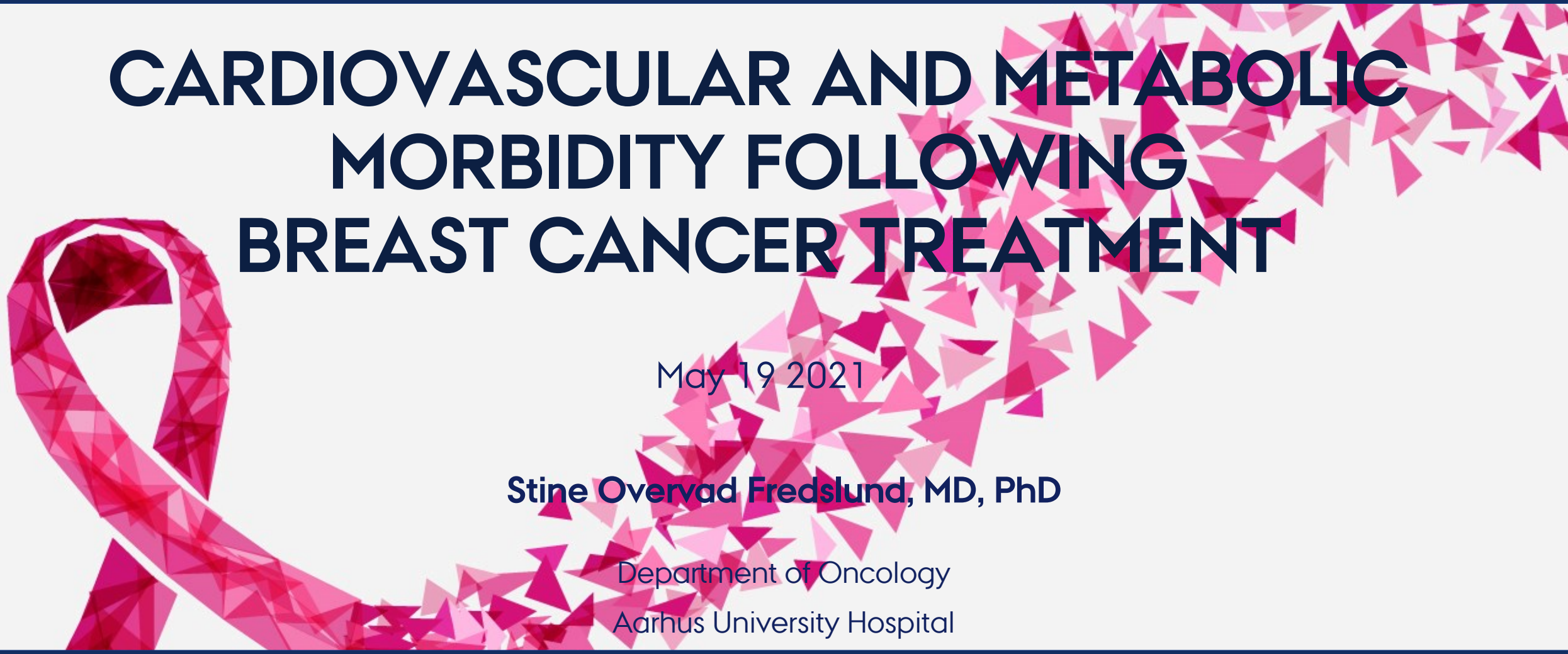
CARDIOVASCULAR AND METABOLIC MORBIDITY FOLLOWING BREAST CANCER TREATMENT



May 19 2021

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Department of Oncology

Aarhus University Hospital

BACKGROUND

AARHUS
UNIVERSITY
DEPARTMENT OF CLINICAL MEDICINE

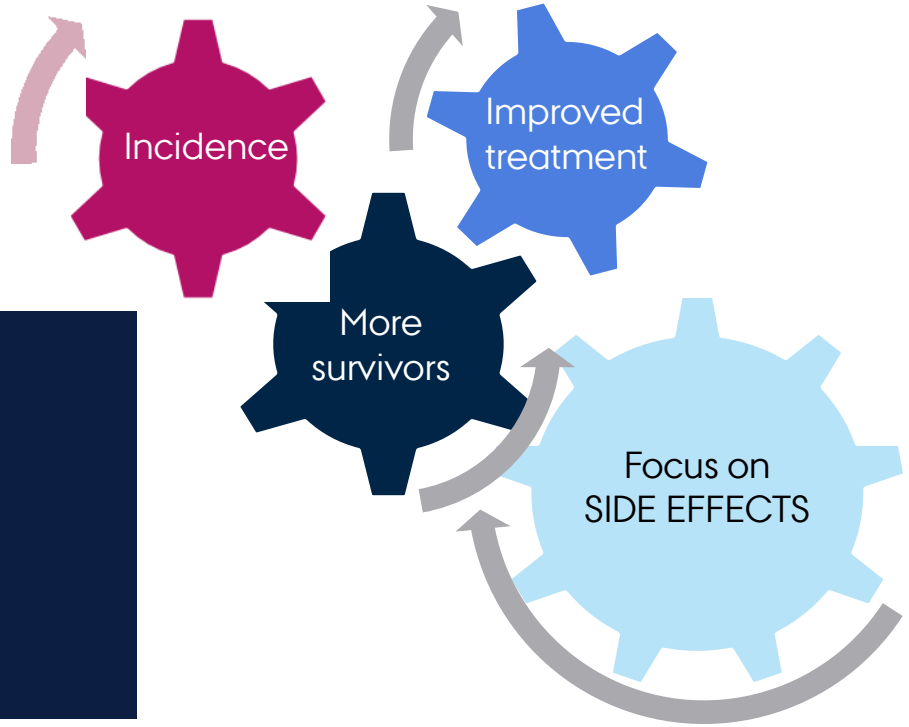
MAY 19 2021

STINE FREDSLUND
MEDICAL DOCTOR, PHD

INCIDENCE

DK: 5000 women are diagnosed every year

5 years survival rates approaching 90%



DK: **70,000**

US: **4.000.000**

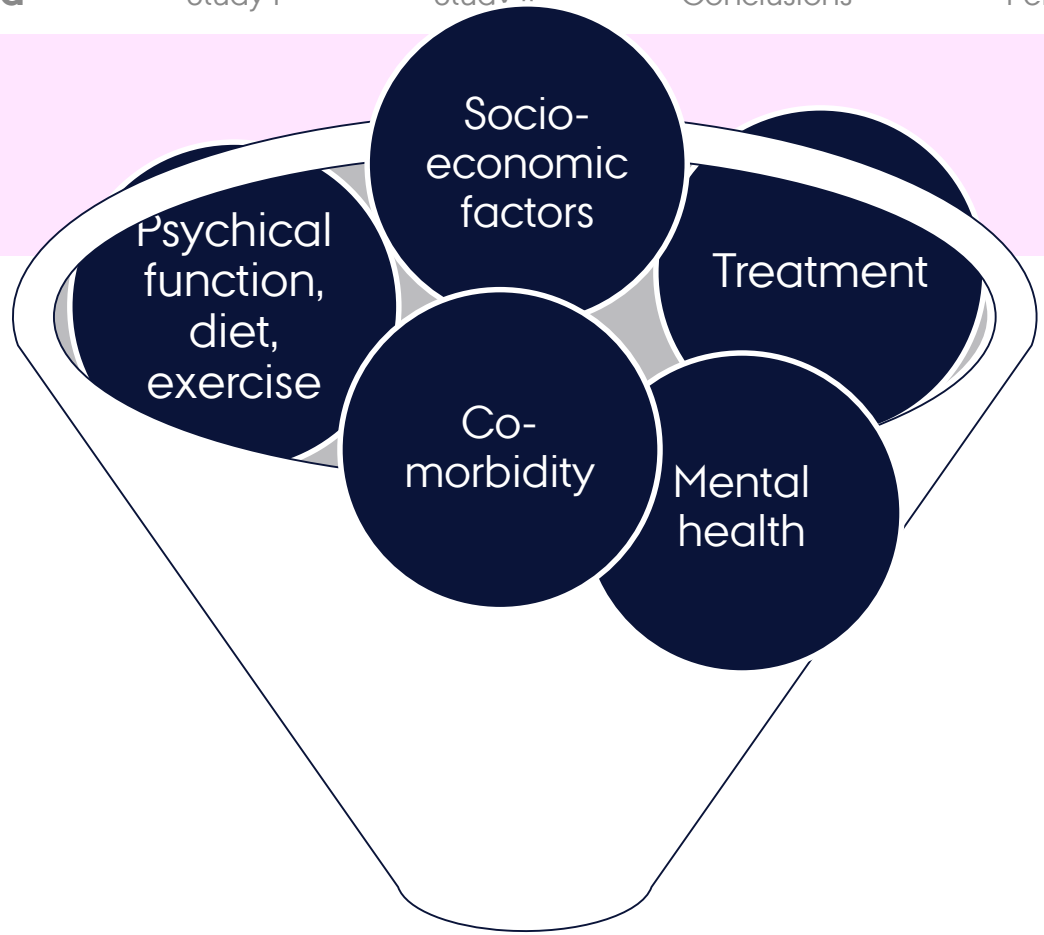
www.breastcancer.org

YOUNG SURVIVORS

Around 1/4 of all BC patients are below the age of 50 years at diagnosis [3], meaning that many BC survivors have a long remaining life expectancy

[3] Anders CK, Johnson R, Litton J, et al. Breast Cancer Before Age 40 Years. Semin. Oncol. 2009

SURVIVORSHIP



Survivorship

BC AND COMORBIDITY

At time of BC diagnosis

Manifest comorbidity

As a result of cancer treatment and/or the cancer itself

Latent comorbidity

- During cancer treatment (side effects)
- After cancer treatment (late effects)

BC AND COMORBIDITY

A high comorbidity score **at time of diagnosis** is associated with

- reduced likelihood of receiving guideline based treatment
- reduced effect of the treatment received
- increased risk of dying from BC as well as from all causes

Wollschläger D, et al. Comorbidity-dependent adherence to guidelines and survival in breast cancer-Is there a role for guideline adherence in comorbid breast cancer patients? A retrospective cohort study with 2137 patients. Breast J. 2018;24:120–127.

Land LH, et al. Influence of comorbidity on the effect of adjuvant treatment and age in patients with early-stage breast cancer. Br. J. Cancer. 2012;107:1901–1907.

Hong C-C, et al.. Comorbidities and Their Management: Potential Impact on Breast Cancer Outcomes. Adv. Exp. Med. Biol. 2015. p. 155–175.

BC AND CARDIOVASCULAR DISEASE

Increased morbidity and mortality **after treatment**

- Cardiovascular diseases (CVD)

Kjaer TK, et al.. JAMA Oncol. 2019

Park N-J, et al.PLoS One. 2017

Gernaat SAM et al.. Breast Cancer Res. Treat. 2018.

Abdel-Qadir H et al., J Natl Cancer Inst. 2019

Patnaik JL, Byers T, DiGuiseppi C, et al. 2011

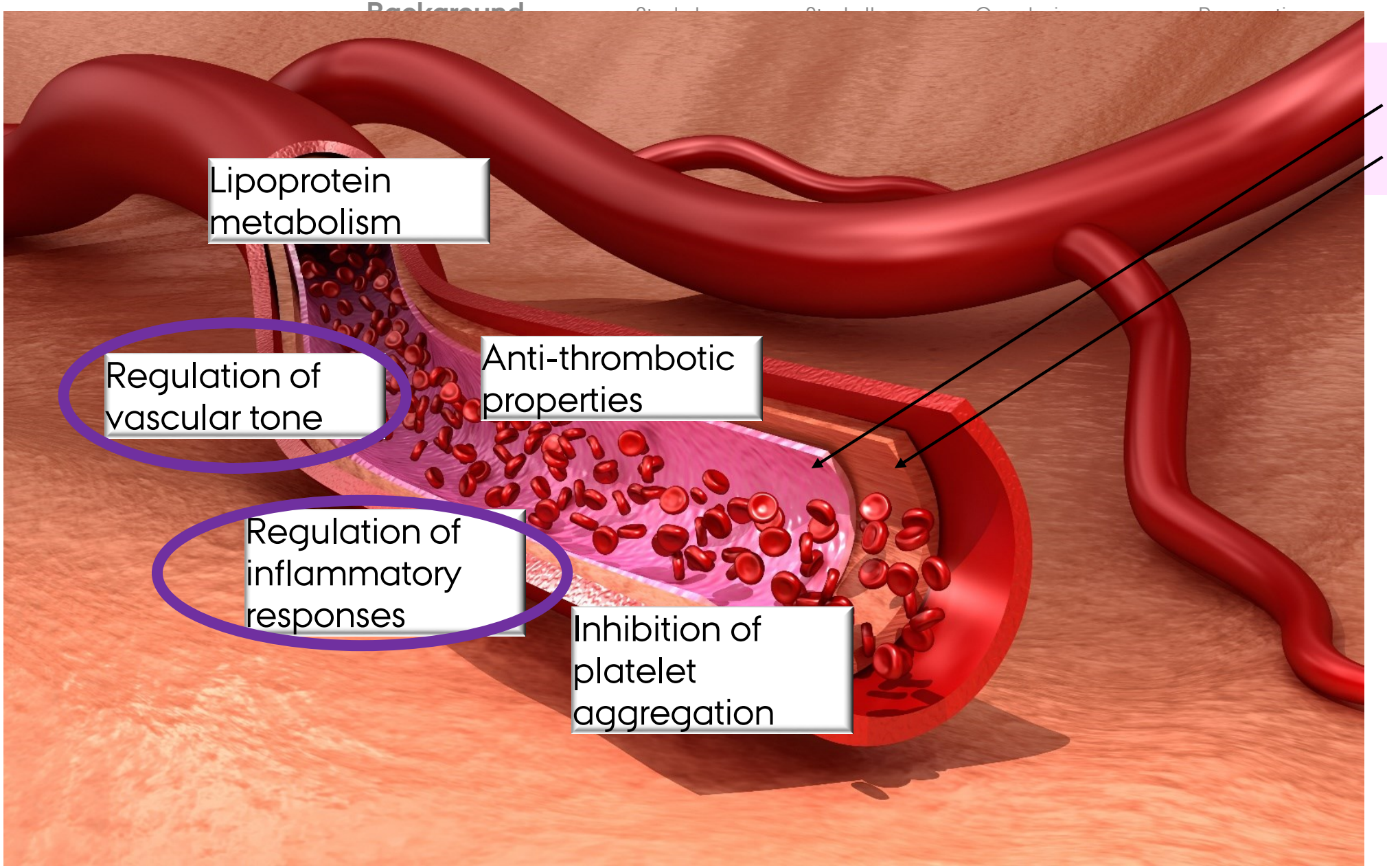
Bradshaw PT, Stevens J, Khankari N, et al.. Epidemiology. 2016

