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Commentary

Will DANCAVAS be the most important screening trial in the last 50 years?

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A B S T R A C T

Screening trials for cardiovascular disease have not demonstrated a reduction in all-cause mortality. The Danish Cardiovascular Screening trial (DANCAVAS) involved men aged 65–74 years old who were randomized to an invitation to undergo screening or not. While the 5-year interim analysis did not show a statistically significant benefit in the primary outcome of all-cause mortality, HR 0.95 (CI 0.90–1.00), a sub-group analysis of men age 65–69 did show a lower hazard ratio of 0.89 (CI 0.83–0.96). Given the widening difference between screened and un-screened participants, as well as the benefit in younger subjects, it is likely that the next analysis will demonstrate a statistically-significant benefit of screening. In this commentary we argue why this trial will almost certainly become one of the most influential screening trials and why heeding its most important lesson, the use of coronary artery calcium scoring, has the potential to save countless lives.

Commentary

Screening interventions, such as colonoscopy for at-risk patients, aim to detect sub-clinical disease to reduce morbidity and/or mortality. However, only rarely do trials of screening interventions reduce all-cause mortality [1,2]. Many argue that *disease-specific* mortality and morbidity reduction should be the focus of screening trials [3]. In fact, most of the United States Preventative Task Force (USPSTF) screening recommendations are based off evidence of disease specific clinical benefit, not all-cause mortality [4]. Despite this challenge, the investigators of the Danish Cardiovascular Screening (DANCAVAS) trial set their primary outcome as all-cause mortality [5]. While the 5-year interim analysis did not show a statistically significant benefit in the primary outcome, a deeper look reveals a potential huge leap forward in the primary prevention of cardiovascular disease.

1. DANCAVAS just missed the mark at 5 years

The DANCAVAS trial involved men aged 65–74 years old who were randomized in 1:2 fashion to an invitation to undergo screening or not [5]. Screening included (1) ECG-gated non-contrast CT of the chest and abdomen to detect coronary artery calcium and aortic aneurysms, with incidental atrial fibrillation noted if present during the scan and validated with a 12-lead ECG; (2) ankle brachial blood pressure index (ABI) to detect peripheral arterial disease; (3) blood pressure measurement to detect systemic hypertension; and (4) measurement of cholesterol and HBA1C levels to screen for hyperlipidemia and diabetes. Positive findings prompted disease specific treatment and/or referrals. The plan was to assess the primary outcome at 3, 5, and 10 years. However, due to the COVID-19 pandemic, the first set of results were the 5-year outcomes.

At 5 years, the primary outcome of death from any cause was not significantly reduced, with a hazard ratio of 0.95 (0.90–1.00) and a *p*-value of 0.06. However, in a pre-specified analysis of the younger half of the cohort (age 65–69), the hazard ratio for all-cause mortality was 0.89 (0.83–0.96). No p-value was calculated since the primary outcome had not been met. This was the closest a screening trial has gotten to reducing all-cause mortality since the National Lung Screening Trial (NLST, 2011) [6]. Notably, the absolute risk reduction in all-cause mortality in the overall cohort of DANCAVAS was actually greater than NSLT (0.6 % vs 0.4 %) although the power of DANCANVAS was lower due to a smaller sample size.

To contextualize the benefit of the cardiovascular screening in DANCAVAS, five influential trials that showed mortality benefit and formed the basis for USPSTF screening recommendations can be compared (Table 1).

Two trials showed a reduction in all-cause mortality: NLST (lung cancer screening) and MASS (aortic aneurysm screening) [1]. Three other trials, which focused on screening for colon, cervical and breast cancer, had an impact on cause-specific mortality but even with long follow-up and massive cohorts, impact on all-cause mortality was either not seen or not reported [7–9]. Lack of impact on all-cause mortality was likely due to low incidence and mortality rates of disease since each of these interventions was relatively effective. This also highlights the high bar of establishing an all-cause mortality benefit in a screening trial. Yet with a *p*-value of 0.06 and a visually compelling late separation of curves, DANCAVAS was very close at 5 years.

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Table 1
Comparison of DANCAVAS with screening trials with cause-specific or all-cause mortality benefit.

Trial	Intervention	*N*	Study Initiation Year	All-cause deaths per 100 patient years (control)	ARR (%) Cause specific	ARR (%) All-Cause	Years of Follow Up	NNS/Year
DANCAVAS [5]	Invitation for one-time subclinical cardiovascular disease screening	46,611	2014	24.7	N/A	0.6 %	6	833 (AC)
Long-Term Mortality after Screening for Colorectal Cancer [7]	Fecal occult-blood testing annually	46,551	1975	23.3	0.6 %*	0.0 %	30	4822 (CS)
Multicentre Aneurysm Screening Study [1]	Ultrasound screening for AAA for men 65–74	67,770	1997	40.3	0.5 %*	0.8 %*	13	2214 (CS) 958 (AC)
HPV Screening for Cervical Cancer in Rural India [8]	HPV testing vs standard of care	131,746	2000	NR	0.1 %*	NR	8	7634 (CS)
Malmö Mammographic Screening Program [9]	Mammography every 1.5–2 years vs. usual care	160,921	1977	NR	0.2 %*	NR	23	5068 (CS)
National Lung Screening Trial [6]	Low-dose CT screening vs. chest radiography in at-risk smokers	53,454	2002	37.4	0.3 %*	0.4 %*	12	1512 (CS) 1026 (AC)

* p value < 0.05. AC= all-cause; ARR = absolute risk reduction; CS = cause-specific; DANCAVAS = Danish Cardiovascular Screening trial; NNS = number need to screen, NR = not reported.

