

Active Surveillance – Having Your Cake and Eating it Too

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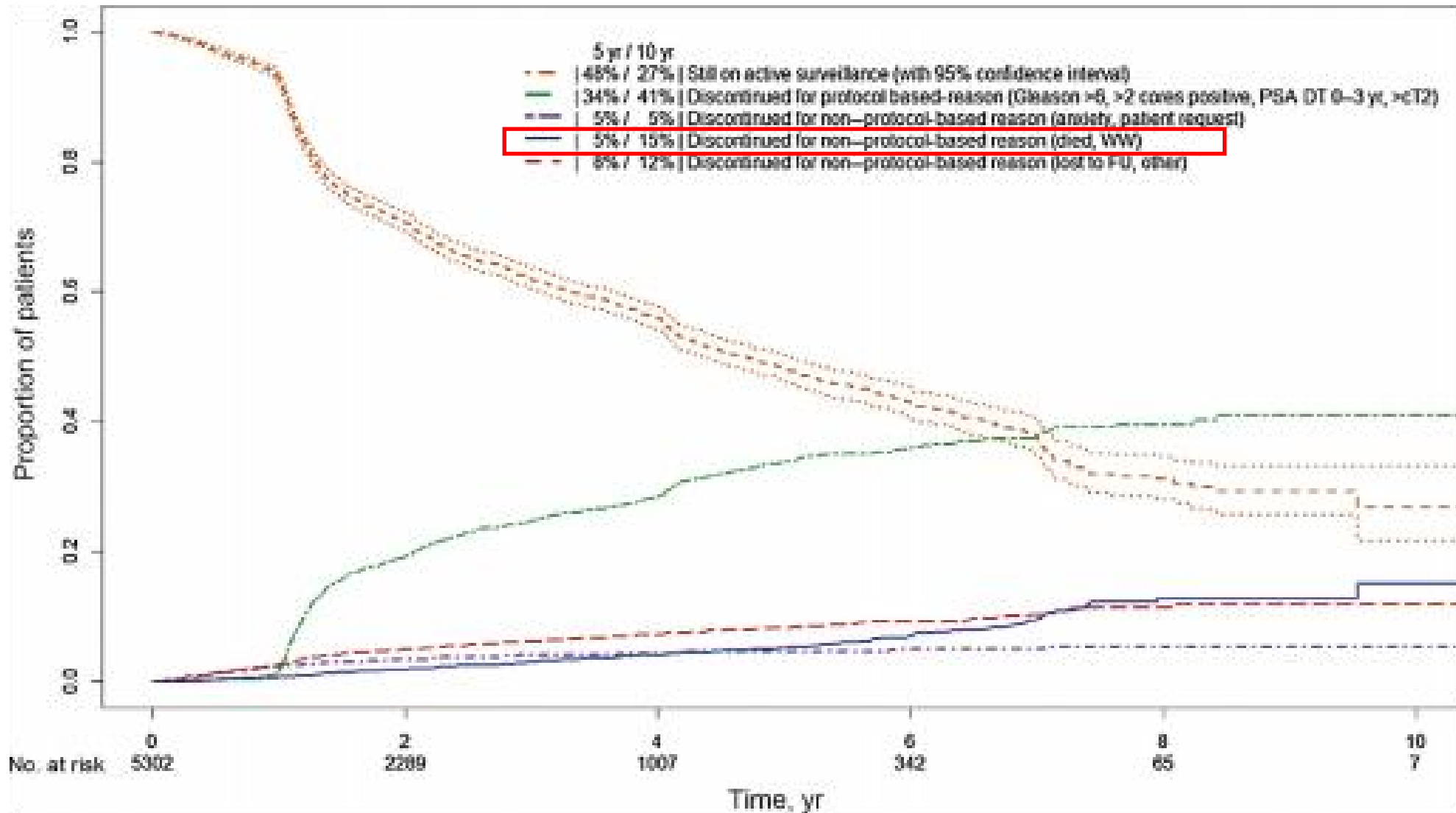
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Objectives

- To review survival expectations in men with PC eligible for AS
- To understand the meaning of competing risks
- To discuss strategies to reduce the competing risk of cardiovascular disease

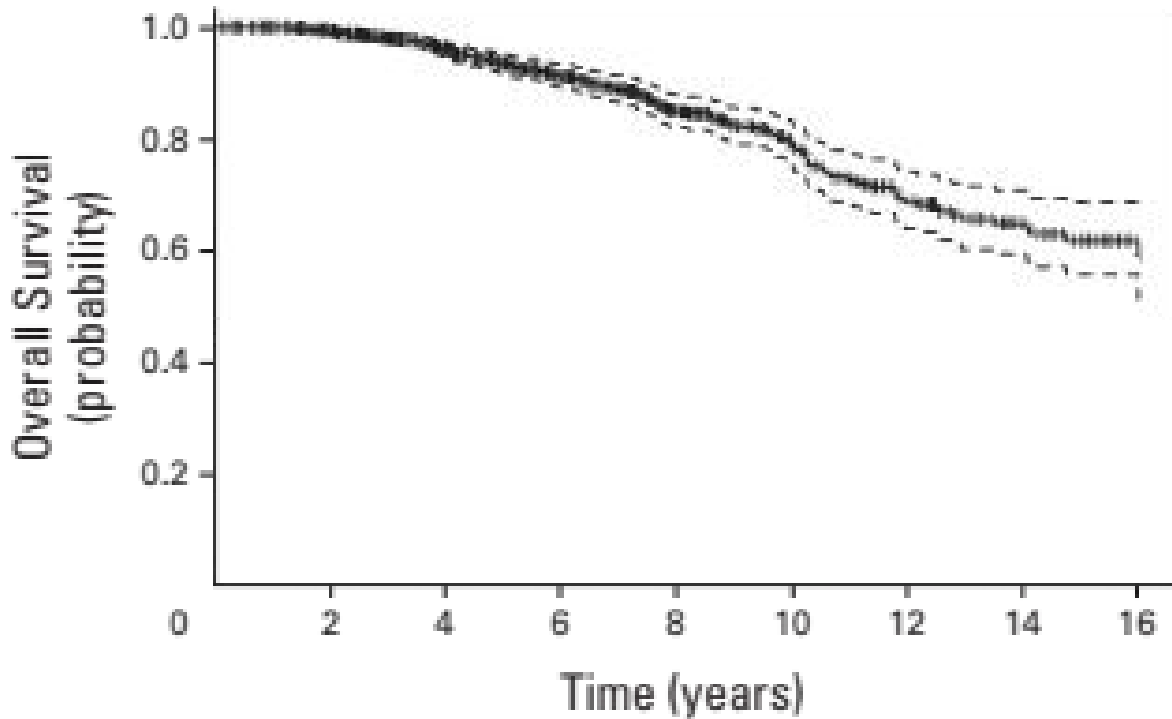
Survival in patients on active surveillance