Cardiovascular disease

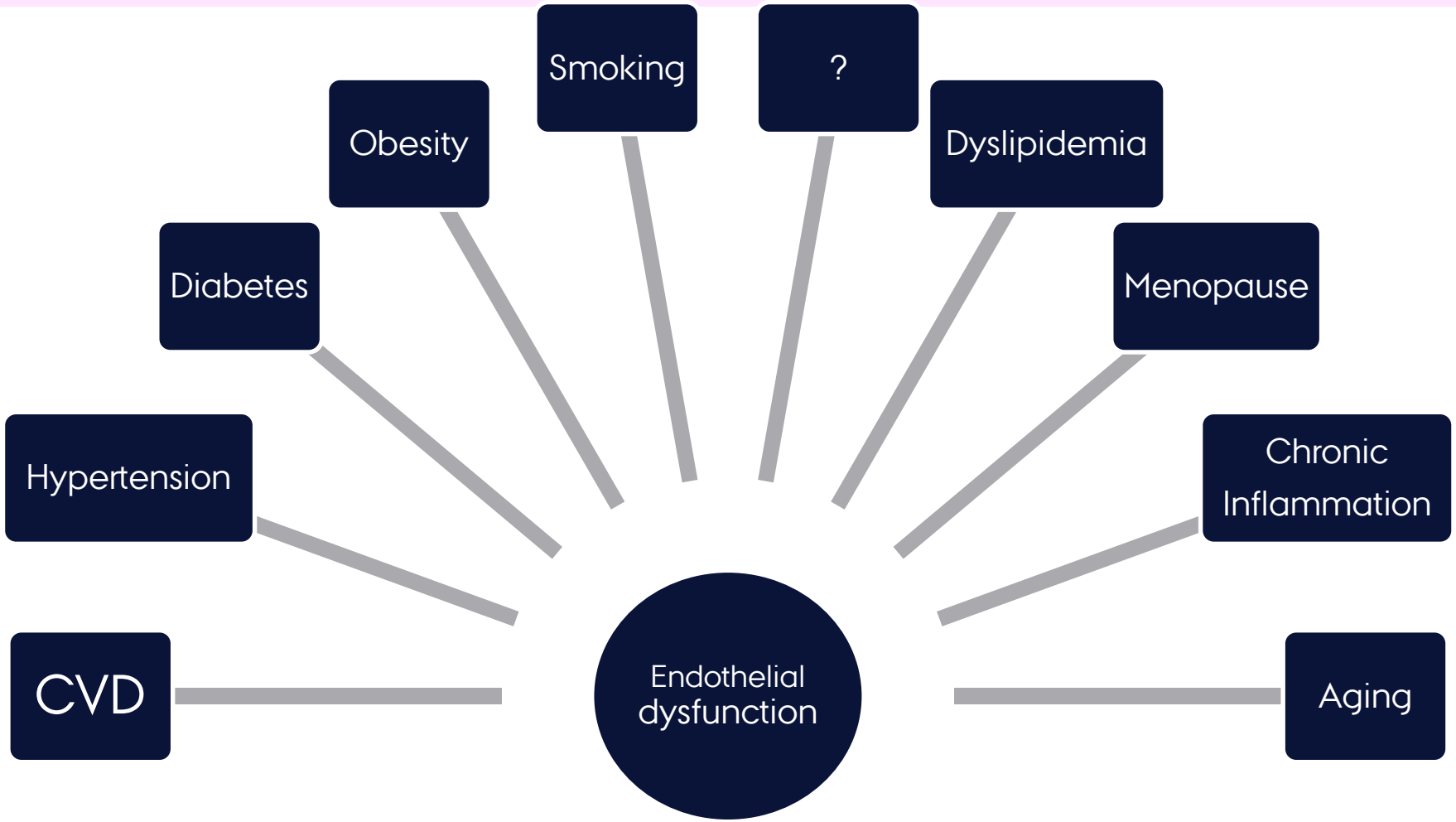
Diabetes

+

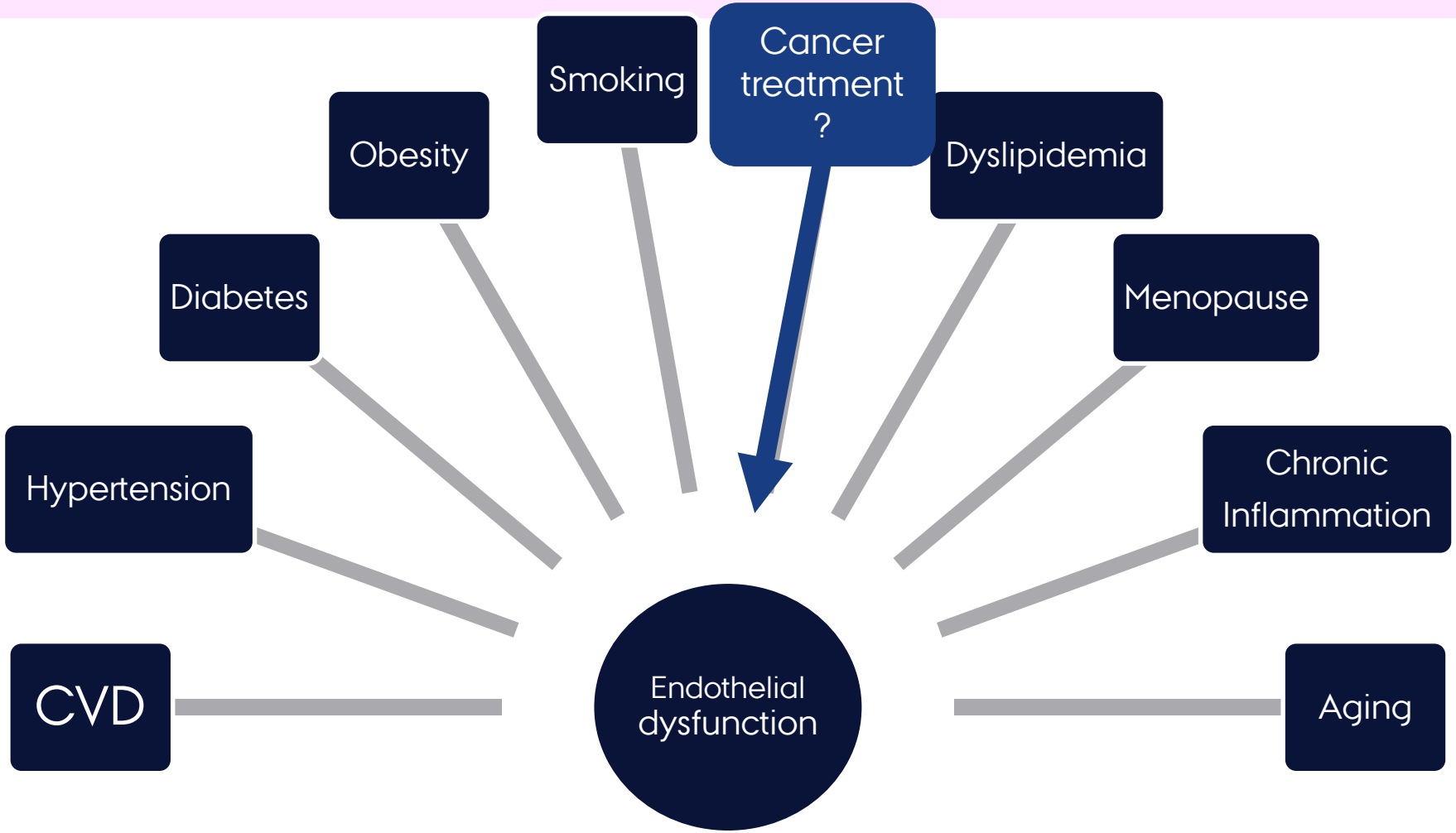
Metabolic syndrome


Lipoprotein metabolism
Regulation of vascular tone
Anti-thrombotic properties
Regulation of inflammatory responses
Inhibition of platelet aggregation
Endothelium
Smooth muscle cells

ENDOTHELIAL DYSFUNCTION



ENDOTHELIAL DYSFUNCTION



BC TREATMENT

Breast surgery	100 %
Radiotherapy	80%
Chemotherapy	40%
Endocrine therapy	80%
Targeted therapy	20%
Bisphosphonates	60%

BC TREATMENT

↑ ↓ ?

	CVD	Diabetes	Dyslipidaemia	Metabolic syndrome	Endothelial dysfunction
Radiotherapy	↑↑↑				↑
Chemotherapy					
Anthracycline	↑↑↑	↑	↑?	↑?	?
Cyclophosphamide	↑↑	↑	↑?	↑?	↑?
Taxane	↑	↑	↑?	↑?	?
Endocrine therapy					
Tamoxifen	↓?	↑↑	↓/↑	↑?	?
Letrozol	↑?	↑↑	↑↑	↑?	(↑)
Trastuzumab	↑↑				?
Bisphosphonates			↓		

BC TREATMENT

↑ ↓ ?

	CVD	Diabetes	Dyslipidaemia	Metabolic syndrome	Endothelial dysfunction	Estrogen depletion
Radiotherapy	↑↑↑				↑	
Chemotherapy						
Anthracycline	↑↑↑	↑?	↑?	↑?	?	↑
Cyclophosphamide	↑↑	↑?	↑?	↑?	↑?	↑
Taxane	↑	↑?	↑?	↑?	?	↑
Endocrine therapy						
Tamoxifen	↓?	↑	↓/↑	↑?	?	↑?
Letrozol	↑?	↑	↑↑	↑?	(↑)	↑
Trastuzumab	↑↑				?	
Bisphosphonates	↓?		↓			

BC TREATMENT ↑ ↓ ?

	CVD	Diabetes	Dyslipidaemia	Metabolic syndrome	Endothelial dysfunction	Estrogen depletion
Radiotherapy	↑↑↑				↑	
Chemotherapy						
Anthracycline	↑↑↑	↑?	↑?	↑?	?	↑
Cyclophosphamide	↑↑	↑?	↑?	↑?	↑?	↑
Taxane	↑	↑?	↑?	↑?	?	↑
Endocrine therapy						
Tamoxifen	↓?	↑	↓/↑	↑?	?	↑?
Letrozol	↑?	↑	↑↑	↑?	(↑)	↑
Trastuzumab	↑↑				?	
Bisphosphonates	↓?		↓			

BC TREATMENT ↑ ↓ ?

	CVD	Diabetes	Dyslipidaemia	Metabolic syndrome	Endothelial dysfunction	Estrogen depletion
Breast surgery	?	? (↑)	?	?	? (↑)	?

British Journal of Anaesthesia, Volume 118, Issue 2, February 2017, Pages 200–206, https://doi.org/10.1093/bja/aew410
J Clin Anesth,1997 Jun;9(4):293-8. doi: 10.1016/s0952-8180(97)00006-8.
Proc Nutr Soc ., 2002 Aug;61(3):329-36. doi: 10.1079/PNS2002168.

PHD PROJECT

Clinical study (study I)

Register study (study II)

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STINE FREDSLUND
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STUDY I

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MAY 19 2021

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THE ABCDE STUDY

Adjuvant treatment of

Breast cancer related to

Cardiotoxicity and

Dysfunctional

Endothelium

AIMS

To do an extensive examination of patients receiving adjuvant treatment for early stage breast cancer

With special focus on changes in parameters related to **endothelial function, metabolic and cardiovascular disease**

DESIGN

A clinical prospective cohort study

PATIENTS

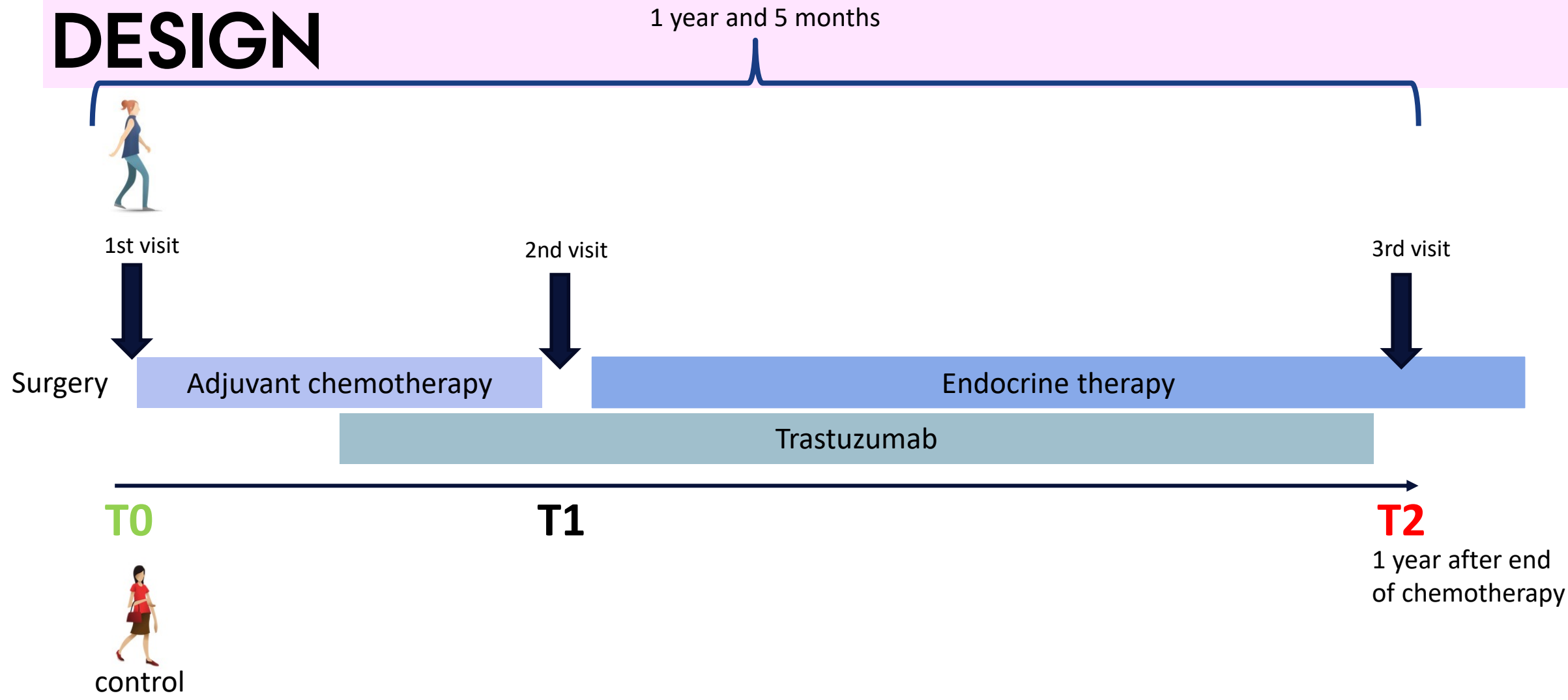
A clinical prospective cohort study

Pre- and postmenopausal women

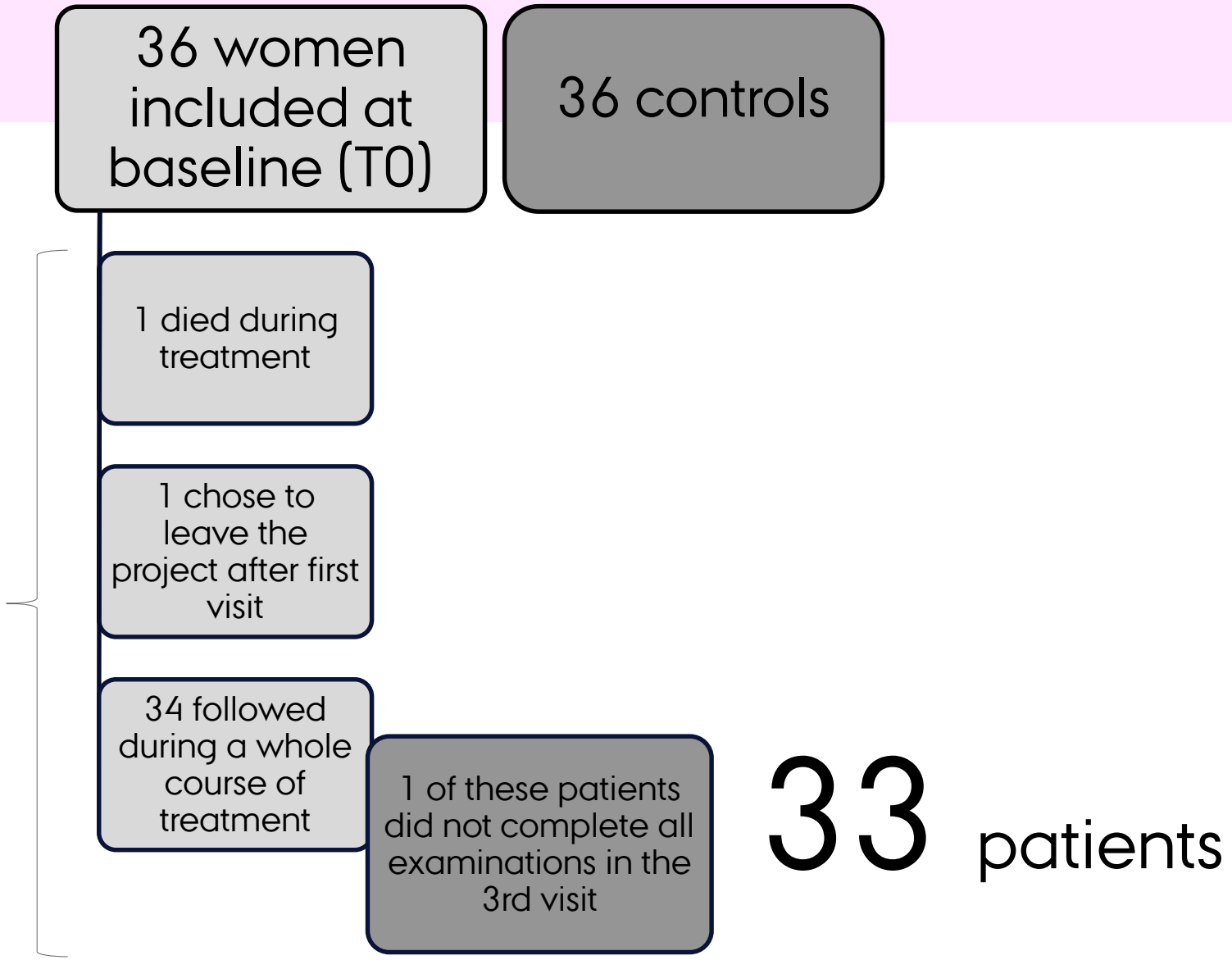
Inclusion criteria;

- 1) newly diagnosed **primary early stage breast cancer**
- 2) assigned to receive **adjuvant chemotherapy** after surgery
- 3) age≥18 years.

