times of the normal segment (13). Ultrasonographic scan could yield a detection sensitivity at 98.9% and specificity at 99.9% (12). This corresponded to a positive predictive value of 97% and a negative predictive value of 99.9%. These performance characteristics have been verified by radiologists around the world (14). There remains one caveat that the aortas of 1% to 3% of people won't be visualized clearly due to bowel gas or

obesity. Intriguingly, the newly developed biomarker diagnostic can overcome this caveat while providing comparable performances (15, 16), with additional advantages over echo screening or to be combined as discussed below. Meta-analysis of population-base screenings indicates a single abdominal echo scan among elderly men would lower the risk of aneurysm rupture by nearly 50% in 10 years (17).

A. Establishment of National AAA Selective Screening Programs

AAA diagnotics satisfies the ten principles defined in WHO publication on *Principles and Practice of Screening for Disease*. To be more specific, on Principle I, AAA is an important health problem based on prevalence and mortality rate (2, 18). On Principle II, treatment options are available though surgical correction (open repair and EVAR) (4, 14) of large aneurysms at present, or pharmacological regiments based on latest breakthroughs potentially adaptable to clinic (e.g., anti-hypertensives combined with folic acid) (19, 20) for small aneurysms. On Principle III, facilities (e.g., radiology labs) are operating with proficiency audits program in place. On Principle IV, the growth of AAA generally takes years (faster growing ones take several months to a year for significant expansion) to reach the verge of rupture., allowing clinicians ample time to contemplate optimal treatment options. On Principle V, a reliable test (i.e., ultrasonography) is well established (12) and a novel biomarker assay recently developed has the potential of being capable to deliver better performance of broad application and early detection at molecular levels before aneurysms are over echo diagnosable size of 3.0 cm (16). On Principle VI, these tests are readily accessible for the public (21). On Principle VII, preliminary statistics on the size of AAA and its risk of rupture has been analyzed (13). On Principle VIII, multiple cohorts studies have jointly formulated inclusion criteria for at-risk popoluation eligible for screening (8, 18, 22). On Principle IX, cost-efficiency analyses have been done to justify financial merits (20, 23); On Principle X, cohort studies also created a set of re-screening guideline for people diagnosed at early stages (8, 18, 22). These overall characteristics we summarize here are up to date and supportive of the concept for large scale screening of AAA as defined. Indeed, as discussed below, earlier efforts have put AAA screening into practice since 2005.

Citing the results from four classical cohort studies (Table 1) (8, 18, 22, 23), US led the world to announce its AAA screening program in 2005 (24), which was followed by UK (25) , then Sweden (21). The first cohort study at Chichester, UK recruited 15,775 men and women aged 65-80 (22). In the screening group, acceptance rate was 68.4% and ultrasound was able to visualize the aorta for 97.3% of those accepted. AAA was detected in 4.0% members of this cohort and 7.6% among men. During this 5 years study, aneurysm rupture rate decreased by 55% among men (9 compared with 20) in the screening group compared to the control group, largely attributable to elective surgery. The much larger Multicentre Aneurysm Screening Study (MASS) at UK enrolled 67,800 men aged 65-74 (8) with an average follow-up of 4 years in the early reports. The 27,147 individuals out of 33,839 in the screening group accepted invitation (80%), and 1,333 aortic aneurysms were detected (4.9%). There were 65 aneurysm-related deaths (0.19%) in the screening group compared to 113 (0.33%) in the control group. This translated into a risk reduction of 42% as reported (p = 0.0002). The Australian study recruited 41,000 men at the age between 65 and 83 (18). In the screening group, the acceptance rate was 70% and AAA prevalence was at 7.2%. As a result, twice as many men in the screening group underwent elective surgery compared to that of control group (107 versus 54). During the course of this study (average 4.1 years follow-up (8), Table 1), 18 in the screening group and 25 in the control group passed away, corresponding to a mortality ratio of 0.61 (0.33 to 1.11, 95%CI). If the age range of this cohort was refined to 65-75 years old, the mortality ratio would improve to 0.19 (0.04 to 0.89, 95% CI), exhibiting significant benefits. The Danmark study focused more on cost-benefit analyses (23). A cohort of 12,658 men at the age range of 65-73 was assembled; the attendance rate for the screening group was 76% with a mean observation time of 5.13 years. AAA was found in 4% of the screened individuals. A total of 60 patients in the screening group received surgery and only 7 of those had to be performed in an emergency setting. On the other hand, 41 patients in the control group had a chance for surgery and 27 out of the 41 were done as emergency. During this study, 6 patients died of AAA in the screening group compared to 19 in the control group, translating into a 68% reduction in mortality rate. The 74% decrease in emergency operations (7 versus 27) lowered medical expenses as well. The Danish group concluded a proper screening program would not only save lives

but also save healthcare expenditure.