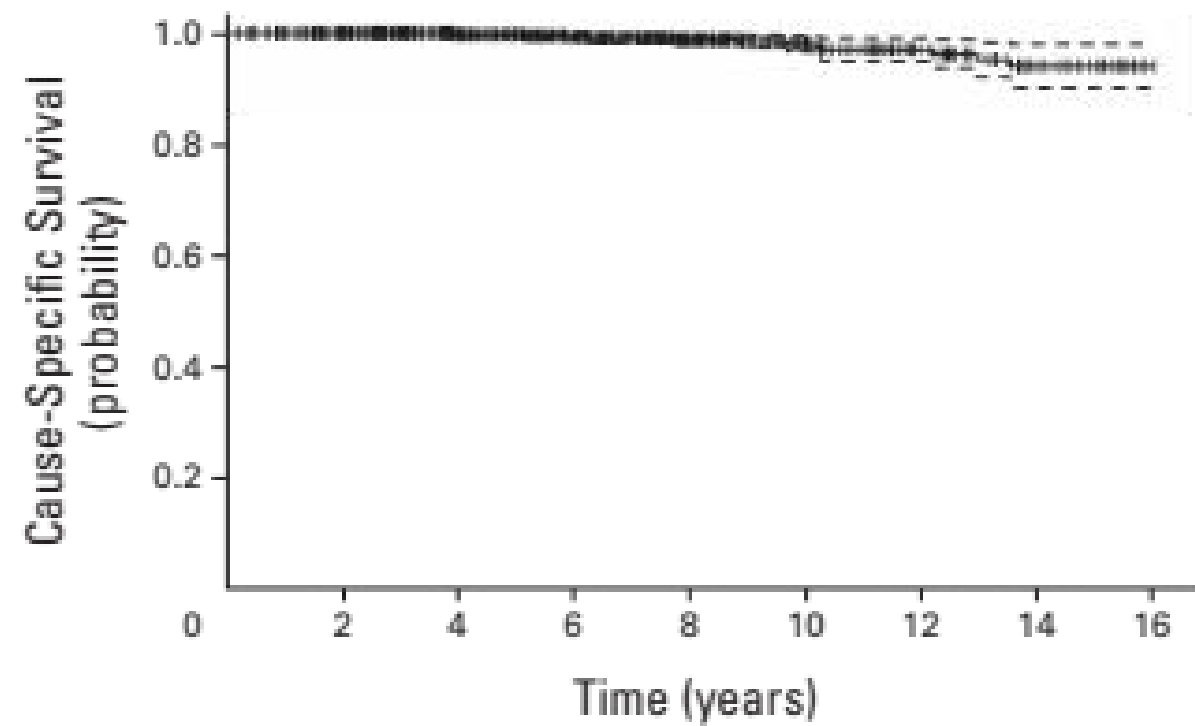
Bokhorst, *et al. Eur Urol* 2016; 70: 954

Survival in patients on active surveillance

80% alive 10 years; 62% alive 15 years



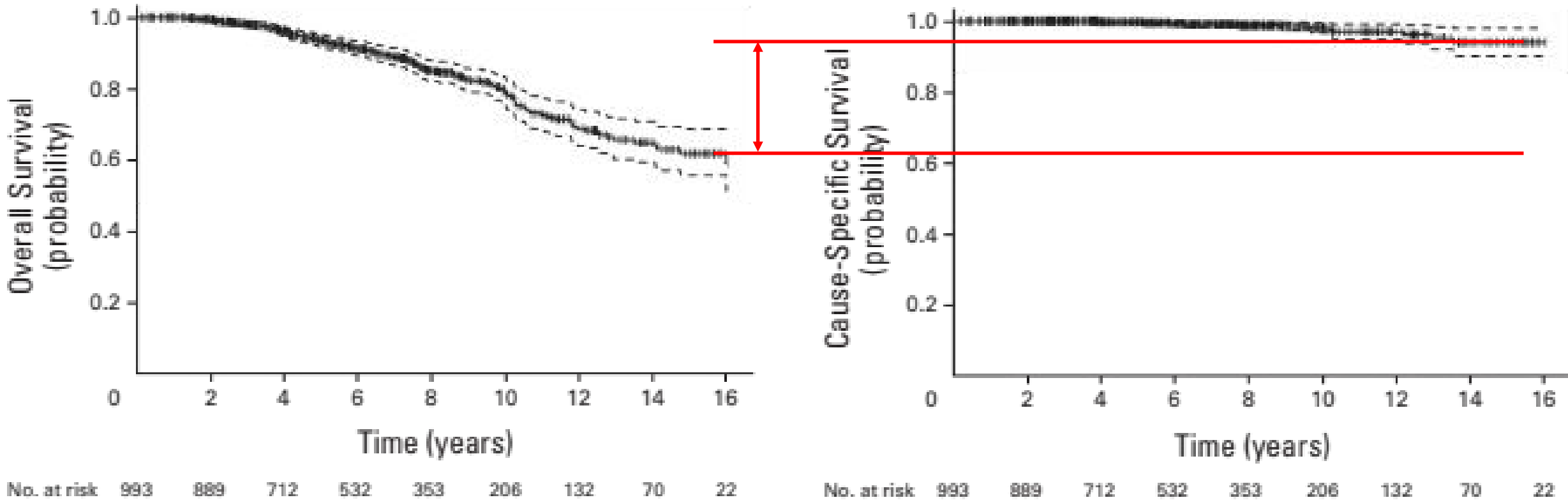
No. at risk 993 889 712 532 353 206 132 70 22