DESIGN


1 year and 5 months
1st visit
2nd visit
3rd visit
Surgery
Adjuvant chemotherapy
Endocrine therapy
Trastuzumab
T0
T1
T2
1 year after end of chemotherapy
control

ENROLMENT

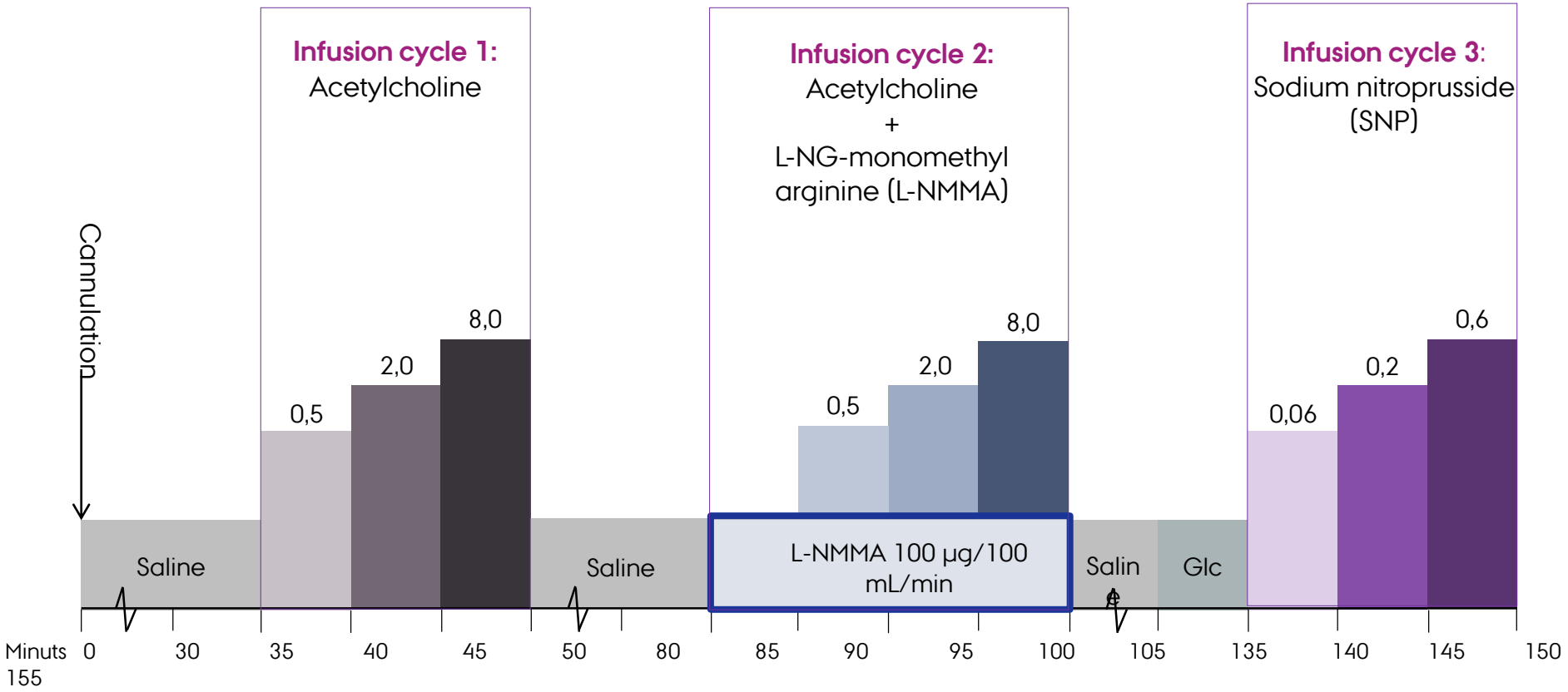

36 women included at baseline (T0)
36 controls
1 died during treatment
1 chose to leave the project after first visit
34 followed during a whole course of treatment
1 of these patients did not complete all examinations in the 3rd visit
Sept. 2015-
June 2018
33 patients

EXAMINATION PROGRAMME

- Blood samples
  - Inflammation markers, BNP, L-arginine, ADMA, hormones, blood glucose, lipids
- Venous occlusion plethysmography (VOP)
- Sphygmocor®
  - Pulse wave velocity (PWV) → arterial stiffness
  - Pulse wave analysis (PWA) → central blood pressure
- 24 hour blood pressure measurement
- Whole body DEXA scan → Body fat, BMD

VENOUS OCCLUSION PLETHYSMOGRAPHY

ENDOTHELIAL FUNCTION



Infusion dose:
(µg/100 mL/min)

Fredslund et al. J Transl Med (2019) 17:105
https://doi.org/10.1186/s12967-019-1850-2

Journal of Translational Medicine

RESEARCH Open Access

Key metabolic parameters change significantly in early breast cancer survivors: an explorative PILOT study

Stine Overvad Fredslund[1*], Claus Højbjerg Gravholt[2,3], Britt Elmedal Laursen[1,3,4] and Anders Bonde Jensen[1]

Received: 19 May 2020 | Revised: 3 March 2021 | Accepted: 10 March 2021

DOI: 10.1111/bcp.14837

ORIGINAL ARTICLE

Changes in vascular function during breast cancer treatment

Stine Overvad Fredslund[1] | Niels Henrik Buus[2,3] | Cecilie Højgaard Skjold[3] | Esben Laugesen[4] | Anders Bonde Jensen[1] | Britt Elmedal Laursen[1,2,5]

[1]Department of Oncology, Aarhus University

RESULTS - BASELINE

At baseline, there was no statistical significant difference between BC patients and controls in...

- Metabolic profiles
- Inflammation markers
- Forearm blood flow
- Central blood pressure
- Heart rate
- Meassures of arterial stiffness

RESULTS

Premenopausal BC patients

	Mean/median			Paired *t*-test/signed rank[c]	
	T0	T1	T2	T0 vs. T1	T0 vs. T2
Weight (kg)[a]	73.3 ±9.56	74.3 ±9.31	74.7 ±10.7	*0.1*	*0.1*
			25.2 [23.0; 29.2]	***0.1***	*0.2*
			87.7 ±7.91	*0.2*	*0.008**
			36.7 ±5.87	***0.06***	*0.01**
			5.22 ±1.01	*0.3*	*1.0*
			2.77 ±0.87	***0.06***	*0.5*
			1.76 ±0.49	*0.003**	*0.8*
			1.20 [0.80; 2.10]	***0.05****	*0.03**
			5.28 ±0.41	*1.0*	*0.02**
			36.7 [27.3; 49.1]	***0.05****	*1.0*
			116 ±9.16	*0.3*	*0.1*
			74.3 ±7.01	*0.3*	*0.04**
			27 [15; 252]	*0.002**	*0.07*
			0.7 [0.3; 0.7]	*0.005**	*0.006**
			39 [24.2;50.3]	*0.002**	*0.03**
			25 [16.3;28.8]	*0.004**	*0.2*

Metabolic syndome

Waist

HDL

Triglycerides

Blood pressure

Blood glucose

* Significantly different

RESULTS – INFLAMMATION MARKERS

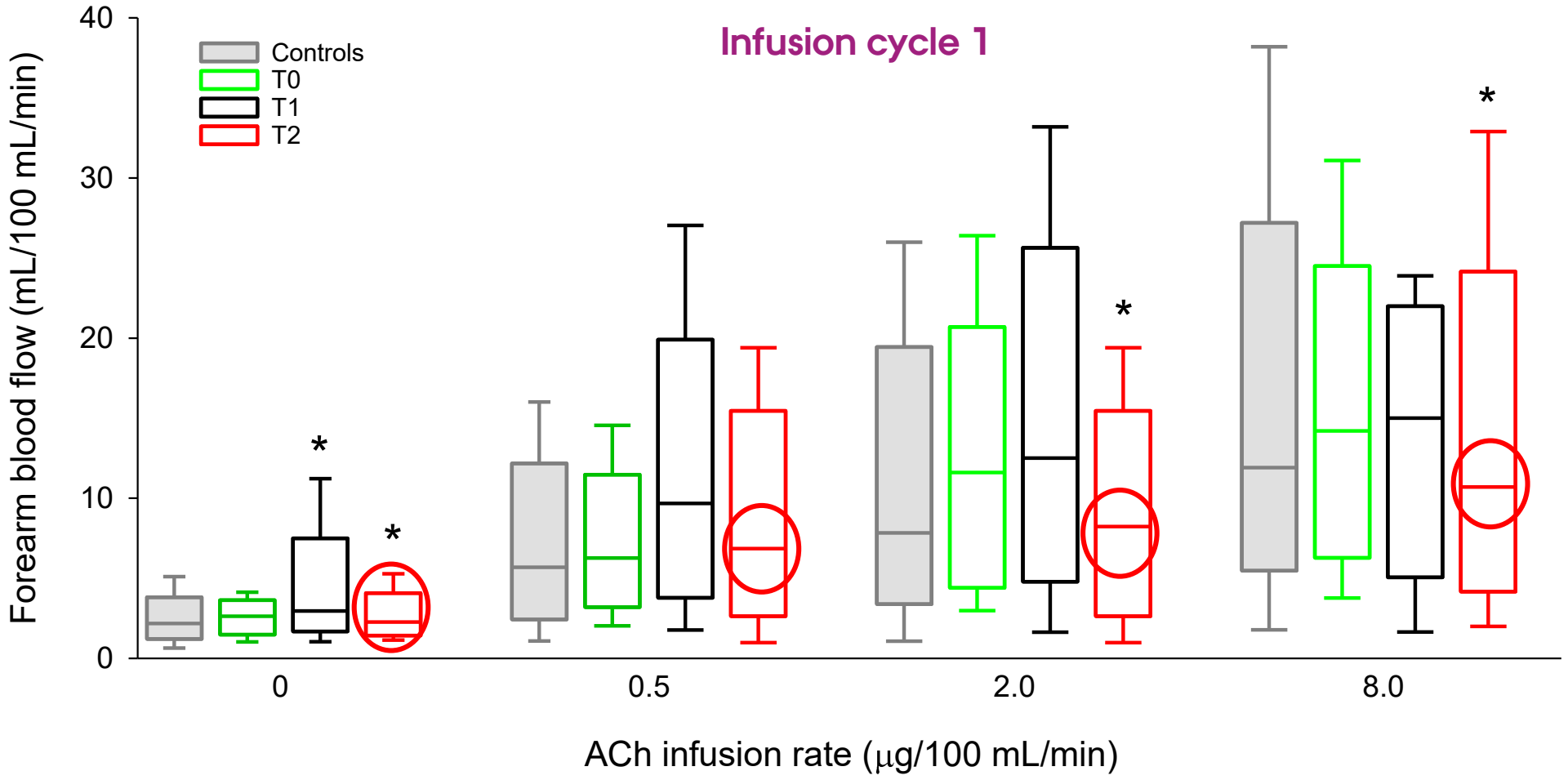
Premenopausal women

	Controls	BC patients		
		T0	T1	T2
Hs-CRP (mg/ L)	0.63 [0.6; 1.2]	1.04 [0.68; 2.45]	1.94 [0.96; 3.15]	1.21 [0.64; 2.15]
CD163 (mg/ L)	1.54 [1.40; 2.04]	1.66 [1.27; 2.10]	2.33 [1.58; 2.69]*	1.71 [1.40; 2.22]
CD206 (mg/ L)	0.20 [0.15; 0.24]	0.21 [0.17; 0.25]	0.23 [0.20; 0.32]*	0.23 [0.20; 0.28]*

* Significantly different from cases at baseline (T0), p-value<0.05

RESULTS

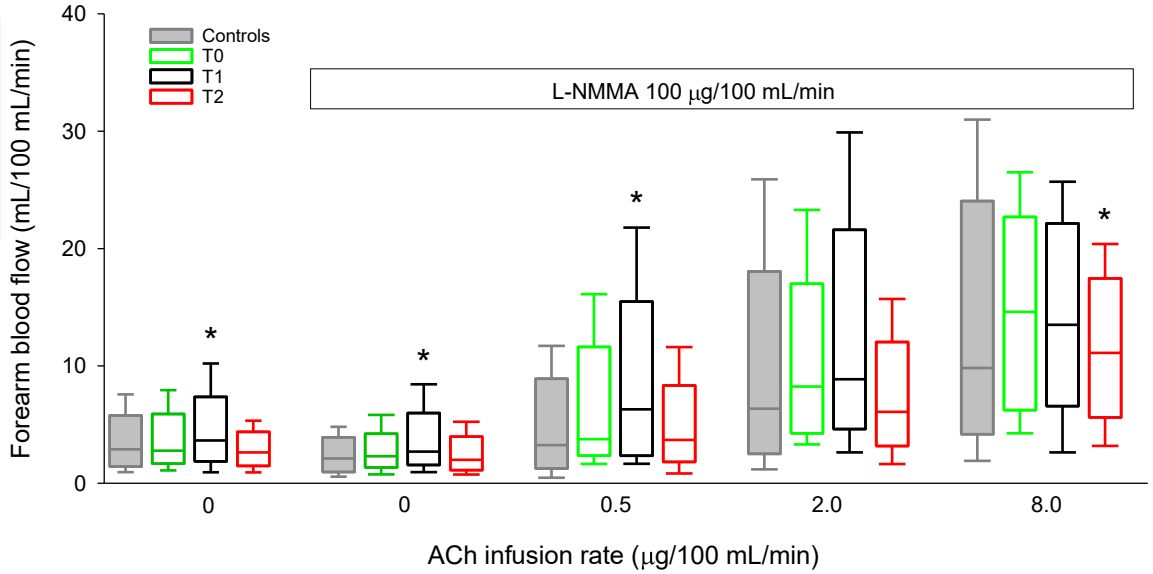
ENDOTHELIAL FUNCTION

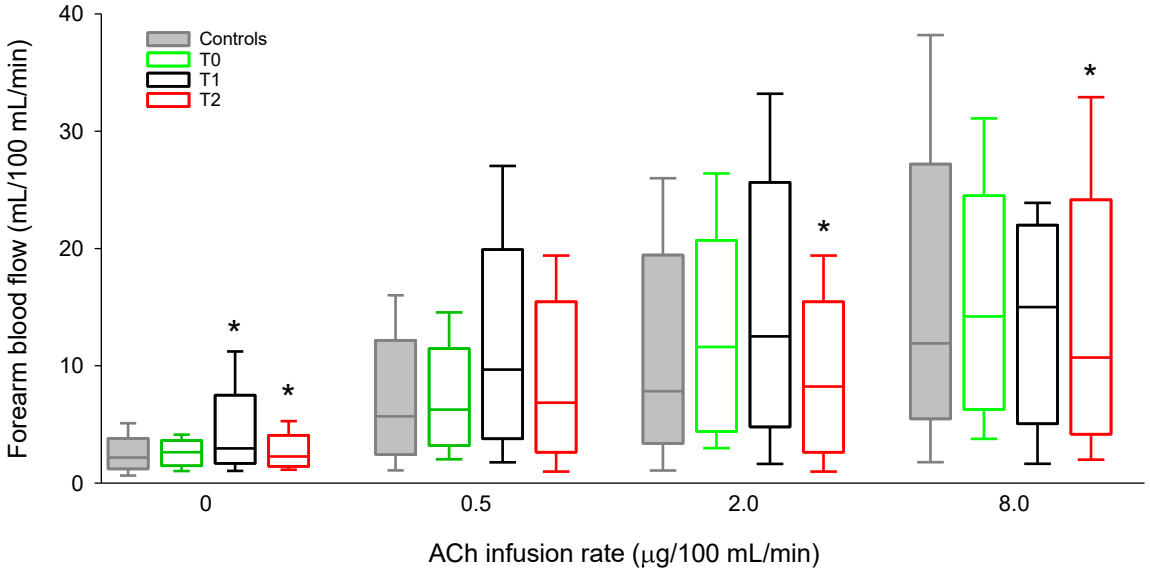


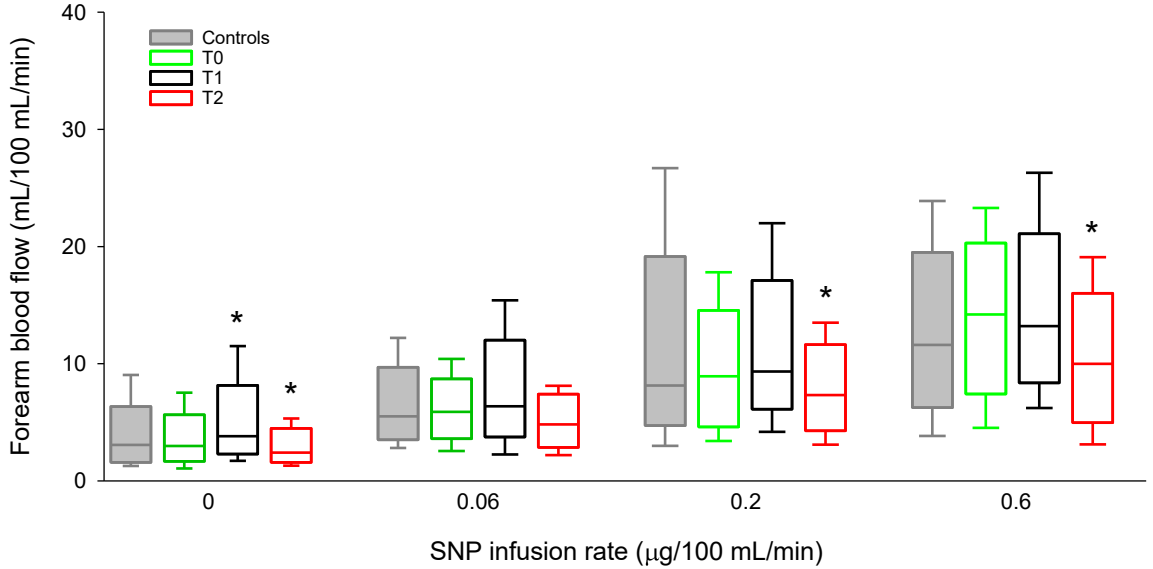
* Significantly different from cases at baseline (T0), p-value<0.05

RESULTS

VOP







* Significantly different from cases at baseline (T0), p-value<0.05

CONCLUSIONS – STUDY I

- The metabolic profile of BC patients at baseline was similar to that of healthy age-matched controls
- The metabolic profile of the BC patients changed significantly during adjuvant cancer treatment, and remained pathologically impaired 1 year after.
- In premenopausal BC patient inflammation markers increased significantly during treatment and remained increased 1 year after.
- In general premenopausal patients was shown to be more vulnerable compared to postmenopausal patients

CONCLUSIONS – STUDY I

- The vascular function of BC patients at baseline right after surgery was similar to that of healthy age-matched controls.

- The vascular function of BC patients 1 year after cessation of adjuvant cancer treatment was significantly impaired.