The cohort studies discussed above provided convincing evidence that paved a solid foundation for the US national AAA screening program to lauch in 2005. As the follow-up period extended further, the 'profit' margin is expected to grow bigger. As suggested in the 2002 MASS study report, the longer the follow-up period is, the larger benefits in reducing all-cause mortality of an AAA screening program (8). In 2005, the average follow-up time of these studies were in the range of 4 to 5 years. In parallel, a mathematic power analysis was done for each of the four cohort study to set a target number of people to be recruited (15,775, 12,658, 67,800 or 41,000, respectively), sufficient to conclude on whether a screening program would meet statistical threshold of being beneficial for targeted population (65-80, all gender, Chichester cohort; 65-73, men, Viborg cohort; 65-74, men, MASS cohort; 65-79, men, Wetern Australia cohort; Table 1). Thus, if investigators wants to evaluate risk factors in addition to age and gender in the context of screening, these delimiters require data from more patients. Given time, the national scrrening program will be the source of ample data to further our understanding on AAA epidemiology to facilitate discoveries in eitology and targeted intervention.

There are notable differences in patient recruitment criteria among the four cohort studies (Table 1). These variances shaped the provisions enshrined in the screening guidelines (24). Chichester study (22) was the only one that included women in the cohort. In the age group of 65-80, men had a 5-fold higher chance of AAA identification. This study falls short to show significant benefits of screening for women. In the Western Australia study (18), the results from enrollees of this study indicated significant benefits for men aged 65 to 74, but not 75 to 83, partially due to not excluding those unlikely to attending screening due to ineligible for surgery or compliance issue as authors discussed. Moreover, the analyses of the ADAM study identified several significant risk factors for AAA by association of incidence (9). Many of these findings (e.g., age range, gender, smoking history) made into specific inclusion criteria of the latest screening guidelines published by USPSTF (26), the Society for Vascular Surgery (SVS) (14), and American College of Cardiology/American Heart Association (ACA/AHA) (27).

The healthcare spending structure varies country by country. In the UK, National Institute for Health and Care Excellence (NICE) guideline stated that AAA screening is cost-effective as long as the prevalence of this disease exceeds 0.35% in the target population (28). Reports from Norway, Netherland (29), Sweden (30), UK MASS (31) indicated a cost-effectiveness threshold as low as 1%. Thus, AAA screening programs can be significanly expanded in these countries and still acheive cost-effectiveness advantage. Latest comparison of US with other 10 high-income countries, revealed that US healthcare spending per capita is about 50% higher than that in Denmark and Sweden, 200% higher than that in UK (32). Meanwhile, the life expectancy in the US is the lowest among these high-income countries, at more than 2 years less than the average. The root causes for this shorter lifespan in the US are complex. Implementing an effective nationwide AAA screening program with high participation holds the promise to make a positive impact. In developing countries, analyses on cost-effectiveness are largely lacking. However, a report from China showed that mortality caused by aortic aneurysm increased by 136% from 1990 to 2019 (33). A cohort study in China defined four predictors: age ≥ 65, smoking history, hypertension and/or diameter > 3 cm at aortic root (34). The prevalence of AAA increased with the number of independent predictors identified (0.6% for one predictor, 1.0% for two predictors, 4.8% for three predictors and 10% for four predictors). As the proportion of senior citizens increase in developing countries, so does the burden of AAA prevalence.

In 2005, US Preventive Services Task Force (USPST) made grade B recommendation on one-time screening of AAA for men aged 65 to 75 who ever smoked, grade C for men aged 65 to 75 who never smoked and grade D for women smoked or never smoked (24). Grade B is recommended to get screening; grade D is recommended not to get screening and grade C to follow clinical advice per physician's discretion. This recommendation had the intent to prioritize population at most risk. Medicare coverage starts at the age of 65 in the US. Congress enacted the Screen for Abdominal Aortic Aneurysms Very Efficiently (SAAAVE) Act in 2007 to mandate Medicare rolling out this program. Men identified with a large AAA (≥ 5.5 cm) were eligible to receive surgical repair. The national AAA

screening guideline of UK was composed in 2005, announced in 2008 and implemented in 2009 (25). All men with age over 65 were eligible. Vascular surgeons in UK routinely follow up men with aneuryms larger than 5.5 cm. In Sweden, AAA screening was offered in the Uppsala county in 2006 and gradually expanded into national coverage (21 counties) by 2011 (21). Follow-up measures vary among counties, due to the autonomies afforded in their public health system.