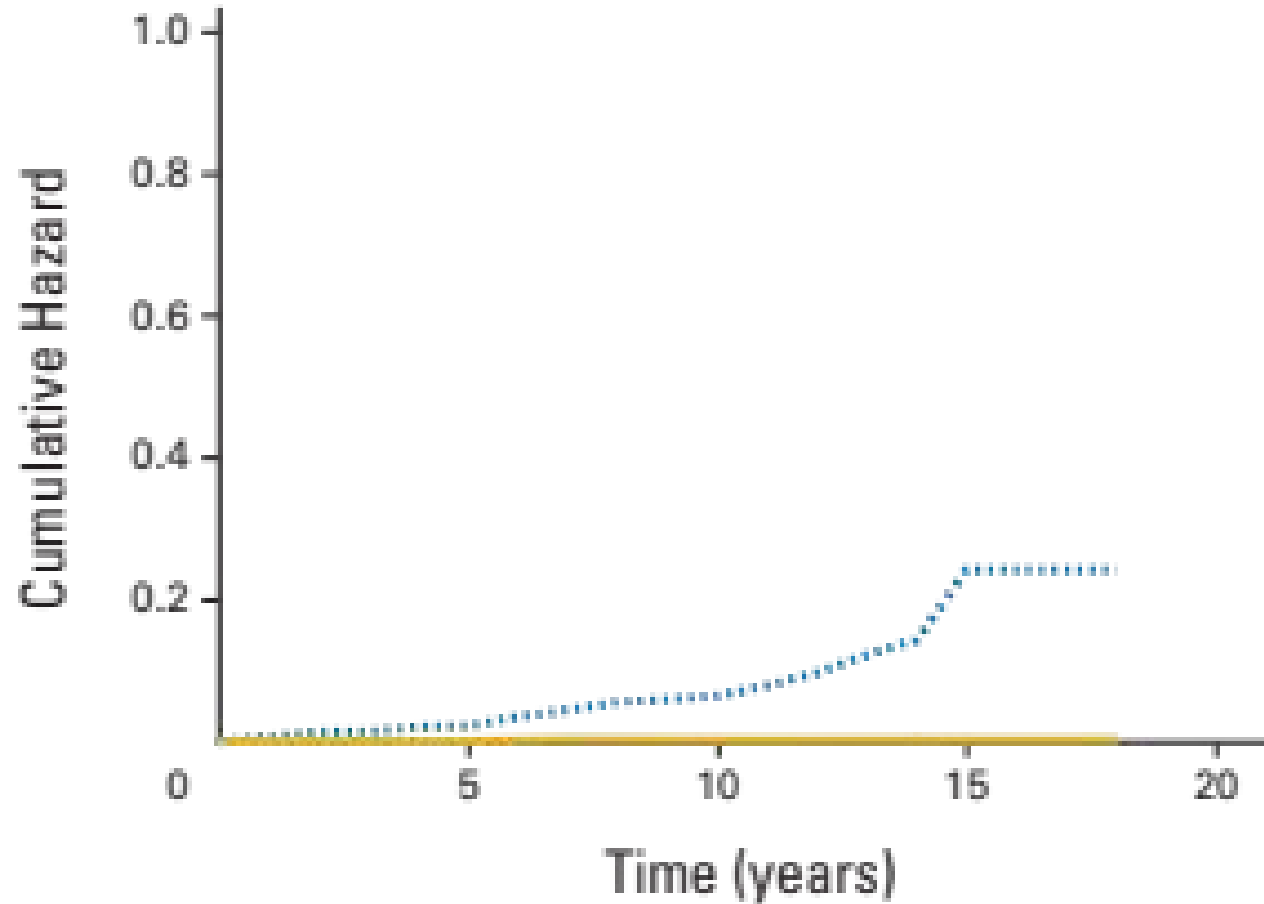
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Survival in patients on active surveillance

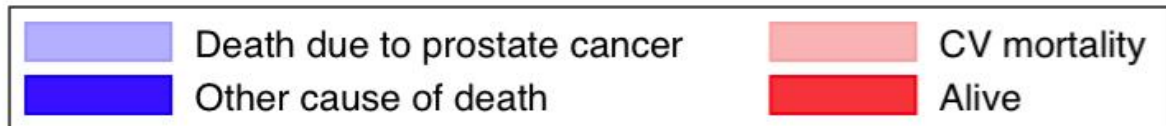
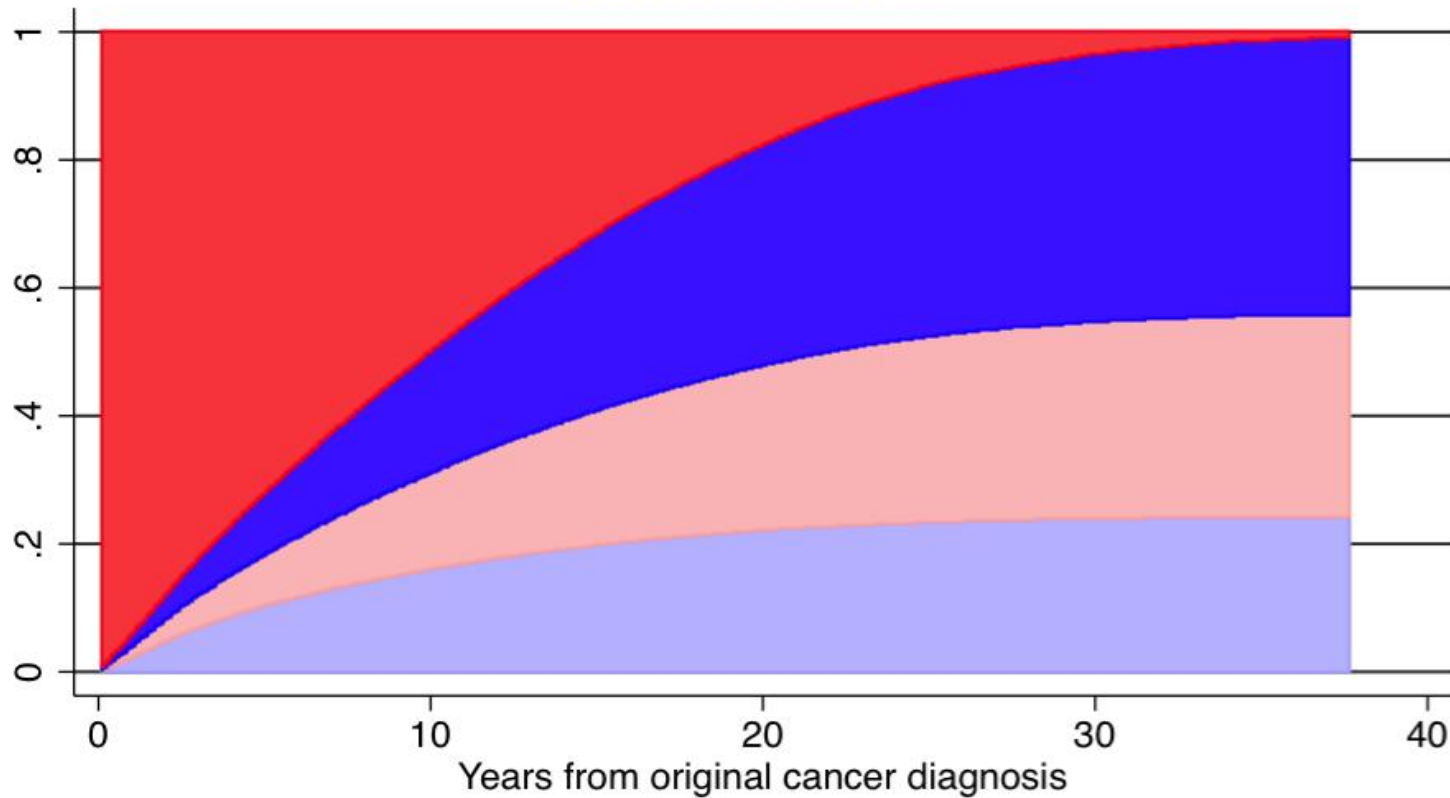