STUDY II

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MAY 19 2021

STINE FREDSLUND
MEDICAL DOCTOR, PHD

AIMS

The aim of this register study was to determine

acute and long-term morbidity in Danish women treated for breast cancer

described by means of both

- hospital contacts
- medicine use

METHODS

Data from the following registries:

A nationwide registry-based cohort study

The Clinical database of Danish Breast Cancer Cooperative Group (DBCG)

Statistics Denmark

The Danish National Patient Registry

The Danish National Prescription Registry (NPR)

The Danish Register of Causes of Death

METHODS

BC PATIENTS

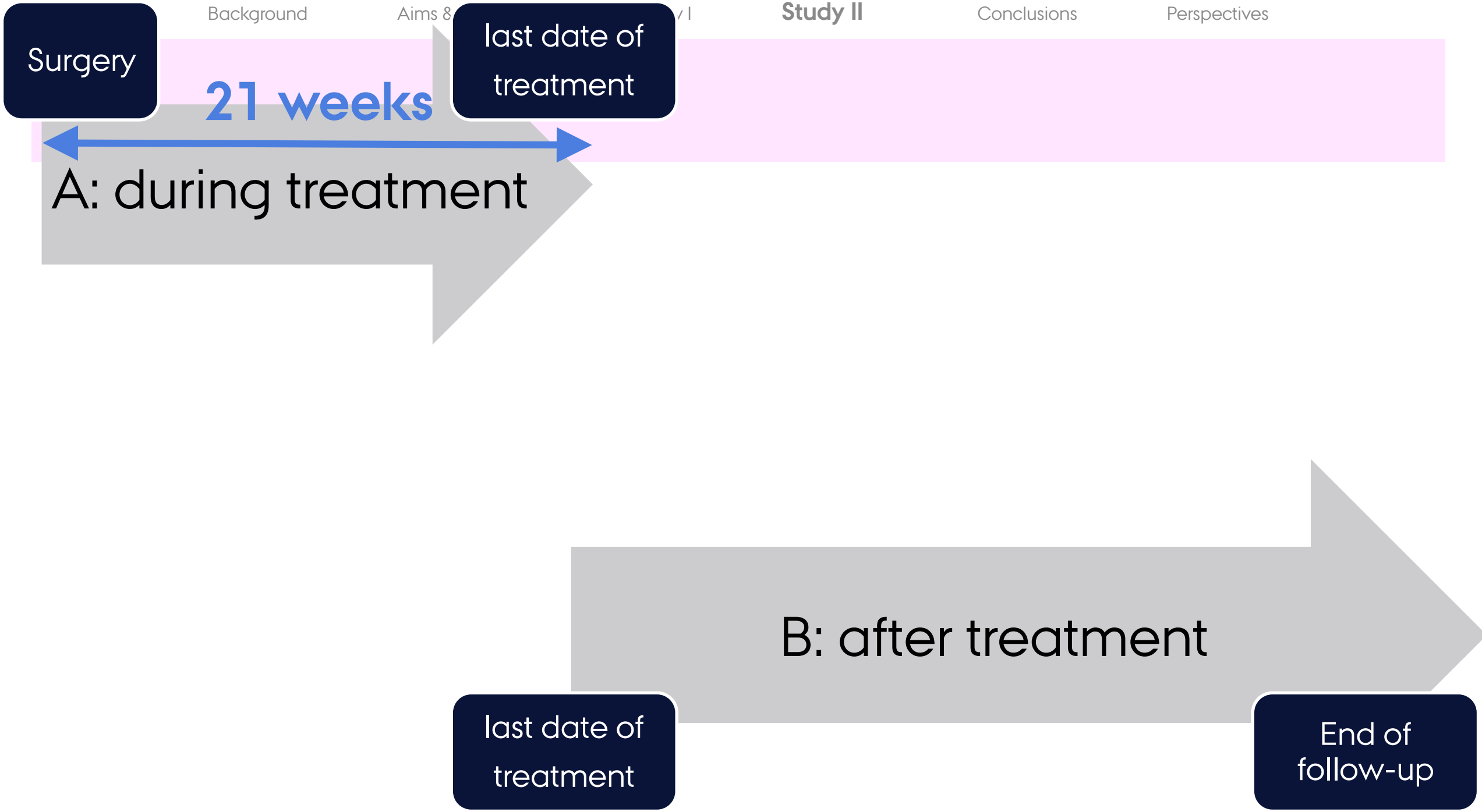
All females diagnosed with primary BC, stage I-III and registered in the DBCG Database from 1990 to 2017

In total 105,268 women.

CONTROLS

1,051,660 healthy female controls

matched on age, and included in the year of diagnosis of their respective case.


Surgery
last date of treatment
21 weeks
A: during treatment
B: after treatment
last date of treatment
End of follow-up

RESULTS – STUDY II

RE

Hospitc

Hospital contacts **during** treatment

	Age ≤ 52 years [#]					Age > 52 years [##]				
	Events in cases	Events in controls	HR	95% CI	p-value	Events in cases	Events in controls	HR	95% CI	p-value
Infections	19	308	11.3	[7.12;18.1]	*<0.0001**	52	1,164	3.80	[2.86;5.00]	*<0.0001**
Neoplasms	14,373	1,492	16.1	[15.3;17.1]	*<0.0001**	35,82	5,921	11.3	[10.9; 11.6]	*<0.0001**
Blood/immune system	9	158	8.06	[4.11;15.8]	*<0.0001**	29	954	2.92	[2.02;4.23]	*<0.0001**
Endocrinology	10	1,079	3.96	[2.12;7.38]	*<0.0001**	96	3,724	2.59	[2.11;3.17]	*<0.0001**
Mental disorders	26	283	13.1	[8.71;19.7]	*<0.0001**	46	814	5.15	[3.82;6.93]	*<0.0001**
Nervous system	9	1,036	2.66	[1.38;5.13]	*<0.0001**	37	2,883	1.72	[1.24;2.37]	*<0.0001**
Eyes	5	672	2.72	[1.13;6.56]	*0.03**	77	6,682	1.54	[1.23;1.93]	*<0.0001**
Ears	6	478	3.00	[1.34;6.71]	*0.008**	50	4,202	1.37	[1.03;1.80]	*<0.0001**
Circulation	28	1,503	5.93	[4.08;8.62]	*<0.0001**	316	11,345	3.68	[3.29;4.11]	*<0.0001**
Respiratory diseases	10	883	2.91	[1.56;5.42]	*0.001**	126	5,036	2.79	[2.34;3.33]	*<0.0001**
Gastrointestinal	28	2,042	4.73	[3.26;6.86]	*<0.0001**	159	7,136	2.52	[2.15;2.95)	*<0.0001**
Skin	32	661	7.33	[5.13;10.5]	*<0.0001**	88	1,594	5.84	[4.71;7.24]	*<0.0001**
Musculoskeletal system	34	4,289	2.23	[1.59;3.12]	*<0.0001**	367	14,887	2.37	[2.14;2.63]	*<0.0001**
Genitourinary disorders	318	3,131	16.6	[14.7;18.7]	*<0.0001**	669	5,892	8.41	[7.75;9.11]	*<0.0001**
Pregnancy	7	1,49	1.00	[0.48;2.10]	*1.0*	1	3	7.14	[0.74;68.6]	*0.09*
Perinatal period	1	1	8.49	[0.53;136]	*0.1*	0	3			
Congenit malformation	3	475	0.90	[0.29;2.79]	*0.9*	3	174	1.82	[0.53;5.68]	*0.3*
Unspecified	77	2,468	4.97	[3.96;6.24]	*<0.0001**	263	8,759	3.35	[2.96;3.78]	*<0.0001**
External influences	266	6,193	11.7	[10.3;13.2]	*<0.0001**	926	16,877	5.69	[5.33; 6.08]	*<0.0001**
Factors infuencing health	8,996	23,372	30.0	[29.2;30.8]	*<0.0001**	26,012	82,877	19.4	[19.1;19.7]	*<0.0001**
All	25,205	53,312	**20.4**	[20.1; 20.7]	*<0.0001**	66,675	186,415	**13.2**	[13.1; 13.3]	*<0.0001**

RE

Hospitalcontacts **after** treatment

Hospital contacts **after** treatment

	Age ≤ 52 years [#]					Age > 52 years [##]				
	Events in cases	Events in controls	HR	95% CI	p-value	Events in cases	Events in controls	HR	95% CI	p-value
Infections	120	1,474	3.01	[2.49;3.64]	*<0.0001**	398	4,441	2.01	[1.81;2.23]	*<0.0001**
Neoplasms	7,757	7,128	3.02	[2.92;3.13]	*<0.0001**	14,019	18,357	2.08	[2.04;2.13]	*<0.0001**
Blood/immune system	46	671	4.21	[3.11;5.71]	*<0.0001**	244	2,919	1.84	[1.62;2.10]	*<0.0001**
Endocrinology	231	4,482	2.30	[2.01;2.63]	*<0.0001**	895	12,007	1.53	[1.43;1.63]	*<0.0001**
Mental disorders	61	1,100	2.13	[1.64;2.77]	*<0.0001**	203	2,879	1.64	[1.42;1.89]	*<0.0001**
Nervous system	167	3,802	1.60	[1.37;1.87]	*<0.0001**	586	8,453	1.53	[1.41;1.66]	*<0.0001**
Eyes	139	3,69	2.09	[1.76;2.48]	*<0.0001**	1,819	28,969	1.65	[1.58;1.74]	*<0.0001**
Ears	100	2,653	1.73	[1.41;2.11]	*<0.0001**	1,252	19,074	1.46	[1.38;1.55]	*<0.0001**
Circulation	551	7,696	2.86	[2.62;3.12]	*<0.0001**	2,911	40,415	1.80	[1.73;1.87]	*<0.0001**
Respiratory diseases	171	3,661	2.16	[1.85;2.52]	*<0.0001**	1,117	16,031	1.57	[1.48;1.67)	*<0.0001**
Gastrointestinal	329	8,398	2.03	[1.82;2.27]	*<0.0001**	1,617	23,392	1.59	[1.51;1.68]	*<0.0001**
Skin	362	3,141	2.72	[2.44;3.05]	*<0.0001**	755	5,385	2.08	[1.92;2.24]	*<0.0001**
Musculoskeletal system	702	16,949	1.75	[1.62;1.88]	*<0.0001**	3,599	41,29	1.55	[1.50;1.60]	*<0.0001**
Genitourinary disorders	923	14,693	1.87	[1.75;1.99]	*<0.0001**	1,977	18,944	1.74	[1.66;1.82]	*<0.0001**
Pregnancy	37	2,743	0.89	[0.65;1.24]	*0.5*	1	10	5.91	[0.66;52.5]	*0.1*
Perinatal period	0	6				1	5	6.48	[0.40;104]	*0.2*
Congenit malformation	22	457	2.81	[1.83;4.34]	*<0.0001**	35	451	1.24	[0.88;1.75]	*0.2*
Unspecified	646	9,955	2.59	[2.39;2.80]	*<0.0001**	2,204	27,697	1.75	[1.67;1.82]	*<0.0001**
External influences	1,354	36,064	1.80	[1.65;1.84]	*<0.0001**	4,579	73,219	1.59	[1.54; 1.64]	*<0.0001**
Factors infuencing health	11,361	121,507	2.63	[2.58;2.68]	*<0.0001**	27,440	282,518	1.61	[1.59;1.63]	*<0.0001**
All	26,112	254,923	**2.59**	[2.56; 2.63]	*<0.0001**	67,859	640,159	**1.69**	[1.68; 1.70]	*<0.0001**

RESULTS

Prescriptions

RESULTS

Prescriptions **during** treatment

Prescriptions **during** treatment

	Age ≤ 52 years					Age > 52 years				
	Events in cases	Events in controls	HR	95% CI	*p-value*	Events in cases	Events in controls	HR	95% CI	p-value
Alimentary tract and metabolism	1,604	10,498	1.26	[1.19;1.32]	*<0.0001**	4,849	46,057	1.06	[1.03;1.09]	*<0.0001**
Blood and blood forming organs	228	2,732	1.45	[1.27;1.66]	*<0.0001**	2,192	22,826	1.17	[1.12;1.22]	*<0.0001**
Cardiovascular system	1,545	16,796	1.08	[1.02;1.13]	*0.005**	11,759	127,166	1.09	[1.07;1.11]	*<0.0001**
Dermatologicals	818	9,460	1.11	[1.04;1.20]	*0.003**	1,553	17,709	1.12	[1.07;1.18]	*<0.0001**
Genitourinary systems and sex hormones	548	25,535	0.86	[0.79;0.94]	*0.001**	1,501	43,133	1.06	[1.01;1.12]	*0.03**
Systemic hormonal preparations	552	4,894	1.11	[1.02;1.21]	*0.02**	1,471	16,923	1.01	[0.96;1.06]	*0.8*
Antiinfectives	3,909	21,403	2.01	[1.94;2.08]	*<0.0001**	7,700	35,249	2.05	[2.00;2.10]	*<0.0001**
Antineoplastic and immunomodulating agents	90	361	0.59	[0.47;0.75]	*<0.0001**	722	1,225	0.87	[0.79;0.95]	*0.003**
Musculoskeletal system	1,248	12,451	1.55	[1.46;1.64]	*<0.0001**	3,508	35,874	1.25	[1.21;1.29]	*<0.0001**
Nervous system	5,726	30,970	1.28	[1.24;1.31]	*<0.0001**	16,785	103,954	1.26	[1.24;1.28]	*<0.0001**
Antiparasitics	100	1,958	0.98	[0.80;1.20]	*0.8*	261	3,095	1.12	[0.99;1.27)	*0.08*
Respiratory system	1,101	13,807	1.08	[1.01;1.15]	*0.02**	3,456	37,815	1.14	[1.10;1.18]	*<0.0001**
Sensory organs	530	6,409	1.16	[1.06;1.27]	*0.001**	1,920	24,968	1.10	[1.05;1.15]	*<0.0001**
Various	5	106	1.19	[0.49;2.93]	*0.7*	10	80	1.43	[0.74;2.77]	*0.3*
All	18,004	157,38	**1.37**	[1.35; 1.39]	*<0.0001**	57,687	514,074	**1.24**	[1.23; 1.25]	*<0.0001**

RESULTS

Prescriptions **after** treatment

Prescriptions **after** tr

	Age ≤ 52 years					Age > 52 years				
	Events in cases	Events in controls	HR	95% CI	*p-value*	Events in cases	Events in controls	HR	95% CI	p-value
Alimentary tract and metabolism	1,988	17,136	1.17	[1.12;1.23]	*<0.0001**	6,399	57,797	1.19	[1.016;1.22]	*<0.0001**
Blood and blood forming organs	347	4,262	1.19	[1.06;1.32]	*0.002**	2,704	27,897	1.19	[1.14;1.24]	*<0.0001**
Cardiovascular system	2,650	25,017	1.29	[1.24;1.34]	*<0.0001**	14,970	152,382	1.15	[1.13;1.16]	*<0.0001**
Dermatologicals	1,999	21,111	1.12	[1.07;1.17]	*<0.0001**	3,070	31,360	1.25	[1.20;1.30]	*<0.0001**
Genitourinary systems and sex hormones	924	37,113	0.76	[0.71;0.81]	*<0.0001**	2,098	49,022	0.99	[0.95;1.03]	*0.07*
Systemic hormonal preparations	618	6,829	1.01	[0.93;1.10]	*0.8*	1,875	20,41	1.07	[1.02;1.13]	*0.003**
Antiinfectives	5,307	49,051	1.30	[1.26;1.33]	*<0.0001**	7,444	67,723	1.37	[1.34;1.40]	*<0.0001**
Antineoplastic and immunomodulating agents	116	456	0.51	[0.42;0.63]	*<0.0001**	613	1,334	0.67	[0.61;0.74]	*<0.0001**
Musculoskeletal system	1,965	25,041	1.06	[1.01;1.11]	*0.01**	5,081	52,443	1.18	[1.14;1.21]	*<0.0001**
Nervous system	6,527	44,396	1.07	[1.04;1.10]	*<0.0001**	17.096	131,786	1.16	[1.14;1.18]	*<0.0001**
Antiparasitics	361	4,870	1.23	[1.10;1.37]	*<0.0001**	518	2,276	1.23	[1.12;1.34)	*<0.0001**
Respiratory system	1,062	22,993	1.03	[0.98;1.08]	*0.3*	4,736	49,571	1.15	[1.12;1.18]	*<0.0001**
Sensory organs	1,441	14,889	1.29	[1.22;1.36]	*<0.0001**	3,620	39,251	1.22	[1.18;1.26]	*<0.0001**
Various	6	140	1.01	[0.45;2.30]	*0.1*	9	123	1.01	[0.51;1.99]	*1.0*
All	26,211	273,304	**1.15**	[1.14; 1.17]	*<0.0001**	70,233	686,275	**1.18**	[1.17; 1.19]	*<0.0001**

CONCLUSIONS – STUDY II

The burden of morbidity evaluated on both hospital contacts and medicinal prescriptions was shown to be greater in Danish breast cancer survivors than in age-matched controls

The increased morbidity was evident in all relevant chapter both during and after end of cancer treatment

The increased risk was mainly related with presumed premenopausal status

The most disturbing findings was related to increased morbidity among younger survivors in chapters related to cardiovascular and metabolic disease

FUTURE PERSPECTIVES

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DEPARTMENT OF CLINICAL MEDICINE

MAY 19 2021

STINE FREDSLUND
MEDICAL DOCTOR, PHD

PERSPECTIVES

Treatment induced late effects can have substantial and lifelong consequences

Quality of life, medical expenses, earnings, employability, and even the lifespan could be affected

What we gain from an increasingly intensive treatment, we risk losing to late effects.

The risk of BC recurrence or a new primary cancer could be increased.