B. Progress Interpretation and Renewed Confidence in the AAA Screening Programs

After the commencement of cohort studies (8, 18, 22, 23) and the implementation of screening programs, several cohort studies reported a decrease in the prevalence of AAA and its associated mortality (2, 35). On the other hand, most studies reported that the occurance of AAA was on the rise before national screening (36, 37). The exact time line of this paradigm shift varies from country to country, but it roughly aligned with the inception of cohort studies and screerning programs. A full understanding of the root causes for this transition would be pivotal for our efforts to manage AAA efficiently in the future.

However, putting all of the the moving pieces back together is a difficult task to attempt, with the dataset and toolbox that we have. First, such trend analyses were retrospective, primarily derived from regression analyses (35). Of note, regression analysis has its limits; cause-effect relationship cannot be concluded upon regression analysis alone. Second, AAA screening affects patients in many ways, both directly and indirectly. The uptake of an elective surgery has a direct impact on survival. Patients with risk factor profiles of AAA but currently below diagnostic or surgical threshold, will receive advice on how to manage behavivors to amend higher risks of AAA growth and rupture, such as to quite smoking or to increase physical activity to lower blood pressure. Moreover, a family physician would have the opportunity to use extra causion when prescribing surgical or medicinal regiments in the future as an “indirect” impact of screening. In a 2012 analysis in UK, an increase in elective surgery, a decrease in smoking rate, and an increase in statins prescription were identified as the top three contributors to the decline in AAA (17). Association between decrease in smoking and reduction in

AAA prevalence were reported by other groups via regression analyses as well. Indeed, in the context of declines in AAA prevalence, the necessity of running a national screening program has entered the discussion among some investigators. This also affects interpretation of risk factors, incident rate and mortality of AAA. Screening can potentially alter the risk factor profiles, hence the prevalence and mortality as discussed aboved. Instead, the benefits of the screening overweigh the only downside of expenses to save more lives while reducing health care costs from uncontrolled aneurysms.

Smoking is a known risk factor for AAA (24) and smoking cessation correlates with a reduced risk of mortality associated with arotic aneurysm. But whether a decrease in smoking rate among the general public can fully account for a reduced AAA prevalence remains to be evaluated. A 2014 report showed a significant decease in incidence of AAA rupture in the US from 2006 and 2011, while it was not the case for TAA rupture (38), even though AAA and TAA share some similar risk factors including smoking history. Of note, the decline in smoking in the US started since the 1st Surgeon General's report on 'smoking and its effects on human health' delivered in 1964. This downward trend has been steady ever since, including 70s and 80s. During the same period, multiple indepedent reports indicated however rising trend in AAA prevalence (36, 37). On a separate note, the smoking prevalence is higer in the developing counties (39), while the AAA prevalence is significantly higher in the developed countries (11). These dichotomies seems to indicate that the dynamics of AAA prevalence is complex. Regardless of how smoking stats evolve in the general population, the AAA screening program enables the opportunity to directly instigate smoke-cession for the most at-risk people. It is interesting to speculate that smoking might contribute more to AAA development in those with other risk backgrounds such as aging and family history. Postive AAA diagnosis is considered effectively persuading for quitting, which will show benefits in mortalities of many diseases linked to smoking. The divergence in trends of TAA and AAA prevalence (no change and declining) highlights the necessarities of a screening program or lack thereof in targeted mitigation of risk factors.

Besides smoking history, age and gender, there are less common, yet significant factors correlating

with elevated prevalence of aortic aneurysm. Genetic risk factors include mutated genes causing Marfan Syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, Tatton-Brown-Rahman syndrome, and autosomal-dominant polycystic kidney disease (ADPKD). SNPs of several genes (TFGβRIIb, MTHFR, TES, CYP19A1, 19q13 loci, ABCC6, SORT1, NOX3, 9p21, ALOXAP, FBLN5, and MMP3) have reportedly increase AAA risks. Reported non-genetic pathological conditions predisposing to AAA include giant cell arteritis, Takayasu arteritis, history of atherosclerosis, hypertension, hypercholesterolemia, hyperuricemia, hyperhomocysteinemia, chronic kidney disease, autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome, gout, gallstone disease, to peptic ulcer disease. In addition, the vulnerability to aortic aneurysm can be affected by usage of certain medications, such as fluoroquinolone (40), tyrosine kinase inhibitors, and oral steroid, and by behavior factors such as poor sleep patterns. Exposure to certain pathogens, such as HIV, has been shown to increase the incidents of aortic aneurysm. In time, we would learn whether the COVID-19 pandemic will lead to a dratic global upkick on the prevalence of this chronic disease alongside others. But we do know that endothelial cells are a primary targets of Sars-Cov-2 (41), and the consequent endothelial dysfunction extended during the long COVID-19 may impact on development and progression of vascular diseases. During the pandemic the AAA screening program got interrupted in many countries, together with the prescription of fluoroquinolone for COVID-19 treatment might have impacted on aneurysm formation.