No. at risk	0	5	10	15
Any-cause death	1,298	650	184	26
Prostate cancer death	1,298	650	184	26

Tosoian, *et al. J Clin Oncol*
2015; 33: 3379

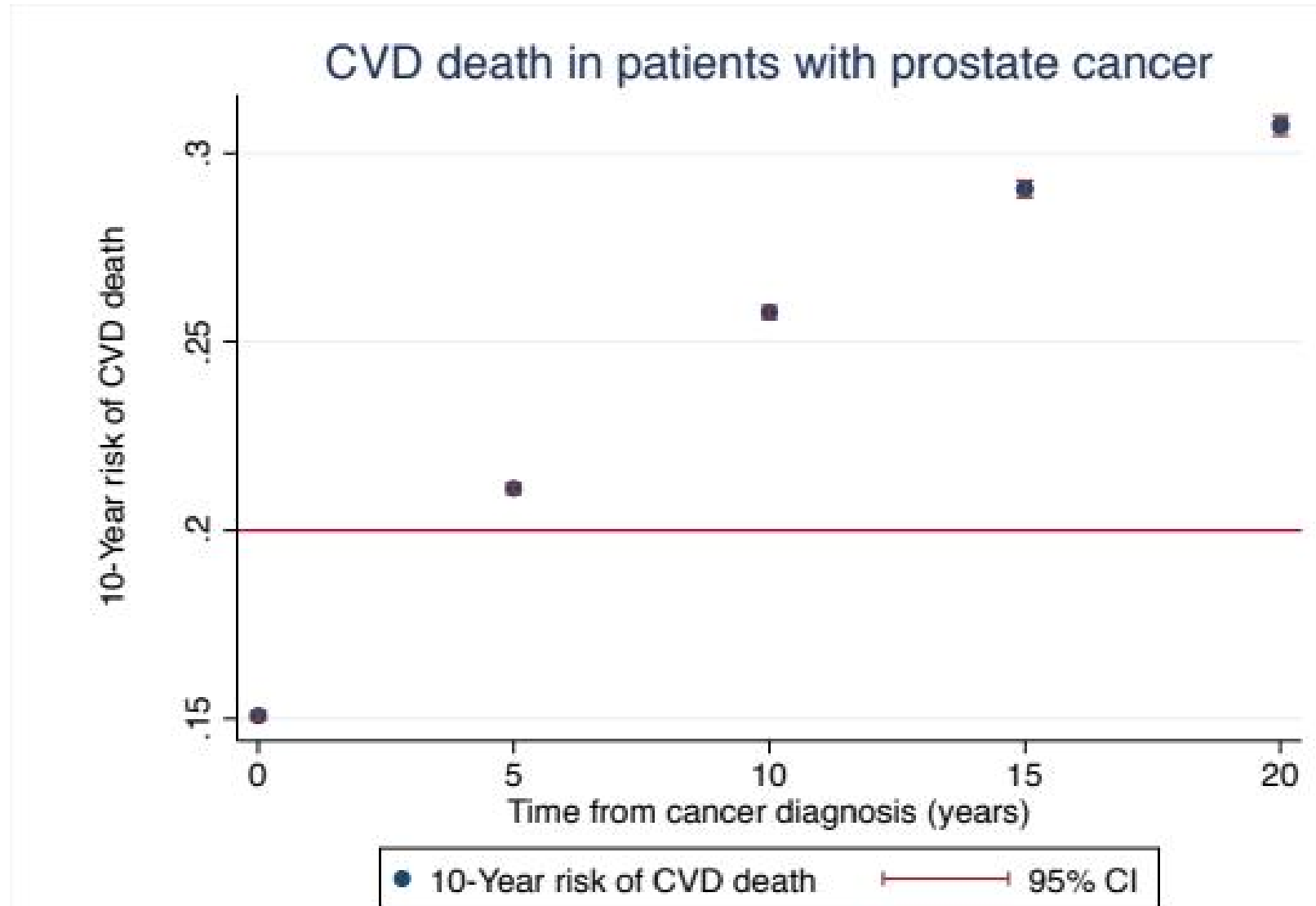
Causes of Death in All Men with PC

Prostate cancer