Special attention should be on cardiovascular and metabolic conditions, especially among younger survivors.

Efforts should be made to determine whether certain characteristics of the patients predispose to the development of late effects

PERSPECTIVES

Beyond the individual costs of each patient, the medical costs of society related to cancer treatment are significant

Improvement of the follow-up programme of Danish BC patients

Responsibility placement – who should be responsible of follow up?

FOLLOW UP

PRIMARY CARE OR...?

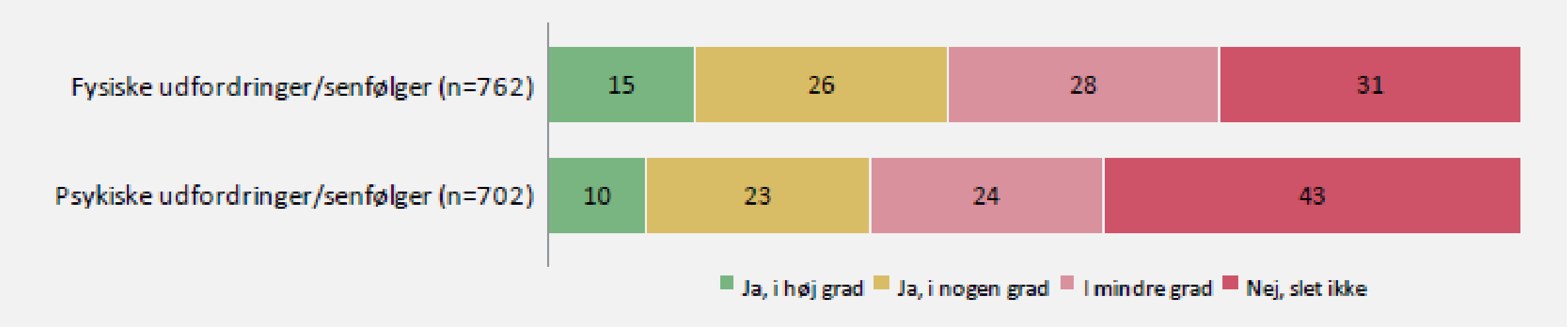
only 8% of Danish cancer patients want their follow up programme to be handled by their general practitioner

only 50% of hospital specialists believe that GPs follow their recommendations correctly

FOLLOW UP

PRIMARY CARE OR...?

FIGUR 38: Har du efter behandlingen på sygehuset blev afsluttet fået den hjælp, du har haft behov for i forhold til:



Delpopulation: Kun opgjort blandt de personer, der havde behov

Kræftens Bekæmpelses Barometerundersøgelse 2019

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GUIDELINES

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MAY 19 2021

STINE FREDSLUND
MEDICAL DOCTOR, PHD

GUIDELINES

No official Danish guidelines regarding oncocardiology exists

ESMO GUIDELINES

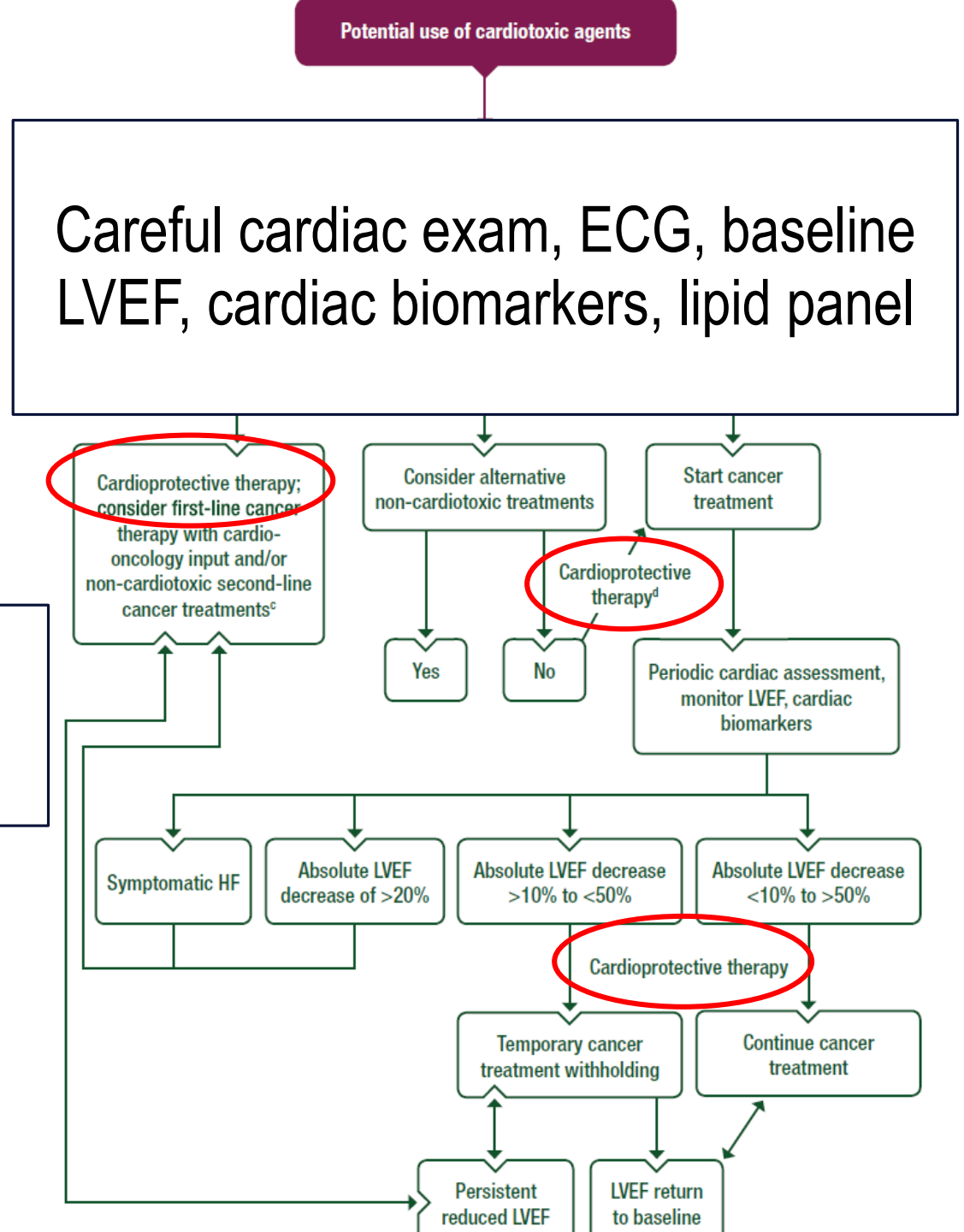
CLINICAL PRACTICE GUIDELINES

An ESMO Product

https://www.esmo.org/guidelines/supportive-and-palliative-care/management-of-cardiac-disease

ESMO GUIDELINES

Cardioprotective therapy



ESMO GUIDELINES

Monitoring of cardiotoxicity

*"At present, the most frequently used modality for detecting cardiotoxicity is the periodic measurement of **LVEF** by using either **echocardiography** or **multigated acquisition scanning**.*

In the future hopefully we will be able to monitor cardiotoxicity using biomarkers alone...

ALTERNATIVE TESTING

Biomarkers

- myeloperoxidase (MPO),
- topoisomerase II beta (TOP2β),
- interleukin-6 (IL-6),
- matrix metalloproteinase (MMP2+MMP9)
- troponin I and T
- NT-proBNP

Circulating levels of **micro RNAs**

- miR-126
- miR-34a
- miR-499
- miR-29a
- miR-423

Sci Rep. 2021; 11: 7954.doi: 10.1038/s41598-021-87209-8
J Am Heart Assoc. 2017 Apr 4;6(4):e004653. doi: 10.1161/JAHA.116.004653.

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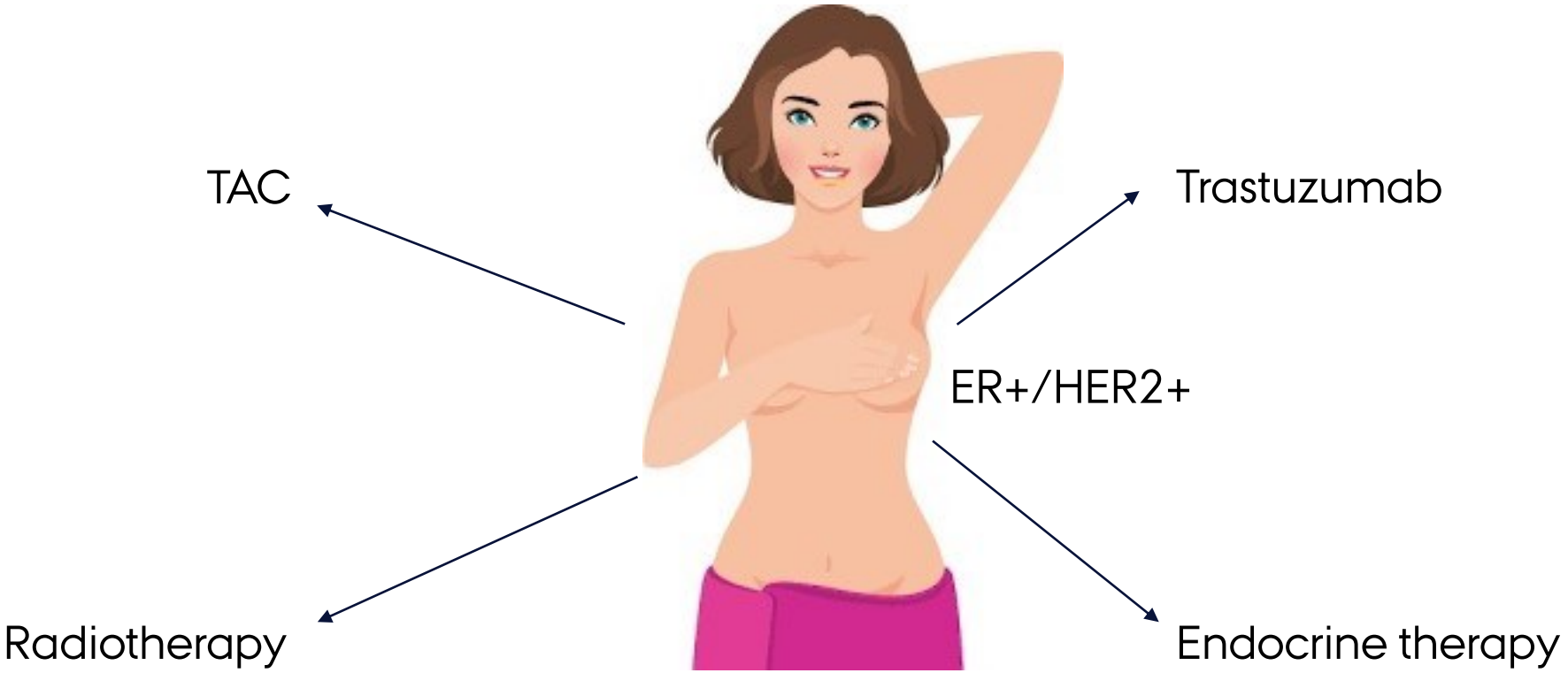
WORST CASE...



ACKNOWLEDGEMENTS

Department of Oncology
- Anders Bonde Jensen
- Britt Elmedal Laursen
- All the doctors and nurses of Team D
- Signe Borgquist

Department of Clinical Medicine
- Claus Gravholt
- Esben Laugesen
- Agnethe Berglund
- Lisa Buus & Lone Kvist

Department of Renal Diseases
- Niels Henrik Buus
- Bente Jespersen
- Ilse Rasmussen, Karin S. Hansen, Birgitte Kildevæld, Maria Arge
- Cecilie Skjold

KFE
- Hanne Hahn

EKO
- Jan Alsner
- All the staff of EKO

Kræftens Bekæmpelse

All the participants of our study

BC AND METABOLIC DISEASE

Metabolic syndrome

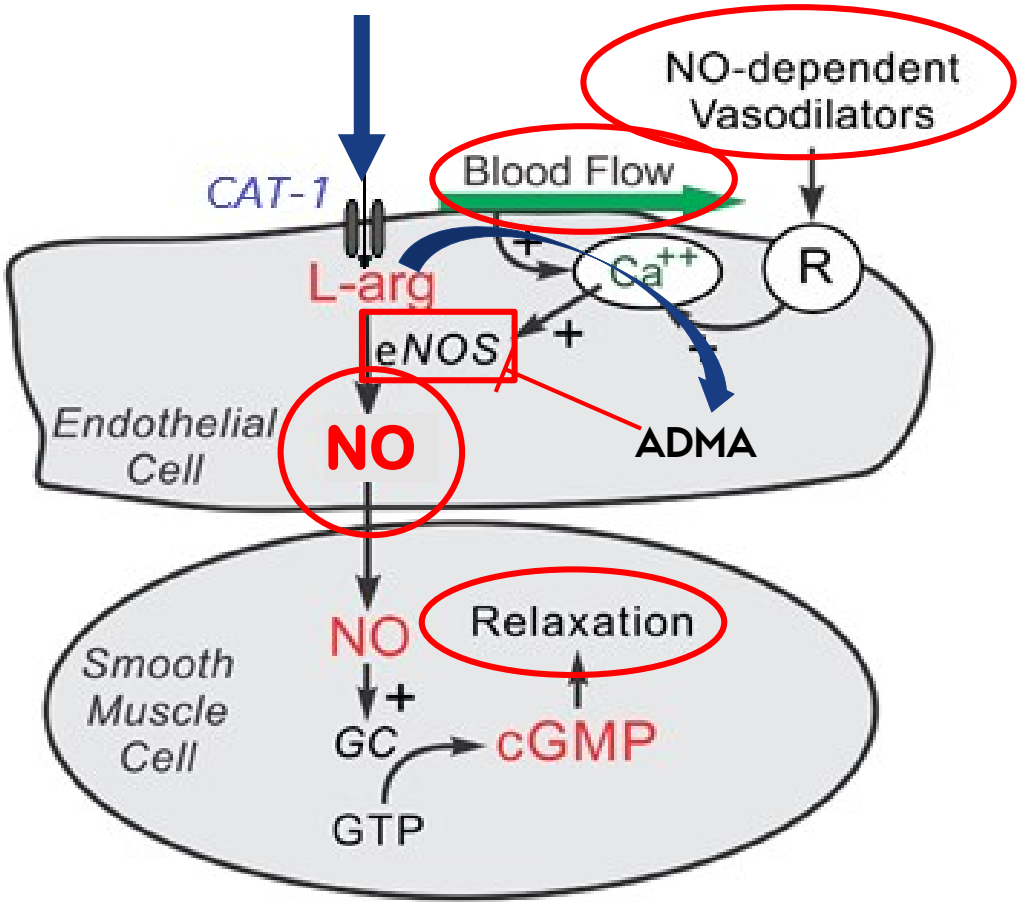
three or more of the following five criteria must be met:

- HDL<1.3
- triglycerides≥1.7
- waist>88 cm
- fasting glucose≥6.1
- blood pressure≥130/85

DYS

ENDOTHELIAL FUNCTION

1.
reduced endothelial NOS-derived NO



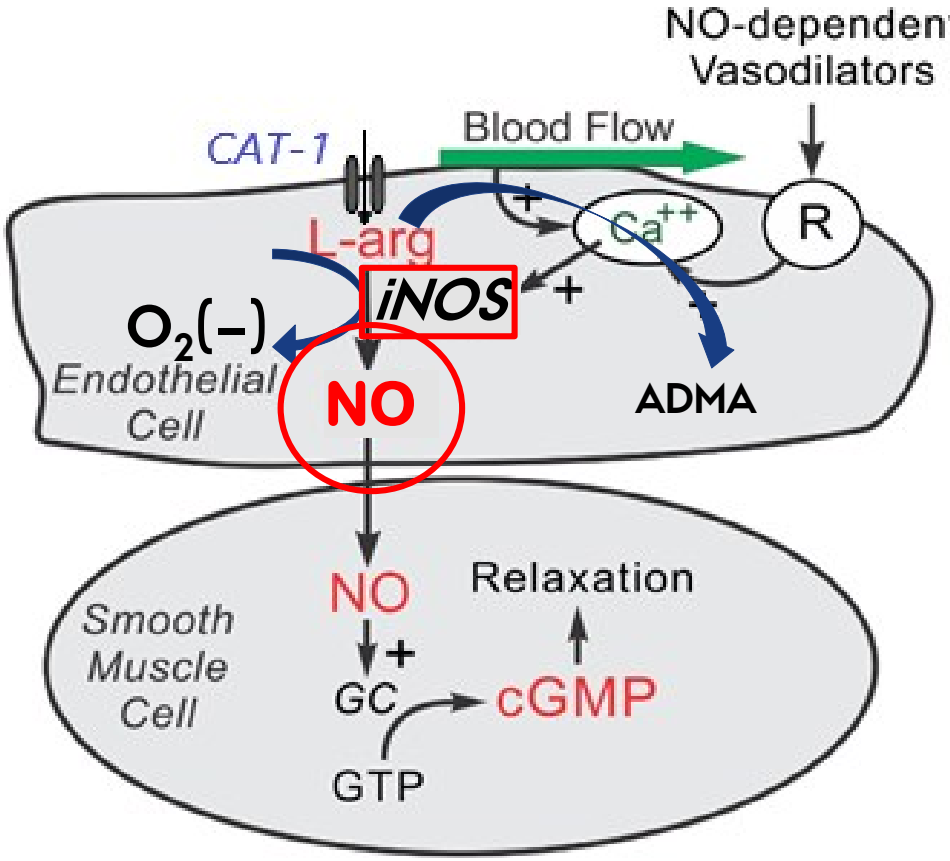
DYS

ENDOTHELIAL FUNCTION (ED)