In the past decade, several cohort studies were conducted, most of smaller size or targeting a specific population. Europe remains to be proactive in AAA cohort studies. After implementing its national screening program, a Swedish cohort study of 35,513 65-years old men between 2010 and 2014 recorded a 78.7% compliance rate (27,951 accepted) and AAA prevalent rate of 2.0% (42). Furthermore, this report documented as many as 43.8% of patients who underwent AAA repair, were actually in need of a complex surgical procedure. It was suggested that earlier detection would boost the opportunity fo resolve aneurysm through a simpler surgical procedure. Progress review of the National AAA screening program in Sweden of 302,957 men over 65 years during 2006-2014 revealed

an overall compliance of 84% and a prevalence rate of 1.5% (43). Within a mean of 4.5 years, 29% of positive cases were surgically treated and the authors praised the effectiveness of the screening program. Likewise in Scandinavia, a cohort study in Olso Norway (44) of 2048 men over 65 year old between 2011 and 2019 (median follow-up time of 7.1 years) asserted that AAA screening was valuable in preventing aneurysm ruption and related mortality. A study of the 2014-2019 cohort of 5,505 people over 67 years old (compliance rate 83.7%) at Viborg, Denmark, indicated an AAA prevalence of 1.9% among men and 0.3% among women (45). Using CT, another cohort study in Copenhagen Danmark (46) enrolled 11,294 individuals with a mean age of 62 (56% women) between 2010 and 2019; among whom the combined prevalence of TAA and AAA were at 2.1% (4.0% among men and 0.7% among women). Among these participants, 95.4% of AAA positive individuals were unaware of it before the screening. Moving slight south in Europe, a Netherlands cohort (1997-2017) of 5,440 men and 1,983 women revealed an AAA prevalence of 2.5% and 0.7%, respectively (47). In Asia, a multicenter (15 hospitals and 5 private clinics) cohort study was conducted between 2012 and 2013 on 1,731 hypertensive patients over 60 years old in Japan. Its conclusion supports the superiority of ultrasound over physical examination in detecting AAA among enrollees (48). In North America, a retrospective review on records of patients underwent ruptured AAA (rAAA) repairs between 2003 and 2019 (5,340 patients, all ages and genders), showed that 66% of them were ineligible for the screening program (49), and suggested an expansion of the screening program to cover male smokers aged 55-64, female smokers over 65 and male smokers older than 75 yet in good health. In parallel, a retrospective cohort analysis on a cohort of 2,638 screening eligible individuals between 2013 to 2016 showed that opportunistic identification of AAA from abdominal scan for other reasons had missed up to 60% of AAA that was later captured by the designated screening program (50). Going further south into Mexico, a multicenter cohort study of 12,936 patients of both gender with a mean age of 69, showed a AAA prevalent of 3.08% with CT scans (51).

USPST's periodic review and revision of guideline demonstrated its confidence in the program (Table 2). In the 2014 revision of the guidelines, women aged 65-75 with a smoking history has been

upgraded from a grade D recommendation to a grade I recommendation, enabling clinicians to offer screening to this group (52). In the 2019 update (26), USPST further upgraded women aged 65-75 who never smoked but had a family history of AAA, from grade D to grade I. Intriguingly, both 2014 and 2019 guidelines apply to adults 50 years or older. In the 2019 release, USPSTF stated its recommendation on screening of men at age range of 65-75 was based on the fact that randomized trial evidence almost entiredly limited to this group. There was not sufficient cohort data for USPSTF to make an official recommendation for expansion. However, it clearly indicated USPST had kept monitoring AAA epidermolgical data when they become available.

In parallel, the 2022 guideline published by the Joint Committee of American Heart Association and American College of Cardiology (AHA/ACC) pushed the evenlope even further on age limit and relevant risk factors to prioritize (Table 2) (27). A class 1 recommendation (equivlant to USPST grade A) was given to all men over 65 years regardless of family or smoking history as well as to women with a family history of AAA. A class 2a recommendation (equivlant to USPST grade B) was given to women with a smoking history. A class 2b recommendation (equivlant to USPST grade C) was given to all men or women younger than 65 but either has a family history of AAA or multiple other risk factors (i.e., smoking history, hypertension, hyperlipidemia, inherited vascular connective tissue disorder, atherosclerotic cardiovascular disease, white race, male sex). A class 3 recommendation (equivlant to USPST grade I) was given to men or woman older than 75 who had a previous asymptomatic screen result. The 2017 guideline published by Society for Vascular Surgery (SVS) (14) had similar recommendations. Class 1 recommendation was given to men and women aged 65-75 with a history of tobacco use; class 2 recommendation was given to never smoker men and women aged 65-75, or over 75 yet in good health with a first-degree relative diagnosed with AAA; class 2 recommendation was also given to men and women over 75, in good health and with a history of tobacco use. Men or women previously identified with AAA at the diameter range of 2.5 cm to 3 cm were recommened to receive a rescreening after 10 years from the initial diagnosis, as a class 2 recommendation.