SEER Registry analysis; UNPUBLISHED

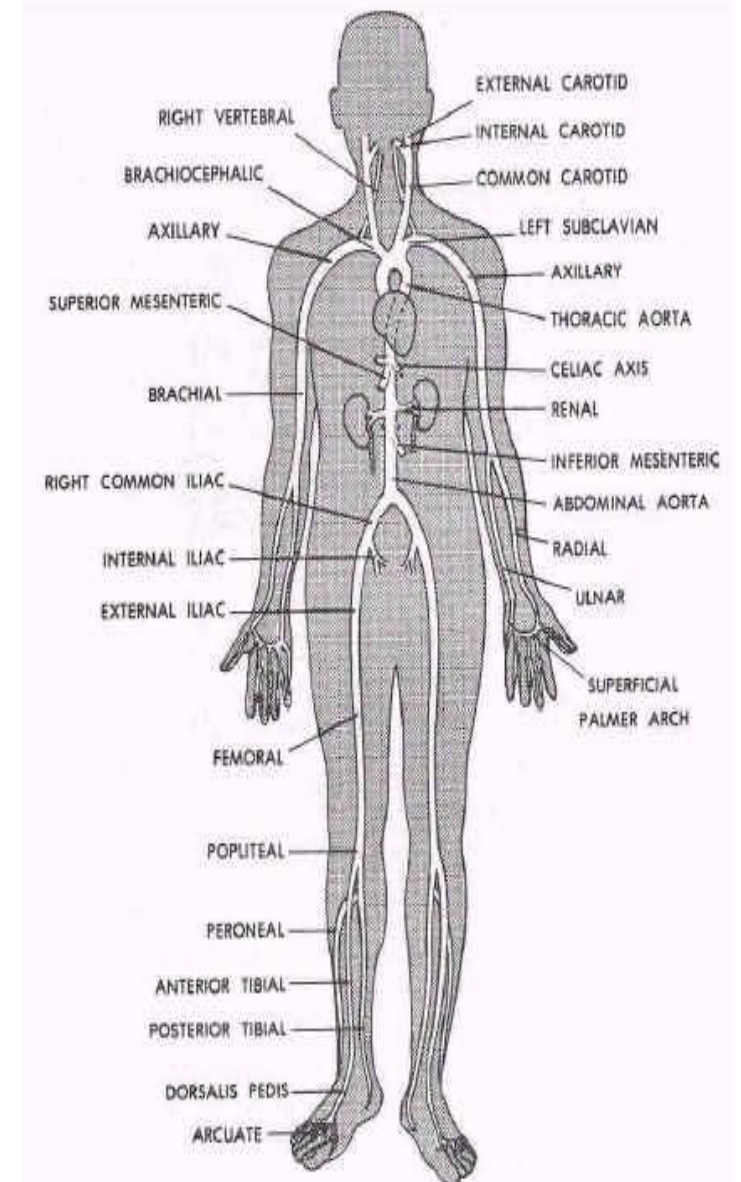
Cardiovascular Death in Men with PC



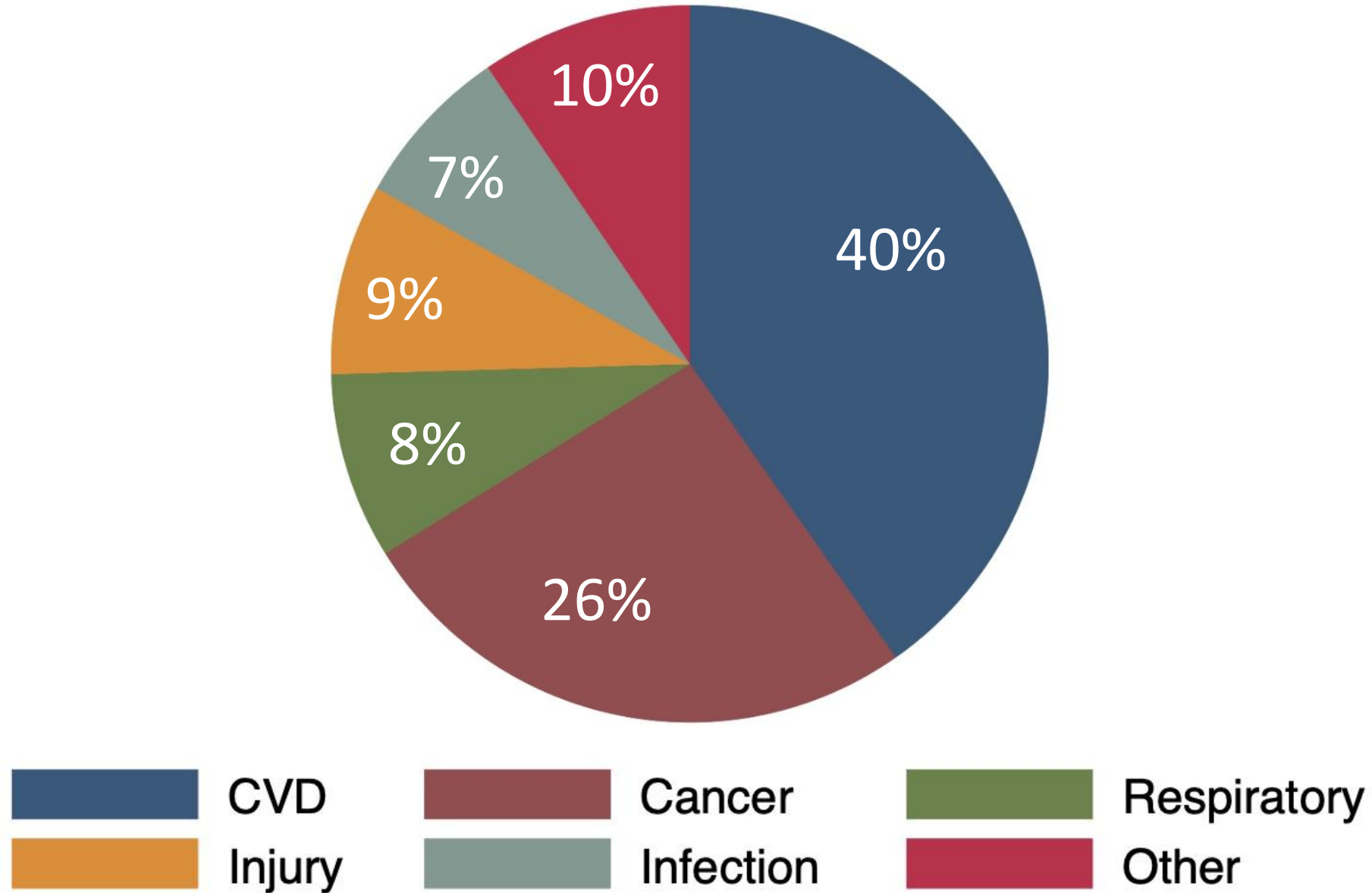
SEER Registry
analysis;
UNPUBLISHED

What is cardiovascular disease?