1.
reduced endothelial NOS-derived NO

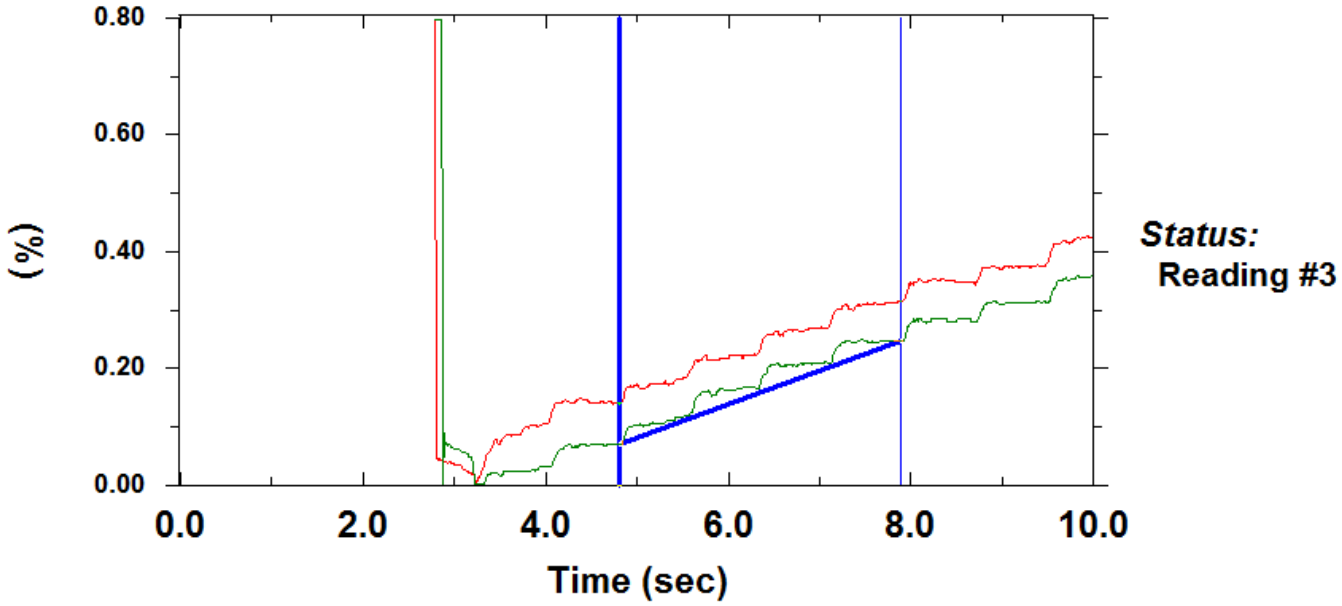
2.
increased inducible NOS (iNOS) expression

3.
NOS uncoupling and generation of superoxide



VENOUS OCCLUSION PLETHYSMOGRAPHY (VOP)

"Invasive VO
gold standar



onsidered a

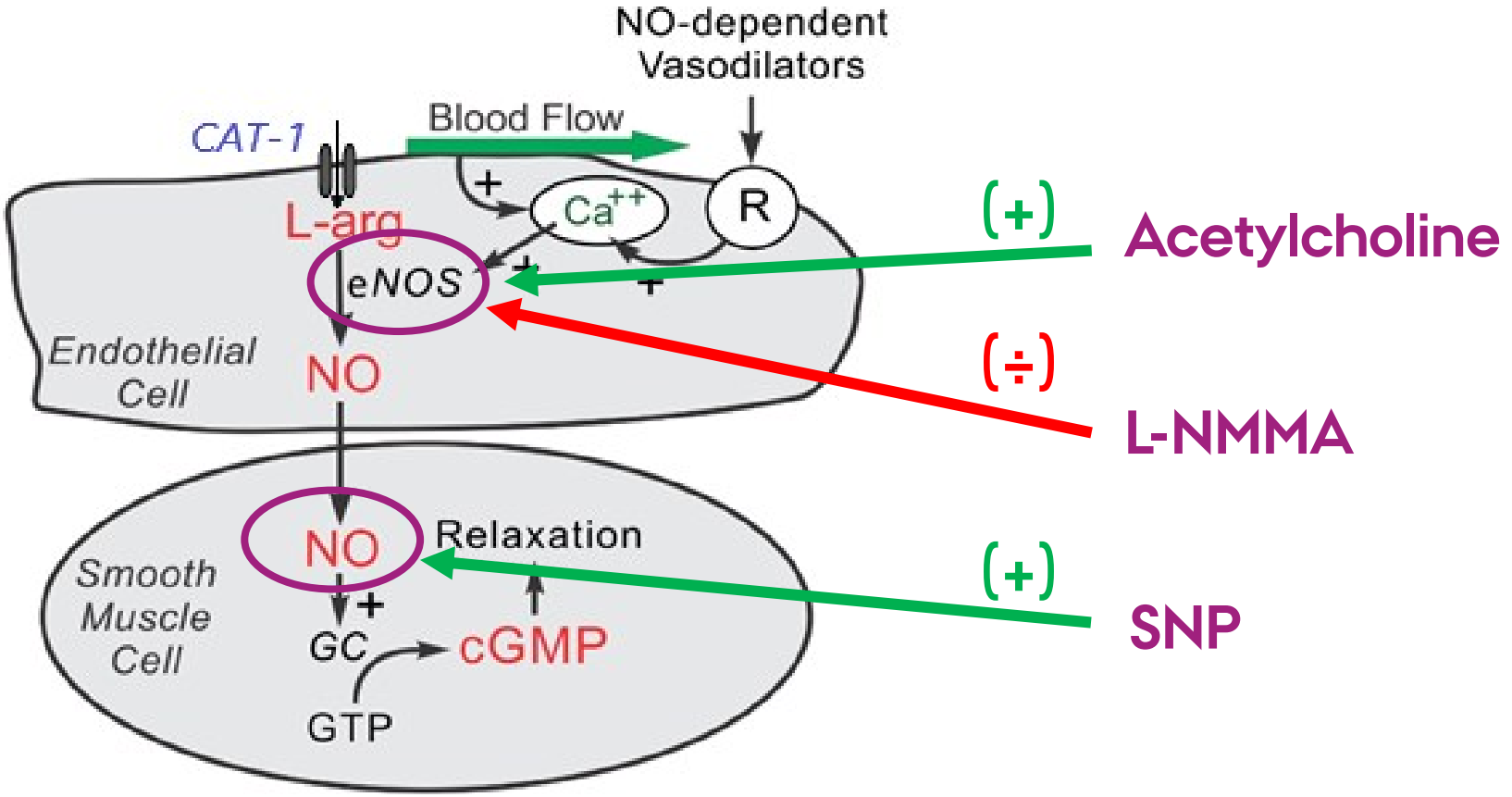
l function assessment

DYS ENDOTHELIAL FUNCTION

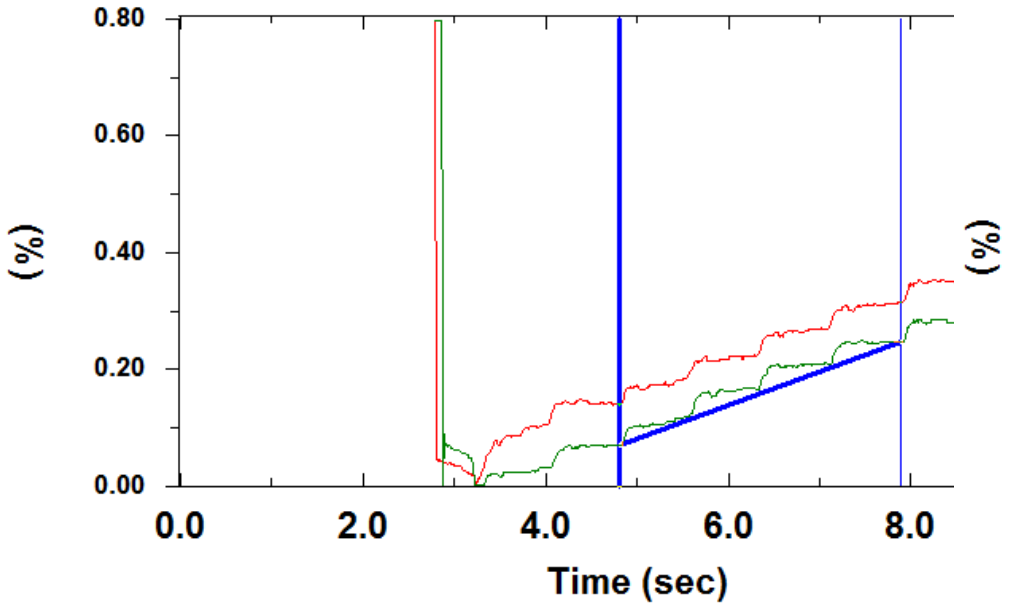
1.
reduced endothelial NOS-derived NO

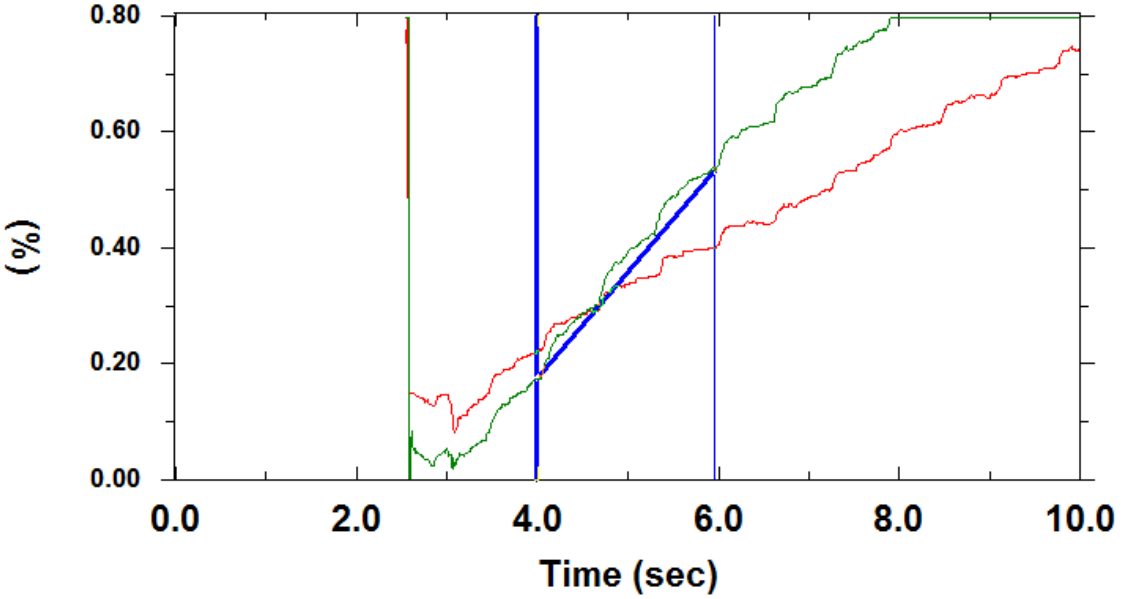
2.
increased inducible NOS (iNOS) expression

3.
NOS uncoupling and generation of superoxide



VOP





Status:
Reading #27

Press 'Tab' key for next channel:

1) IR= 5.37 (%/Min)

2) IR= 10.93 (%/Min)

STUDY II

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DEPARTMENT OF CLINICAL MEDICINE

MAY 19 2021

STINE FREDSLUND
MEDICAL DOCTOR, PHD

Study II

	BC patients	Controls
Participants (n)	100,834	1,008,320
Mean age at diagnosis (years)	61.4 ±13.1	60.9 ±13.1
Age range	8-103	7-102
SURGE		
Mastectomy	48,719 (48%)	
Lumpectomy	44,984 (45%)	
Lumpectomy followed by	1,353 (1%)	
Mastectomy after neo-adjuvant	2,008 (2%)	
Lumpectomy after neo-adjuvant	1,088 (1%)	
Only biopsy	2,657 (3%)	
Other	25 (0%)	
Missing information on surgery	0	
MEDICAL TREATMENT		
Chemotherapy		
Yes	25,570 (25 %)	
Not reported	74,479 (74 %)	
No	785 (1 %)	
Endocrine therapy		
Yes	41,446 (41 %)	
Not reported	58,107 (58 %)	
No	1,281 (1 %)	
Trastuzumab		
Yes	3,717 (4 %)	
Not reported	97,070 (96 %)	
No	47 (0 %)	

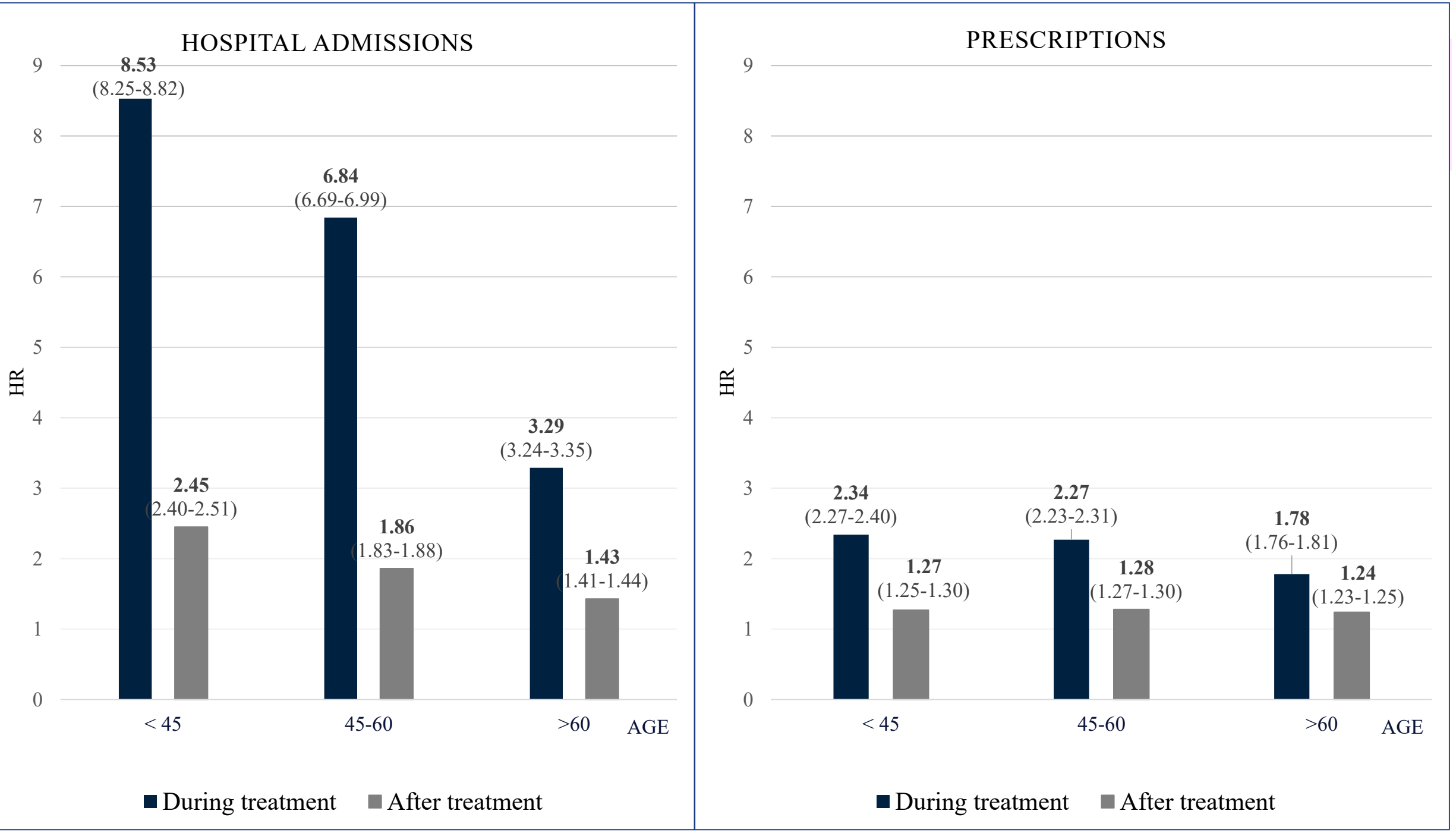
Study design

Observational cohort study:

- An empirical but non-experimental investigation of the effects caused by a treatment.
- What happens to the cohort members (Danish women) that have been exposed to a particular variable (BC) in comparison to the other members who have not been exposed

Randomized trials:

- Introduction of an intervention to study the effects
- Eligible people are randomly assigned to one of two or more groups.
- One group receives the intervention (such as a new drug) while the control group receives nothing or an inactive placebo


HOSPITAL ADMISSIONS
HR
9
8
7
6
5
4
3
2
1
0
8.53
(8.25-8.82)
2.45
(2.40-2.51)
6.84
(6.69-6.99)
1.86
(1.83-1.88)
3.29
(3.24-3.35)
1.43
(1.41-1.44)
< 45
45-60
>60
AGE
During treatment
After treatment
PRESCRIPTIONS
HR
9
8
7
6
5
4
3
2
1
0
2.34
(2.27-2.40)
1.27
(1.25-1.30)
2.27
(2.23-2.31)
1.28
(1.27-1.30)
1.78
(1.76-1.81)
1.24
(1.23-1.25)
< 45
45-60
>60
AGE
During treatment
After treatment

Cancer related hospital contacts

We choose to include all hospital contacts due to diagnosis, treatment and follow-up for breast cancer knowing that these contacts could cover morbidity not directly related to the breast cancer but to comorbidity and side effects.