Taken together, two decades into the screening program, both the regulatory agency and professional societies are in locksteps to offer more people with the benefits of a program expansion on routine AAA screening.

C. The Current Fronts of Large-scale AAA Screening

A clear priority going forward is to address the underutilization of the screening opportunity by the eligible people. In contrast to the participation rate of 85% in Sweden (21) and 77% in UK (53), it was well below 20% in the US (54). Of note, this is even lower than the participation rate in the ADAM study over two decades ago (9). As the initial rollout, Medicare offers it only to patients just turned 65 to be eligible for Medicare benefits, which led to a disappointing less than 1% participation rate. This policy had since changed. Over the years, participation improved to over 10%, but still much behind UK and Sweden. Differences in insurance coverage, accessibility and educational campaign are all likely contributors. In addition to diligently and steadfastly working in these areas, there is also opportunity for new screening strategies to leapfog and offer a better outcome.

Ultrasound based screening had proven its effectiveness, but there are also well-known limitations. The variability among different sonographers has been acknowledged in cohort studies (8, 18, 22, 23). A senior consultant radiologist was placed to conduct quality control reviews (22). The complexity of quality control grew as the screening program went nationwide, making sure proficient standards were consistent at each test location. Moreover, the Australian cohort study drew us a picture of the limited accessibility to an ultrasound facility in certain rural and social-ecconomically challenged areas (18).

Biomarker based assays can greatly improve the throughput, standardization, and accessibility of a screening program. Samples collected in different territories can be tested in a few centralized laboratories, which is easier to ensure standardization and consistent quality control. By periodically sending blind test samples to each of these laboraties, inter-laboratory correlation is readily attenable (55). A valid biomarker needs to afford high sensitivity as well as high predictive value. A lot of efforts

were invested in this quest. As a result, several candidates have been suggested, such as fibrinogen (increase), D-dimer (increase), thrombin-antithrombin complex (increase), interleukin-6 (increase), matrix metalloproteinase 9 (increase), tissue inhibitor of matrix metalloproteinase 1 (increase), C-reactive protein (increase), a1-antitrypsin (increase), tiglycerides (increase), lipoprotein(a) (increase), apolipoprotein A (decrease) and high-density lipoprotein (decrease). Though some candidates are known to associated with certain risk factors of AAA growth or rupture (e.g., hyperlipidemia, arteritis), they fall short to afford sufficient predictive values in a generalized clinical setting. First, the concentrations measured on these markers varied greatly among different studies as summarized in the reviews (56, 57, 58). That is, a concentration reading in the control range in one study would be in the range of AAA in another study, and vice versa. Second, many of these markers (e.g., CRP and IL-6 for inflammation, d-dimer for thrombosis, etc.) are indicative of conditions other than AAA, thus opens doors to fasle postives. Third, the cohort makeup of these exploratory studies does not reflect the AAA prevalence in the general population. The fraction of AAA patient was inflated. Fourth, none of these markers have been tested in the scale comparable to those of ultrasound cohort studies for AAA (8, 18, 22, 23), or to the biomarker study identifying circulating H_4B levels in two reasonable cohorts of AAA and TAA patients as discussed below.

The study on circulating levels of tetrahydrobiopterin (H_4B), as a sensitive and specific diagnostic biomarker for AAA (15, 59), opens a new chapter for the at-risk population. This innovation manifested over a decade of meticulous research, with upstream and downstream molecular mechanisms worked out in several parallel animal models (15, 16, 19, 41, 59, 60, 61, 62, 63, 64, 65, 66, 67). Subsequently, its utilities were verified with patients samples (16). Besides AAA, this assay is uniquely capable of diagnosing and predicting TAA as well. Circulating H_4B levels below 0.2 pmol/μg was set as the threshold for a positive diagnosis of either TAA or AAA (16). In either case, a receiver operating characteristic (ROC) curve of 0.96 is achievable. Moreover, for the 1% to 3% of at-risk population, whose aorta cannot by visualized by ultrasound clearly due to bowel gas or obesity, will get a result via this biomarker assay. Thus, an abnormal H_4B assay result can refer patients to geographical

confirmation by CT. Additionally, biomarker assays can be conducted in automation on IVD instruments. This paves the way to minimize random errors for more reliable results, higher throughput for accommodating more patients, less investments on newly established facilities, and a better competency audit program by sending prociency test samples.