Table 2
Potential impact of interventions in DANCAVAS on the primary outcome.

Intervention	Impacted Outcomes?	Why?
ECG during CT	No	- Only 50 atrial fibrillation diagnoses were made from 16,000+ patients - No difference in anticoagulation rates
Aortic aneurysm detection	No	- Only slight increase (0.7 events per 1000 person-years) in elective aneurysm repair - No impact on restricted mean survival time
Blood pressure measurement	No	- Only slight increase in initiation of anti-hypertensives (0.9 events per 1000 patient years) - No difference in aortic dissection or rupture - No impact on restricted mean survival time if initiated on anti-hypertensive agent
Ankle-brachial index measurement	No	- No difference in peripheral revascularization - No difference in major amputation
Lipid measurement	No	- Patients with pre-existing hyperlipidemia diagnosis benefited more (0.90; 0.83–0.97) than those without pre-existing hyperlipidemia diagnosis (1.00; 0.93–1.07)
HbA1c measurement	No	- No difference in initiation of antidiabetic medication - Patients with pre-existing diabetes diagnosis benefited more (0.91; 0.81–1.03) than those without pre-existing diabetes diagnosis (0.96; 0.90–1.07)
Coronary Artery Calcium Scoring	Yes	- 33.2 % of patients had a coronary artery calcium score > 400, accounting for over half the new positive findings in screening - Patients in the invited cohort were 2.6 and 3.2 times more likely to be initiated on lipid lowering and antiplatelet agents, respectively - Patients initiated on lipid lowering therapy and anti-platelets agents had significantly lower restricted mean survival times reflective of higher risk

2. Coronary artery calcium scoring likely drives the benefit in DANCAVAS

While DANCAVAS employed a variety of screening techniques to detect cardiovascular disease, coronary artery calcium (CAC) scoring likely drove almost all of the clinical benefit. The other interventions in DANCAVAS did not detect enough cardiovascular disease or were likely already occurring at high rates in the usual care arm (in the case of lipid and HbA1c screening) and thus likely did not impact the primary outcome. Table 2 summarizes the interventions in the active screening arm in DANCAVAS and their likely impact on the primary outcome.

CAC scoring was likely the most important intervention that drove the reduction in 1.2 deaths per 1000 person-years based on the following reasons:

1. 33.2 % of patients had a CAC score > 400, which accounted for over half the new positive findings in screening.
2. Patients in the invited cohort were 2.6 and 3.2 times more likely to be initiated on lipid lowering and antiplatelet agents, respectively. Absolute increases in initiation rate of therapy were 2.92 % and 3.72 %, respectively.
3. Patients initiated on lipid lowering therapy and anti-platelet agents had significantly lower restricted mean survival times reflective of the higher risk of patients initiated on these therapies.
4. Patients with a pre-existing hyperlipidemia diagnosis benefited more than those without, suggesting that lipid screening leading to a new diagnosis of hyperlipidemia was not the reason for initiation of lipid lowering therapy.

CAC scoring was almost certainly critical in the increase in the initiation of lipid lowering and antiplatelet agents, which in turn resulted in a numerical decrease in all-cause mortality. In fact, this is what the protocol encouraged:

> "An additional consultation was offered at the screening location if the CAC score was above the age and sex- standardized median or PAD was detected in patients who were not already receiving a statin equivalent to at least 40 mg simvastatin (40 mg simvastatin, 20 mg atorvastatin, or 10 mg Rosuvastatin) and low dose aspirin (75–150 mg)."

Trained study nurses performed these 20-minute consultations in which they provided counseling on smoking cessation, walking/exercise, and a low-fat diet. Additionally, treatment with aspirin 75 mg per day (if no contraindication) and atorvastatin 40 mg per day was started.

External validity of the trial may be limited by the exclusion of women, an almost all-white cohort, and the advantage of performing the trial in Denmark's centralized, national healthcare system.

3. An elevated CAC score *should* change management

For decades, cardiovascular risk was calculated according to the presence of traditional risk factors [10]. CAC scoring has been shown to provide the most accurate assessment of future cardiovascular risk compared to other screening tools in a primary prevention population [11]. Moreover, data from the CONFIRM registry demonstrate that a CAC score > 300 portends as high cardiovascular risk as those with a prior cardiovascular event [12]. Additional data from several studies have informed guidelines from multiple societies that recommend initiation of therapy based on elevated CAC score [13]. Beyond the initiation of lipid lowering and antiplatelet agents, the direct visualization and knowledge of plaque in the coronary arteries is a powerful motivator of lifestyle change and medication adherence [14].

4. Will DANCAVAS be the most important screening trial in the last 50 years?

In the United States, 3.5 % of our monumental expenditure on healthcare is spent on preventive care, which is approximately $200 per person per year [15]. Many argue this isn't enough, yet others point to the fact that most screening trials have not impacted all-cause mortality and few have shown improvements in cause-specific mortality and morbidity. DANCAVAS showed substantial promise with a p value of 0.06, late separation of the Kaplan-Meier curve, and significant benefit in the 65–69 age cohort. As described above, a vast majority of this benefit was likely driven by CAC scoring. At its next planned follow-up in 5 years, DANCAVAS has the potential to be the first screening trial in decades to show an all-cause mortality benefit, with results that would apply to a sizeable proportion of the general population. The question now is should we wait years to heed its lesson or implement its most important component, widespread use of CAC scoring, now?

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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