We believe that excluding these contacts would have underestimated the morbidity of the BC patients, but are also aware that some of these contacts are routine visits not necessarily indicating health problems.

ATC codes

In three instances, drugs are not registered in NPR:

(a) drugs used during hospital admissions;

(b) drugs used by certain institutionalized individuals (e.g. patients with psychiatric illnesses);

(c) drugs supplied directly by hospitals or treatment centers (including chemotherapeutic and anti-hormonal agents).

Data management

1) Cases were not and could not be matched with their controls. Serial numbers were missing.

2) We asked for 10 controls per case, but among the 911,640 controls, there were only 793,986 unique pnr. In addition, 11,752 controls were matched with 2 or more cases. And in addition, almost 9000 controls were in fact a case. So we ended up having to exclude more than 138,000 controls.

3) IDAN data was missing

4) We were given an outdated variable of date of death (DODSDTO), with 28% of the variable missing.

5) The controls consist of equal parts men and women ("matched by age and gender").

6) New extraction; missing the entire Education Register and Migrations

7) The controls are matched with an incorrect match variable. Vital status year rather than year of operation. The entire dataset had to be rerun and re analyzed.

ESTROGEN

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DEPARTMENT OF CLINICAL MEDICINE

MAY 19 2021

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MEDICAL DOCTOR, PHD

ENDOTHELIAL DYSFUNCTION

We found several metabolic changes, that could explain our results:

Obesity:
can lead to release of inflammatory cytokines, activation of macrophages and activation of the Angiotensin II-cascade resulting in oxidative stress (as we heard yesterday)
Superoxide
is a known inhibitor of dimethylarginine dimethylhydrolase (DDAH), a key regulatory enzyme, which controls the metabolism of ADMA.
Increased ADMA levels leads to inhibition of NOs enzymes and CAT-1 (the cationic amino acid transporter 1,) and thereby reduced production of NO

ENDOTHELIAL DYSFUNCTION

Dyslipidemia:
Endothelial release of ADMA is increased in the presence of oxidized LDL cholesterol.
HDL increases endothelial cell NO production

Decreased Estradiol...

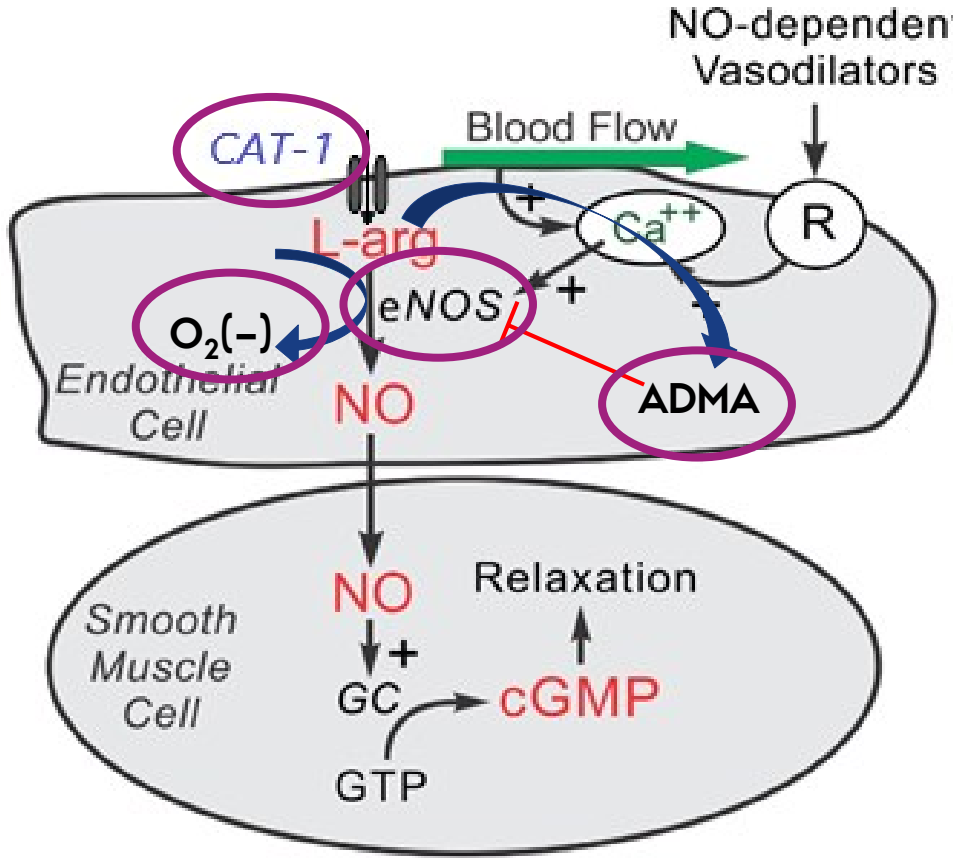
DYS

ENDOTHELIAL FUNCTION

1.
reduced endothelial NOS-derived NO

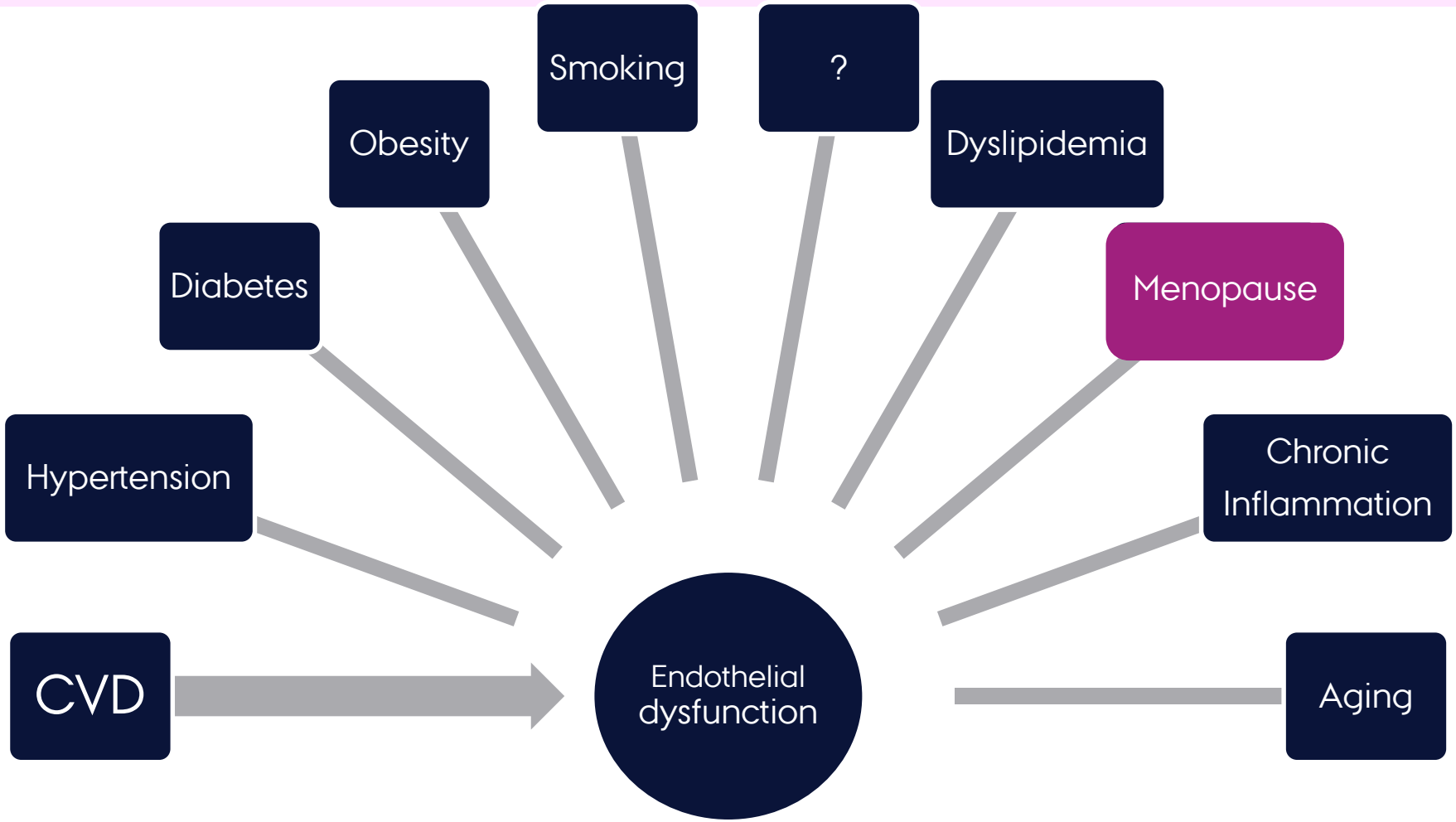
2.
increased inducible NOS (iNOS) expression

3.
NOS uncoupling and generation of superoxide



Estrogen

ENDOTHELIAL DYSFUNCTION



ESTROGEN

- Preventive and protective >< harmful effects
- Estrogen primarily act as a protective parameter in premenopausal women
- Depletion of estrogen occurring during premature (before age 40 years) and early (between ages 40 and 45 years) menopause is especially harmful

ESTROGEN

- **Preventive and protective** >< harmful effects
- Estrogen primarily act as a protective parameter in premenopausal women
- Depletion of estrogen occurring during premature (before age 40 years) and early (between ages 40 and 45 years) menopause is especially harmful
- The prevalence of Metabolic syndrome and CVD is known to increase after menopause

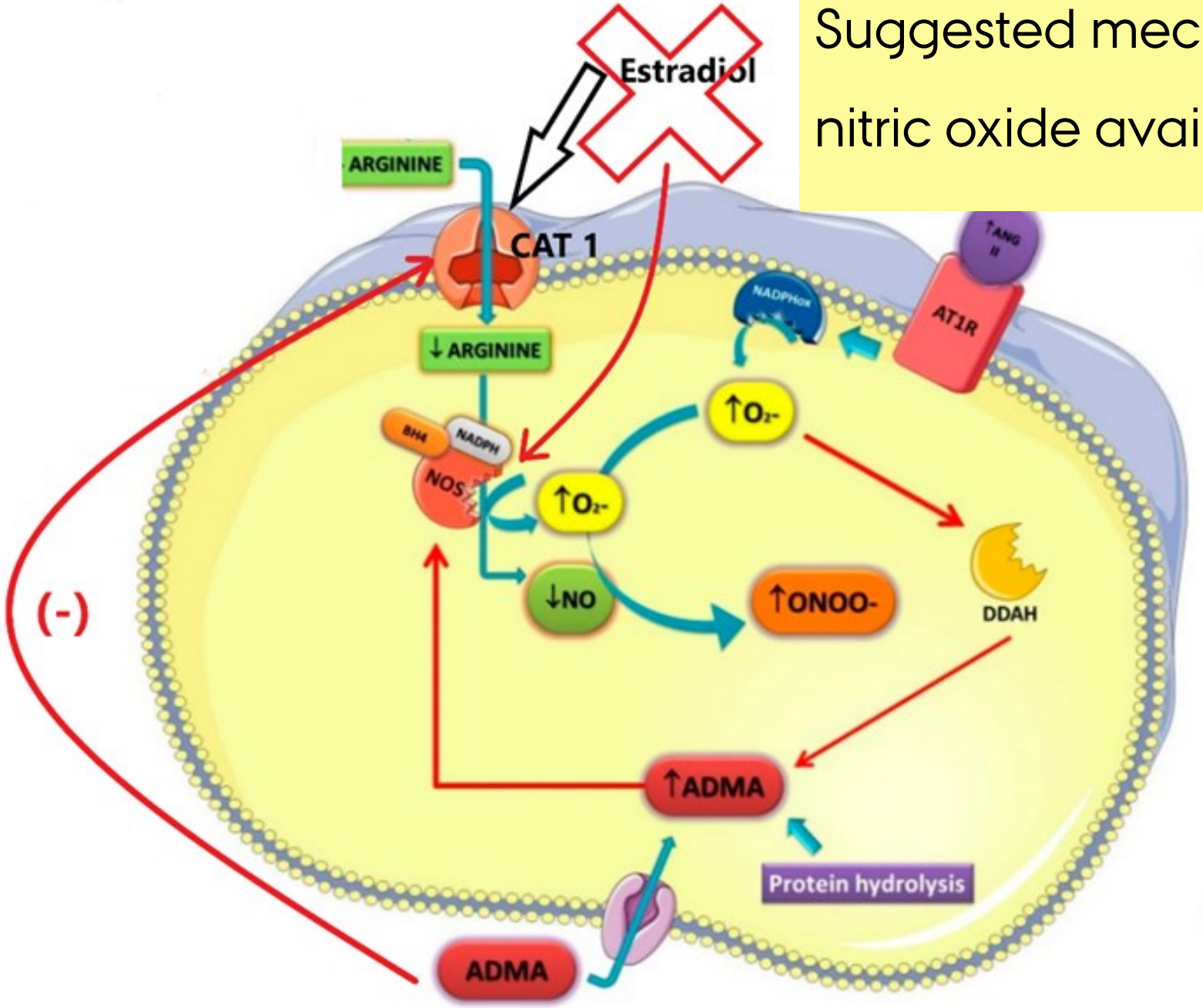
ESTROGEN

- Preventive and protective >< **harmful effects**

- HRT and extranormal estrogen levels in general are found to increase the risk of
  - BC
  - CVD and stroke in postmenopausal women

- Estrogen receptors
- Non-receptor mediated effects of estrogen

Suggested mechanisms for lowering nitric oxide availability in our cases



- Obesity
- Activation of macrophages
- Superoxide
- Increased ADMA
- Increased LDL cholesterol
- Decreased HDL cholesterol
- Decreased estradiol levels

RISK FACTORS

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DEPARTMENT OF CLINICAL MEDICINE

MAY 19 2021

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MEDICAL DOCTOR, PHD

RISK FACTORS...

Breast cancer

Old age
Diet
Smoking
Alcohol
Physical inactivity
Obesity
Diabetes
Metabolic syndrome
Chronic inflammation
Estrogen

Cardiovascular disease

Old age
Diet
Smoking
Alcohol
Physical inactivity
Obesity
Diabetes
Metabolic syndrome
Chronic inflammation
Estrogen

RISK FACTORS...

In BC, some factors can act both as

- risk factors,
- prognostic factors
- and predictive factors,

and this makes it crucial to distinguish whether focus is on risk of primary BC, on BC prognosis, on treatment outcome, or on all-cause morbidity

BISPHOSPHONATES

AARHUS
UNIVERSITY
DEPARTMENT OF CLINICAL MEDICINE

MAY 19 2021

STINE FREDSLUND
MEDICAL DOCTOR, PHD

BC TREATMENT

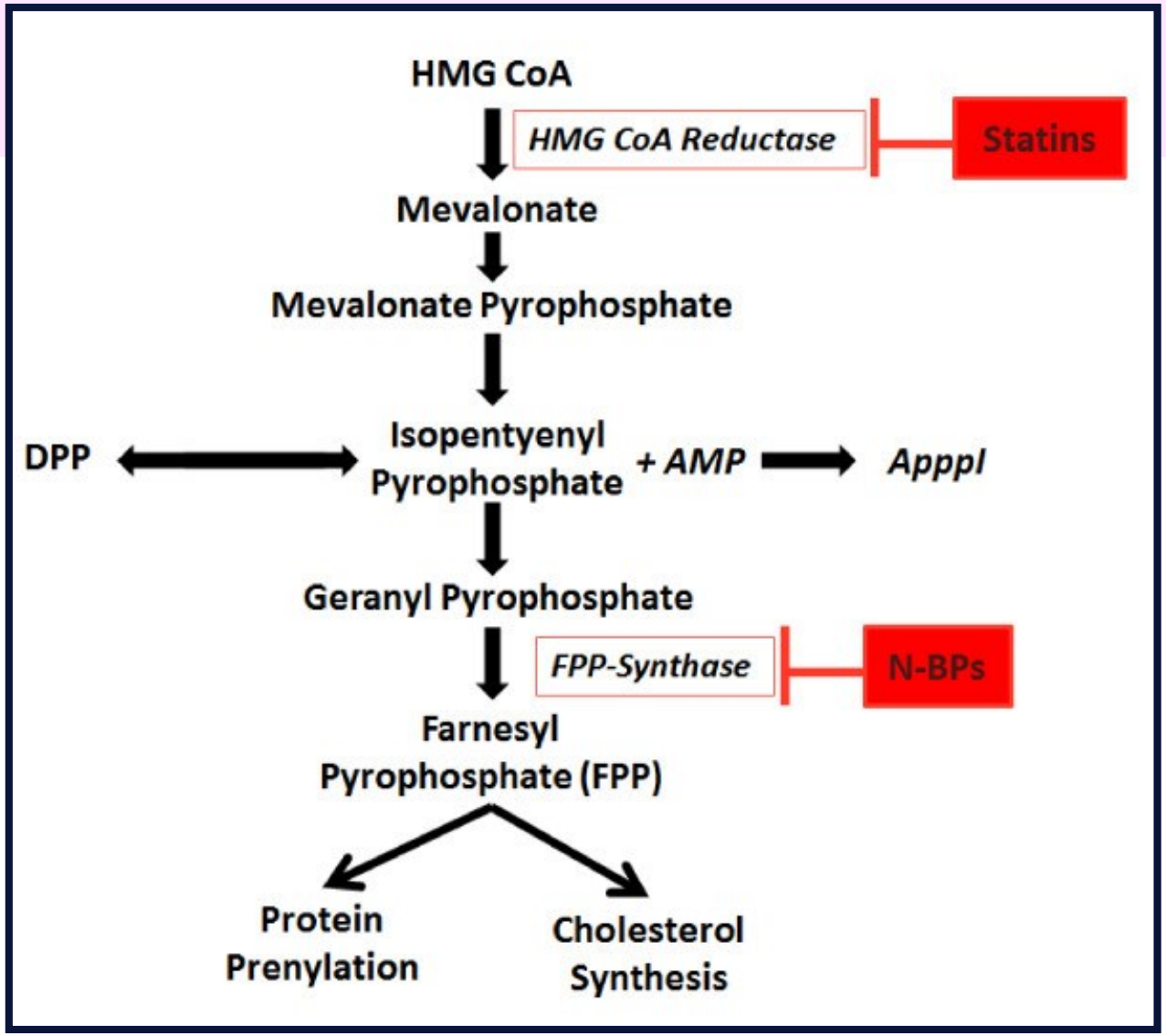
Bisphosphonates...

all postmenopausal BC patients are offered Zoledronic acid to reduce risk of bone metastases and increase overall survival

O'Carrigan B, Wong MHF, Willson ML, Stockler MR, Pavlakis N, Goodwin A.