Artificial intelligent (AI) or machine-learning algorithm-based AAA surveillance techniques are relatively new and exciting additions to our toolbox. This includes automated imaging analytics system for diagnotics (68) as well as predictive modeling of pathogenesis progression (69). We are still at early stages and tremendous amount of efforts remain to be invested to ready it for wide clinical implementation. CT comes with higher burdens in accessibility, compliance and cost compared to ultrasounds. However, targeted deployment of CT and AI technology among the cohort with an abnormal biomarker result would justify its application in pragmatic terms.

D. Advancements in Intervention Strategies

In the days of Dr. Einstein, a valid management of AAA was simply wrapping it with polyethene cellophane to stimulate fibrosis on the exterior of the aortic wall. The hope was that extra fiberous tissue will strenghthen the aortic wall, and slow down the process leading to its eventual burst. This approach extended the life cyle of this estimated 12 cm aneurysm six more years, but it also rendered a graft replacement almost impossible afterward. The famous scientist was able to remain productive for 5 out of the 6 years after the wrapping operation.

Shortly after, open repairs with homographs and later synthetic graphs became the standard. Endoaneurysmorrhaphy then takes the center stage as it could achieve a more physiological repair with less blood loss and less trauma to surrounding tissues (70). These open repair protocol represents the interventional strategy available to patients with large AAA (e.g., > 5.5 cm) (8, 18, 22, 23). In the reports of these cohorts, the risk of mortility of receiving an open repair is about 6%, which seemed high but much better than the 30% to 70% risk associated with an emergency treatment. This

rate reduction in mortality was a fundermental factor for USPST to set up a screening program for selected at-risk population.

Endovascular repair of AAA (EVAR) was introduced in 1991. Nowadays about 80% of AAA patients are treated by EVAR in the US (14). Compared to open repair, EVAR historically offers a significantly lower rate of perioperative complication and lower short term mortility rate. This advantage may dissipate gradually over time post operation (71). As a relative new procedure, EVAR has much room to improve. However, as new devices debut and experise mounts, the edge of EVAR over open repairs grew and extended to long term gains (14). More significantly, EVAR opens doors to AAA patients ineligible for open repair surgeries (e.g., >75 years old). Efforts continously poured in to further improve the effectiveness of inventional approaches as evidenced by the amount of registered clinical studies. The most active area is the introduction of new design of stent-grafts (e.g., NCT01328197, NCT00604799, NCT00803075, NCT00802984, NCT00646048, NCT00593814, NCT00233688, NCT01541410, etc).

Medicinal management of AAA has also gone a long way. With animal models, our studies have innovatively established a central role of dysfunctional endothelium in the pathogenesis of AAA and TAA (Table 3) (15, 16, 19, 41, 59, 60, 61, 62, 63, 64, 65, 66, 67, 72). At the molecular level, endothelial specific dihydrofolate reductase (DHFR) function was compromised, leading to uncoupling of endothelial nitric oxide synthase (eNOS) and subsequent reduction in NO bioavailability as well as increase in oxidative stress-driven matrix degradation. Folic acid (FA) supplement has been shown to restore DHFR protein expression and activity, thus put a halt to the pathogenetic process (15, 16, 19, 41, 59, 60, 61, 62, 63, 64, 65, 66, 67, 72). Furthermore, microRNA-192-5p was identified as a negative regulator of DHFR function and targeting microRNA-192-5p was highly effective in attenuating AAA formation (66). Nifedipine is a calcium channel blocker and antihypertensive drug. At dosages of 5 or 20 mg/kg/day, it was able to inhibit AAA development in vivo in either hypertensive and non-hypertensive animal models, while the high dose of 20 mg/kg/day can treat hypertension at the mean

time benefiting patients with co-existing hypertension and aortic aneurysm (63). Most intriguingly, results showed that the beneficial effects of nifedipine and FA were additive or synergistic (19), enabling maximal protection. Managing aneurysm growth is likely a long term endeavor for affected individuals. Thus, the safety profile over chronic usage for a reagent is as important as its efficacy. Since the safe dosage range and potential side effects of both oral medications of nifedipine and FA have been thoroughly scrutinized as a prescription drug or a dietary supplement, they are primed to be rapidly translated into clinical arena.

E. The Priorities to Expand the AAA Screening Program

The screening guideline by USPST in 2005 was constructed upon the data available at that time by the four large cohort studies (8, 18, 22, 23). The benefit-risk and cost-effect matrices have changed significantly over two decades.