- Heart
 - Ischemic heart disease
 - Coronary artery disease
 - “Heart attack”
- Brain
 - Stroke
- Legs
 - Peripheral vascular disease
 - Peripheral arterial disease
 - Intermittent claudication



Why is cardiovascular disease important?



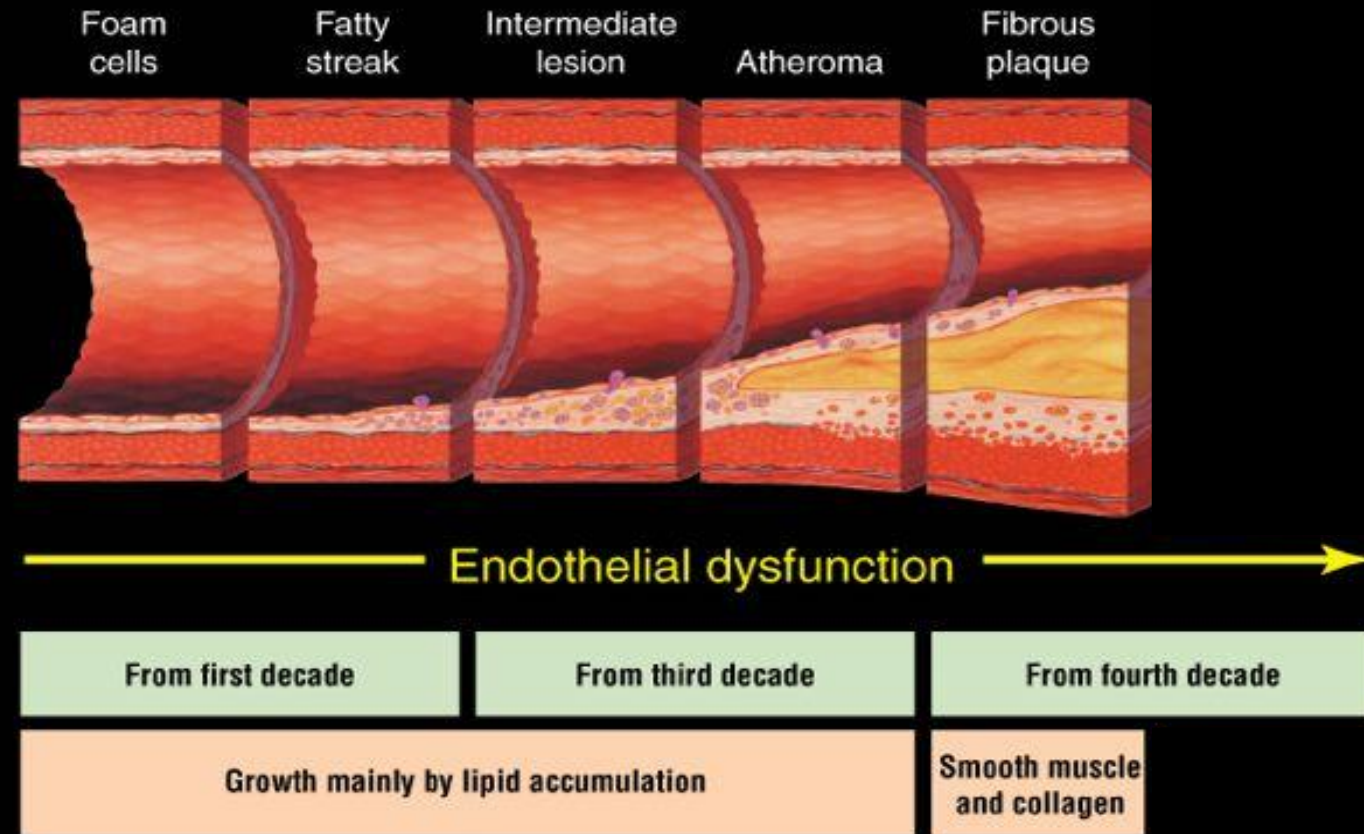
Coronary Disease

Stable

Acute/ unstable

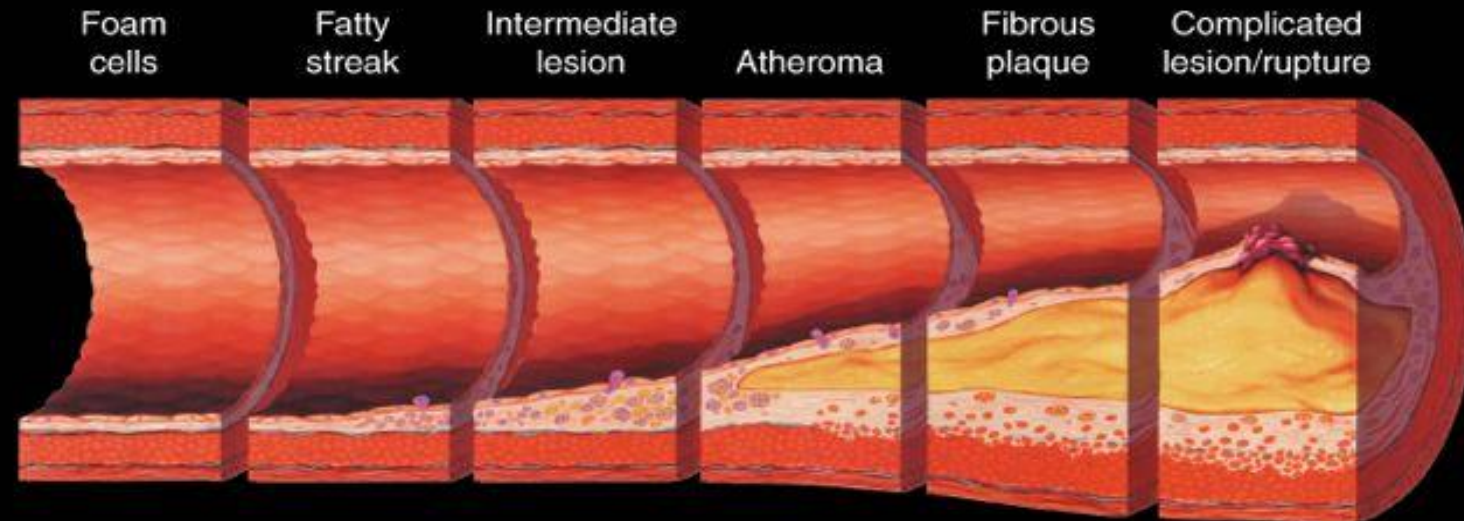


Atherosclerosis timeline



Adapted from Pepine C.J. *Am J Cardiol.* 1998;82(suppl 104).