Bisphosphonates and other bone agents for breast cancer.

Cochrane Database of Systematic Reviews. 2017.


HMG CoA
HMG CoA Reductase
Statins
Mevalonate
Mevalonate Pyrophosphate
DPP
Isopentyenyl Pyrophosphate
+ AMP
Apppl
Geranyl Pyrophosphate
FPP-Synthase
N-BPs
Farnesyl Pyrophosphate (FPP)
Protein Prenylation
Cholesterol Synthesis

METHODS STUDY I

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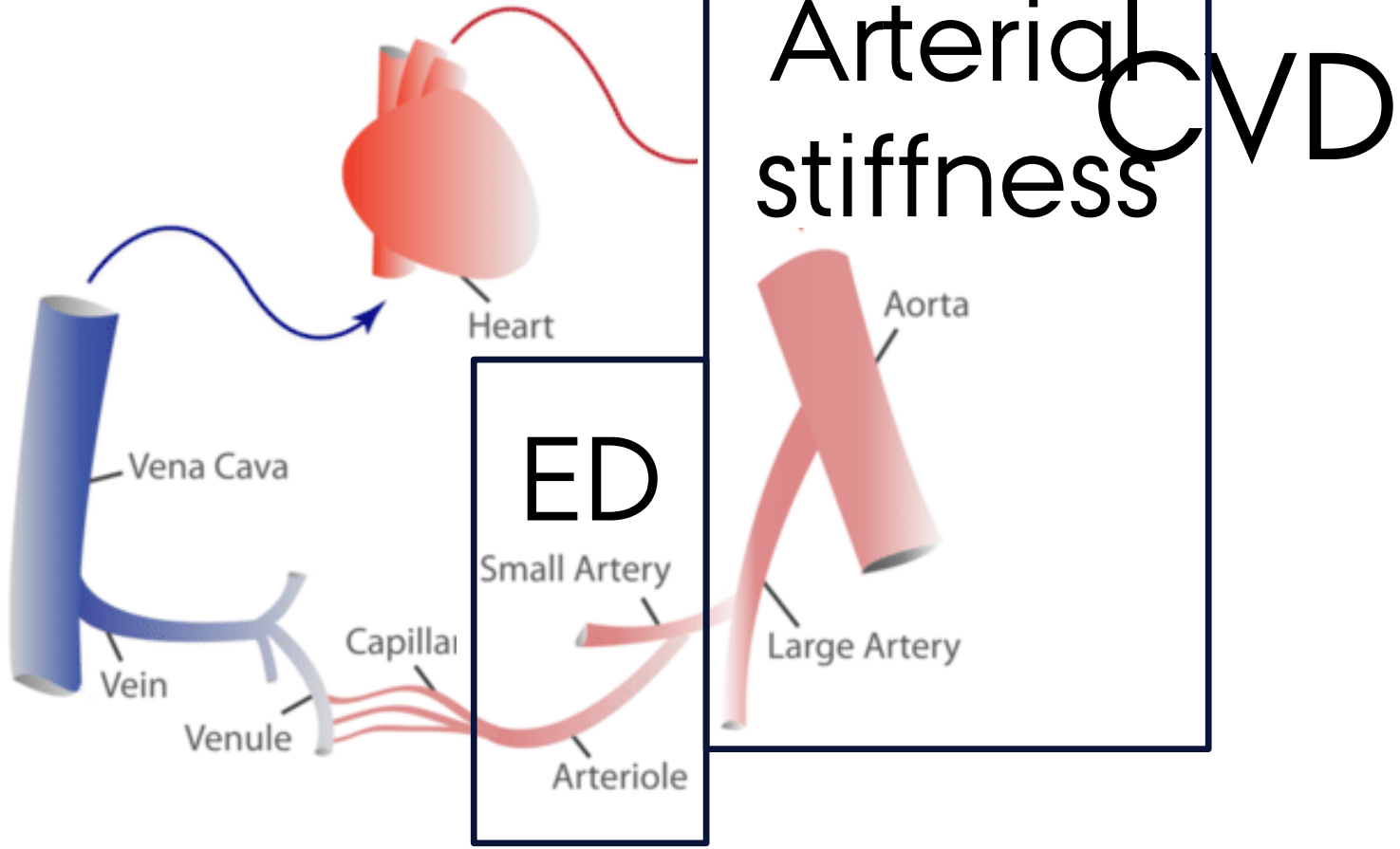
ED VS. ARTERIAL STIFFNESS

E



Alternative methods

Vascular function can be described and evaluated in numerous way.

Indirectly, the function of the endothelium can be described by measurement of different biochemical compounds or physiological assessment of different cardiologic and vascular measures, including arterial stiffness.

Non-invasive methods are often preferred in order to avoid discomfort of the participants, to minimize time consumption, and to keep costs at a minimum. For this purpose the non-invasive tool Endopat® can be used.

However, venous occlusion plethysmography as used in our study is considered gold standard for the evaluation of endothelial function

Alternative methods - **EndoPat®**

"The EndoPAT measures changes in pressure that indicate changes in arterial blood volume and result in a value called EndoScore. The EndoPAT test, which can be performed in a doctor's office, takes 15 minutes.

The test is uniquely performed at the fingertip and proven to be accurate, sensitive and reproducible"

It is shown that measurements from SphygmoCor and EndoPat correlated well.

Though no measurements with simultaneously injection of vasoactive substances.

ARTERIAL STIFFNESS

Pulse wave velocity (PWV)

Measurement of pulse wave velocity (PWV) is considered the gold standard method for assessment of arterial stiffness.

PWV is reported as meters/second, and the calculations are based on recordings of travel speed of the pulse wave (generated by cardiac contraction) over a known distance.

CENTRAL BLOOD PRESSURE

Pulse wave analysis (PWA)

The PWA at the radial artery was determined non-invasively during 10 seconds of recording by aMillar tonometer.

Based on these recordings, central blood pressure in the ascending aorta was computed using the inbuilt transfer function of the SphygmoCor software.

CENTRAL BLOOD PRESSURE

Increased BNP levels (both BNP and NT-proBNP) is known to be associated with CVD

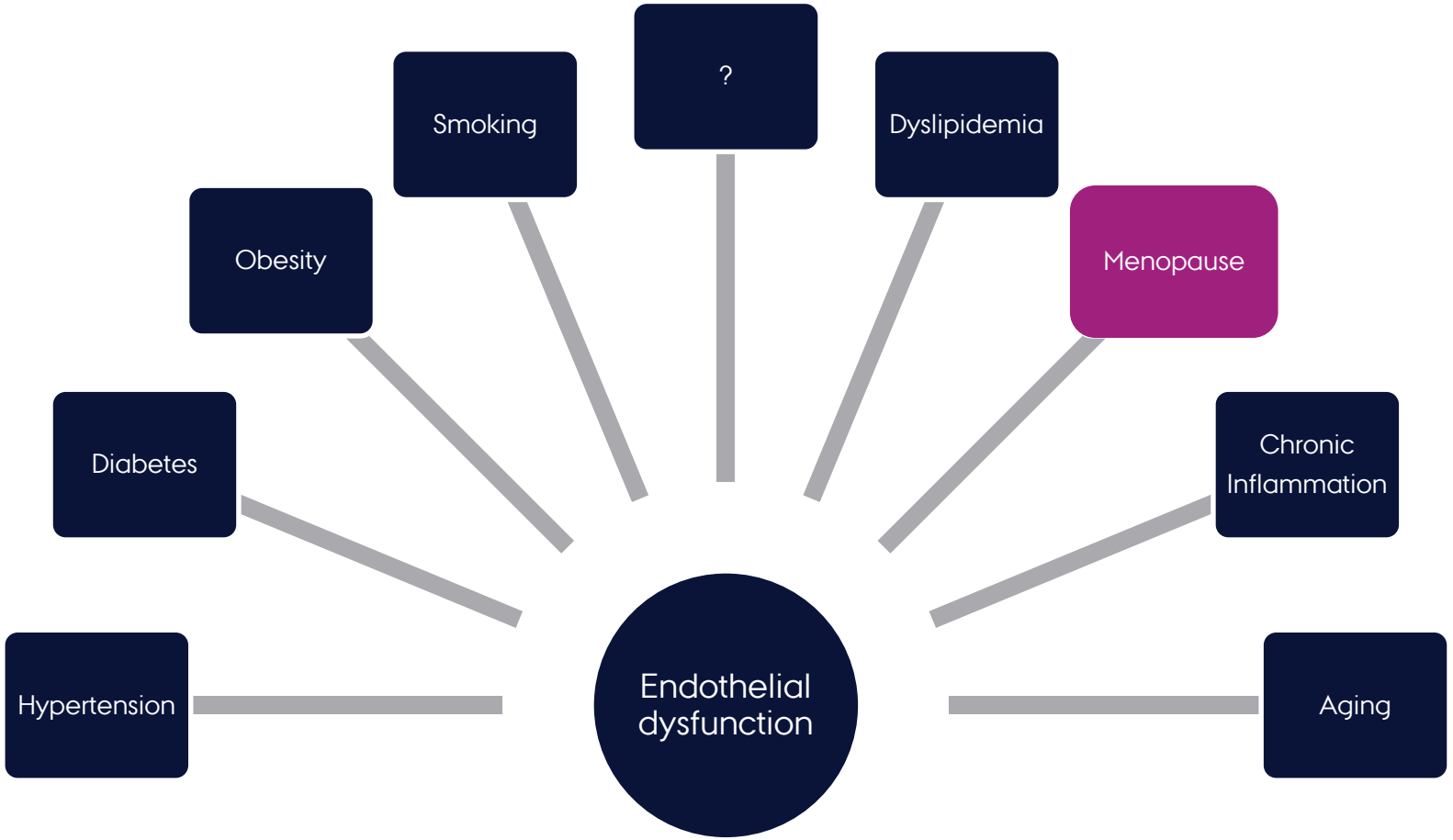
Studies have recently revealed that even small elevations in BNP level have prognostic value for future CVD.

The levels shown to be associated with increased risk were well below the range, that is traditionally used as dia[96.0 ng/L]eart failure. Specifically, BNP levels exceeding 20 pg/mL we[96.0 ng/L]gnificantly increased risk of both heart failure and atrial fibrillation.

As a result of these and others studies, the European Society of Cardiology has lowered the threshold for the detection of heart failure from 400 pg/mL for NT-proBNP to 125 pg/mL, respectively.

1pg/mL equals 1ng/L, the latter unit is used in our study and is more commonly recognized in practice compared to pg/mL

ENDOTHELIAL DYSFUNCTION – CAUSALITY?



Critisism:

Treatment effects could have been more appropriately studied within the cohort of breast cancer patients with comparisons between different types of treatment, refined time periods since

diagnosis and omitting hospital contacts due to the breast cancer diagnosis per se.

Unfortunately treatment effekts was not possible to evaluate, due to a lack of information from the DBCG data base

Optimally we would have categorized the patients according to standard treatment on basis of tumor characteristics

Critisism:

In respect to hospital data, this

covers stratifications on time since diagnosis, age at diagnosis and type of hospital contact, and it is difficult to get a clear overview by reading the result section. The result section concerning prescriptions is straightforward and much easier to follow than the section on hospital contacts.

Critism:

somewhat difficult

to find a red line going through the discussion. For example inclusion of data on prescriptions are

rightfully emphasized as an advantage of the study, but this is mentioned in two paragraphs at

separate places in the discussion. Comparisons with previous studies are included both in the

beginning and in the last sections of the discussion. The previous Danish study (Kjaer et al) is

actually mentioned here, but it has not been recognized that the data in the current study

overlaps to a great extent with the previous study, and therefore findings of the latter cannot be used to support those of the former.

BREAST CANCER TREATMENT

TAC

Taxanes
Anthracycline
Cyclophosphamide

- Radiotherapy
- Systemic treatment
  - Chemotherapy
  - Trastuzumab (HER2)
  - Endocrine therapy

Yun-Jiu Cheng MD et al., J Am Heart Assoc. 2017 May; 6(5)
Long-Term Cardiovascular Risk After Radiotherapy in Women With Breast Cancer

Eschenhagen T et al., European Journal of Heart Failure (2011) 13, 1–10
Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology

Matthews A et al., BMJ. 2018 Oct 8;363:k3845.
Long term adjuvant endocrine therapy and risk of cardiovascular disease in female breast cancer survivors: systematic review.

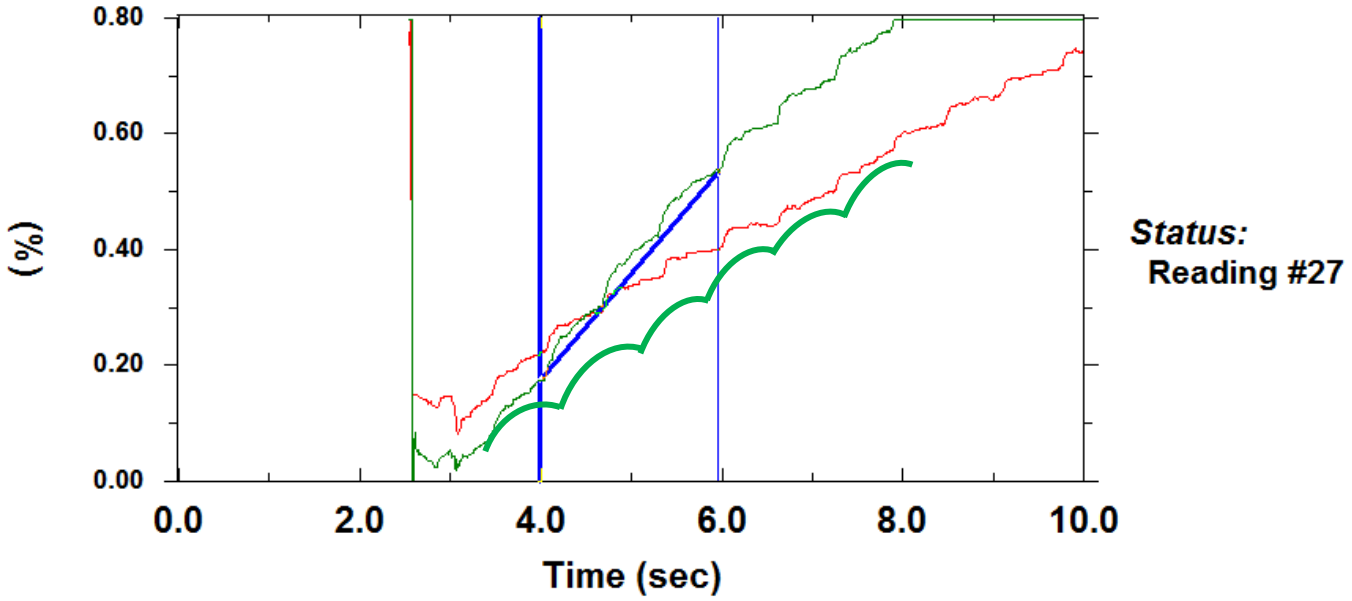
N J Bundred et al. Br J Cancer. 2005 Aug; 93(Suppl 1): S23–S27.
The effects of aromatase inhibitors on lipids and thrombosis

Lipscombe LL et al., Cancer. 2012 May 15;118(10):2615-22.
Association between tamoxifen treatment and diabetes: a population-based study.

Azizian H et al, Int. Immunopharmacol. 2018 Oct 10;65:190-198.
Therapeutic effects of tamoxifen on metabolic parameters and cytokines modulation in rat model of postmenopausal diabetic cardiovascular dysfunction: Role of classic estrogen receptors.

RESULTS

VOP



Status:
Reading #27

Press 'Tab' key for next channel:

1) IR= 5.37 (%/Min)

2) IR= 10.93 (%/Min)

Strengths and limitations

- Ordinary linear regression predicts the expected value of a given unknown quantity (the *response variable*, a random variable) as a linear combination of a set of observed values (*predictors*). This implies that a constant change in a predictor leads to a constant change in the response variable (i.e. a *linear-response model*). This is appropriate when the response variable has a normal distribution (intuitively, when a response variable can vary essentially indefinitely in either direction with no fixed "zero value", or more generally for any quantity that only varies by a relatively small amount, e.g. human heights).

- The calculation is just the difference between the incidence proportion of a disease/event in the control group and the incidence proportion of the same outcome in the treated group