In the US, the baby boomer generation (born between 1946 and1964) are now at the age range of 60 to 78. This largely overlaps with the target population outlined by USPST. In the final report by the MASS group (17), the observed benefit margin is slight lower than predicted in the first report of this study (8) 10 years ago. In the earlier report (8), it was also suggested the benefit margin will grow over time. According to the authors of the final report, a number of patients, who did not meet the threshold of intervention in earlier report (8), eventually developed AAA over the 13 year followup period. This observation strongly advocates to offer senior citizens more than just one time screening, thus, AAA developed after initial screening can be captured and dealt with. Compared to open repair, EVAR is better tolerated by patients over 75. In the 2018 guideline released by SVS, it is recommended that the age group over 75 should be included in the eligibility for screening. A recent evaluation in UK by the National Institute for Health and Care Excellence asserted that the AAA screening program is cost-effective as long as prevalence exceeds 0.35% (54). Other analyses (29, 30, 31) also favored screening where prevalence over 1%. Applying this standard, the screening program should be expanded by including younger age groups and further crossing the gender barrier.

However, there are still important benefits that are not calculated in aforementioned cost-benefit analyses. First, the screening program saves lives beyond mitigating the burden of AAA rupture. In light of positive or borderline screening results, patients had the opportunity to develop a solution to implement drastic changes in life style. This may include but not limited to smoke cessation, healthy dietary habits with lower salt and calory intake, and better compliance to statins, and/or antihypertensive prescriptions based on our mechanistic studies over the recent decades (19, 63). These patients can also therefore reap the rewards of lowered risks to cancer, chronic obstructive pulmonary disease (COPD), as well as heart conditions. Second, the new biomarker-based assay (16) was able to capture TAA in addition to AAA, a significant improvement in the cost-benefit calculation. Third, in sparsely populated areas, it would be significantly cheaper to ship out blood samples versus setting up and maintaining radiology laboratories. Thus, cost can be decreased significantly to facilitate better compliance and expansion. Fourth, women have a lower tendency to develop AAA compared to men, but theirs are more prone to rupture. Since aforementioned cost-effect analyses are primarily based on male cohorts, a lower prevalence threshold for budgetary justification should be applied to women. Taken together, extending age and gender limits would be a logic next step. In the context of AAA surveillance, biomarker assays work hand-in-hand with imaging analyses. The former is ideally suited for large scale screening due to its larger throughput capacity and the ability to accommodate patients that echo is not amenable in getting clear images. Imaging analyses, including echo and CT, can provide necessary conformation. Patients with TAA would have a positive result on the biomarker assay and a negative result on the echo analyses, hence a subsequent CT or MRI scan will be used to pinpoint locations of the aneurysm for surgical preparation and additional treatment plans.

Since winter 2019, COVID-19 had ravaged the world through multiple waves and counting via different variances of SARS-CoV-2 virus. Endothelial cells are among the primary target cells by the virus, to mediate multi-organ injuries. A significant portion of COVID-19 patients developed chronic symptoms.

According to an editorial published in March 2023 on Lancet (73), more than 65 million people struggled with post-acute sequelae of SARS-CoV-2 (aka., long COVID). The toll is still rising. It affects 10 to 20% of the cases and people of all ages. By CDC stats, over 7% of US adult population has experienced long COVID. To date, a great number of people still suffer from symptoms, for which endothelial dysfunction also serves as a key contributor (74). Offering screening to patients suffered from acute or chronic COVID-19 episodes would have the potential to save many lives, since work over the past two decades have established the central mediator role of endothelial dysfunction in aortic aneurysm formation (15, 16, 19, 41, 59, 60, 61, 62, 63, 64, 65, 66, 67, 72).

Conclusion

All countries with a national AAA screening program are benefiting from such a program and seeing mortatlity rates decreasing. The development and maturation of new surgical procedures, as well as better calculation of cost-effect matrices, shape a consense among administrative agencies and professional organizations to gradually make more people eligible for the screening to enable elective surgeries or oral medication treatment. Additionally, the benefits of a screening experience on oneself's healthy lifestyles can be transformativen and long-lasting. Expanding of the screening program is thus considered substantially beneficial. Newly validated biomarker-based diagnostics is ideally suited to serve more patients at an affordable rate and scale. Patients with AAA but ineligible for surgery or can't tolerate invasive approaches, can have the opportunity to receive pharmalogical regiments to cease the progress of the disease to prevent inadvertent rupture (19, 59, 60, 61, 62, 63, 64, 65, 66).

The success of the screening program set root in decades of steadfast commitments. Breakthrough and innovations have been made on multiple fronts of this campaign. With unwavering dedication and an enhanced screening program combining utilities of biomarker and oral medications, the healthcare burden of AAA on families and society will keep on dwindling, saving lives from the devastating cardiovascular disorder of aortic aneurysms.

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Table 1. Overview of the 4 Randomized Controlled Trials that Paved the Way for the Initial AAA Screening Program.