Atherosclerosis timeline

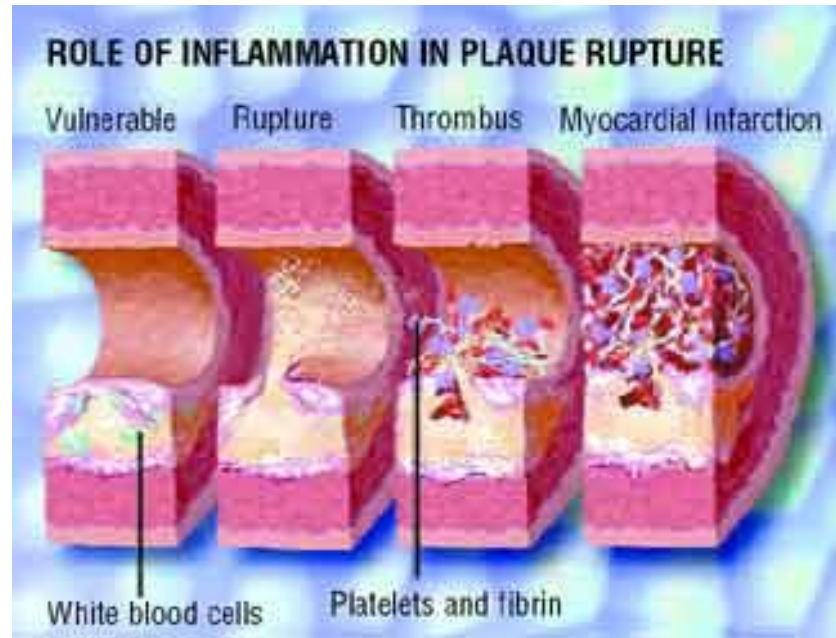


———— Endothelial dysfunction ———→

From first decade	From third decade	From fourth decade
Growth mainly by lipid accumulation		Smooth muscle and collagen
		Thrombosis, hematoma

Adapted from Pepine C.J. *Am J Cardiol.* 1998;82(suppl 104).

Acute coronary syndrome pathophysiology



Falk E, et al. *Circulation*. 1998;92:657-671.

Causes of Myocardial Infarction

In the **general population**, $\geq 70\%$ of the risk of MI in the population accounted for by:

1. Smoking
2. Diabetes
3. Hypertension
4. Abdominal obesity
5. Alcohol (protective at low levels; harmful at high levels)
6. Psychosocial characteristics
7. Low fruit & vegetable intake
8. Low physical activity
9. Cholesterol levels
10. Low muscle strength

Yusuf, *et al. Lancet* 2004; 364:937

Yusuf *et al. Lancet* 2005; 366: 1640

Teo *et al. Lancet* 2006; 368: 647

Rosengren, *et al. Lancet* 2004; 364: 953

Leong *et al. Circulation* 2014; 130: 390

Smyth, *et al. Lancet* 2015; 386: 1945

Leong *et al. Lancet* 2015; 386: 266

Causes of Myocardial Infarction

In the **general population**, $\geq 90\%$ of the risk of MI in the population accounted for by:

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2. Diabetes
3. Hypertension
4. Abdominal obesity
5. Alcohol (protective at low levels; harmful at high levels)
6. Psychosocial characteristics
7. Low fruit & vegetable intake
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Epidemiology of CVD in PC patients

- patients are deemed to be high risk if they have a global risk estimate for hard CVD events of $\geq 2\%$ per year

Greenland *et al.* 2010 American Heart Association Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults. *Circulation* 2010; 122: e584

US Veterans with Locoregional PC

Incidence of CVD (% per year)

Treatment	Coronary heart disease	MI	Sudden Cardiac Death	Stroke
No ADT	8.1	0.73	1.15	1.08

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GnRH agonist	14.4	1.28	2.16	1.85

US Veterans with Locoregional PC

Incidence of CVD (% per year)