	Chichester, UK (22)	Viborg, Denmark (23)	MASS, UK (8)	Western Australia (18)
Gender	men and women	men	men	men
Cohort size	15,775 (6,433 men; 9,342 women)	12,658	67,800	41,000
Age	65-80	65-73	65-74	65-83
Recruitment	1988-1990	1994-1998	1997-1999	1996-1998
Attendance	68.4%	76%	80%	70%
Prevalence	4% overall (7.6% men; 1.3% women)	4%	4.9%	7.2%
Mean follow-up	2.5 years	5.1 years	4.1 years	3.6 years[#]

[#] Median value was reported in the Western Australia cohort report.

Table 2. The Latest Practice Guideline for AAA Screening from Different Associations.

Associations	**American College of Preventive Medicine (ACPM) (75)**	**The Society for Vascular Surgery (SVS) (14)**	**The United States Preventive Services Task Force (USPSTF)** (26)	**American College of Cardiology/American Heart Association (ACA/AHA)** (27)
Release Date	2011	2018	2019	2022
1 (ACA/AHA) / 1 (SVS)		Men or women 65-75 with a history of tobacco use.		Men >65 who have ever smoked or with a family history of AAA. Women >65 with a family history of AAA.
B (USPSTF) / 2a (ACA/AHA) / 2 (SVS)	Men aged 65-75 who have ever smoked.	Men or women 65-75 or >75 and in good health who have a first-degree relatives with AAA. Men or women >75 with a history of tobacco use and in good health. Repeat for those identified with an aortic diameter: 2.5 to 3 cm (10 year); 3.0 to 3.9 cm (3 year); 4.0 to 4.9 cm (1 year); 5.0 and 5.4 cm (6 month).	Men aged 65- 75 who have ever smoked.	Women >65 who have ever smoked.
C (USPSTF) / 2b (ACA/AHA)			Men aged 65-75 who never smoked.	Men or women <65 who have multiple risk factors or a family history of AAA.

I (USPSTF) / 3 (ACA/AHA)			Women aged 65-75 who have ever smoked or have a family history of AAA.	Men or women >75 asymptomatic with a negative initial screening.
D (USPSTF)	Routine AAA screening in women not recommended.		Women who have never smoked and with no family history of AAA.	

Table 3. New potential methods for AAA treatment by targeting dysfunctional endothelium.

Potential Target(s)-Drugs	Year	Molecular Mechanisms
DHFR-Folic Acid (FA) (61)	2012	▪ eNOS uncoupling/H_4B deficiency plays a causal role in AAA formation. ▪ Oral FA administration and DHFR gene therapy block eNOS uncoupling and AAA development in a novel and most robust model of AAA – Ang II infused hph-1 mice.
DHFR-Folic Acid (FA) (62)	2014	▪ FA recouples eNOS via enhanced DHFR activity, increased H_4B and NO bioavailability in the classical model of AAA – Ang II infused apoE null mice. ▪ FA abolishes elastin breakdown and macrophage infiltration to prevent AAA.
Uncoupled eNOS/NOX-Nifedipine (63)	2015	▪ Expansion of abdominal aorta/AAA formation is inhibited by both low and high does of nifedipine in Ang II infused hph-1 mice. ▪ Nifedipine recouples eNOS/inactivates NOX that increases NO bioavailability and reduces superoxide production, resulting in attenuated oxidative stress and matrix degradation. ▪ Nifedipine at higher dose can be used for AAA patients with co-existing hypertension.
NOX1/2/4-KO mice (64)	2017	▪ NOX isoforms 1, 2 or 4 are upstream of DHFR functional deficiency for eNOS uncoupling and AAA formation. ▪ NOX1/hph-1, NOX2/hph-1 or NOX4/hph-1 DKO mice were prevented of AAA formation when infused with Ang II.
DHFR-Mitochondrial targeted ROS scavenger (65)	2019	▪ DHFR knockout mice infused of AngII exerted eNOS uncoupling and consequent mitochondrial dysfunction to result in exaggerated hypertension and AAA formation. ▪ Mitochondrial targeted ROS scavenger (Mito-TEMPO) attenuates AAA formation.
MicroRNA-192-5p-	2021	▪ miR-192-5p expression is updated in human AAA patients.

Specific miR inhibitor (66)		▪ miR-192-5p mediates NOX-dependent DHFR deficiency and AAA formation. ▪ Inhibition of miR-192-5p by selective miR inhibitor is robustly effective in attenuating AAA development.
DHFR-Combinition of FA & Nifedipine (19)	2022	▪ The combinatory therapy (FA & Nifedipine) completely abolishes AAA formation, versus significant partial effects by either alone. ▪ Aortic H_4B bioavailability is further improved by combining FA with Nifedipine to maximally preserve eNOS coupling activity to result in complete attenuation of oxidative stress-dependent matrix degradation and AAA formation.

Ethical Statement

No conflicts of ethical aspects.

All data reviewed and discussed are derived from published cohorts with institutional approvals.

Conflict of Interest

No conflicts is being disclosed