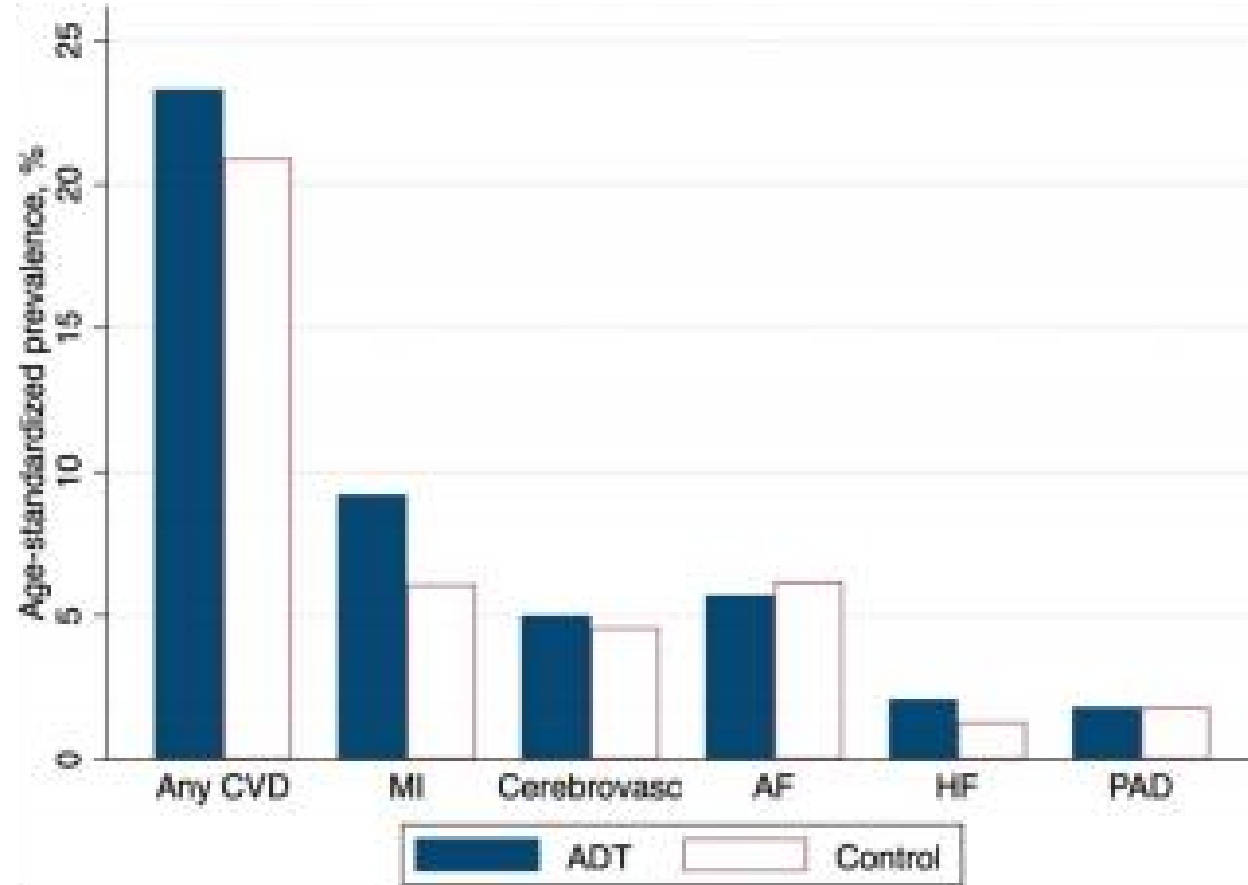
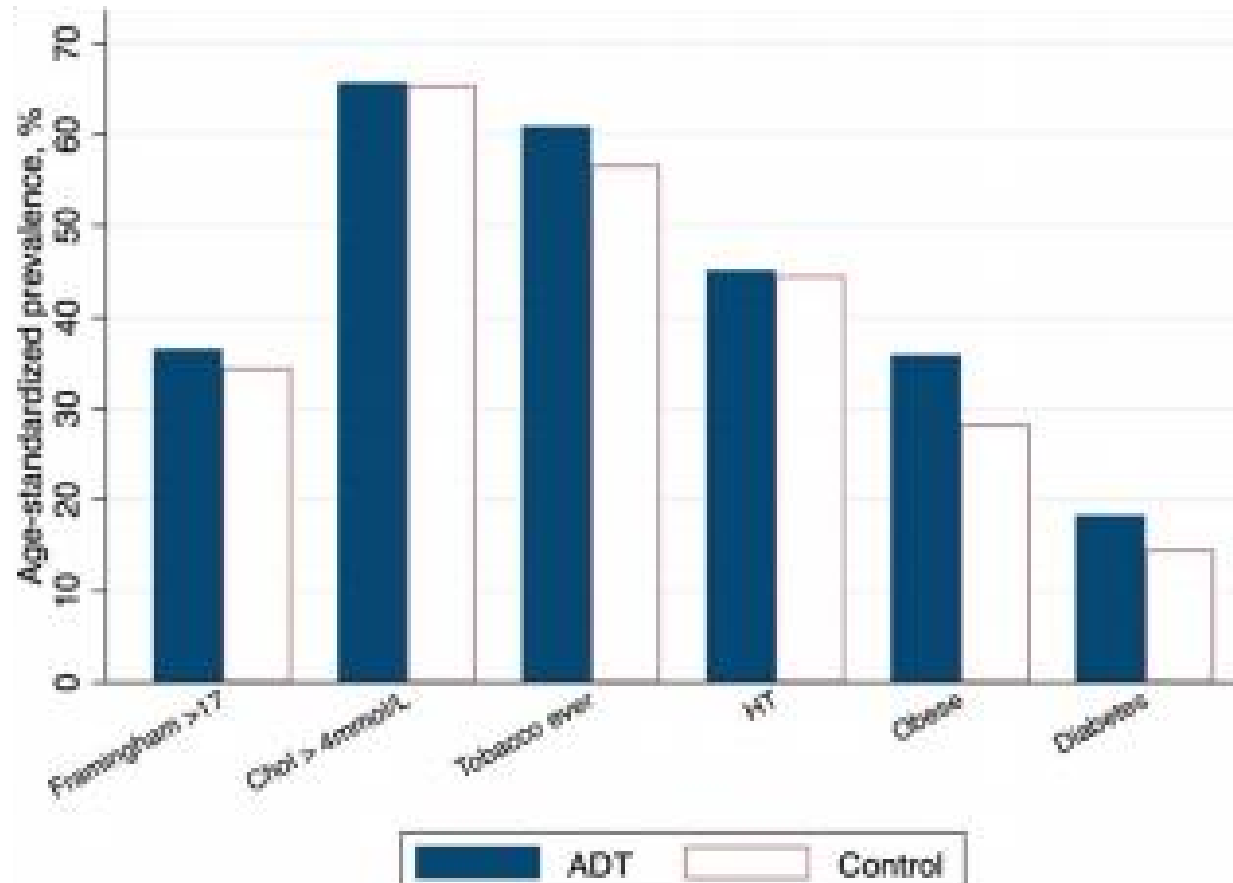
Treatment	Coronary heart disease	MI	Sudden Cardiac Death	Stroke
No ADT	8.1	0.73	1.15	1.08
GnRH agonist	14.4	1.28	2.16	1.85
Orchiectomy	21.1	2.43	2.33	2.62
Combined androgen blockade	15.8	1.02	2.01	1.48
Oral antiandrogen	14.3	1.12	1.88	1.49



The Role of Androgen Deprivation Therapy in Cardiovascular Disease – A Longitudinal Prostate Cancer Study (RADICAL PC1)

A RandomizeD Intervention for Cardiovascular And Lifestyle Risk Factors in Prostate Cancer Patients (RADICAL PC2)

Baseline Characteristics



Preventing Cardiovascular Disease (in Individuals without known CVD)

1. Use a risk-prediction tool (e.g. Framingham risk score)
2. Healthy diet
3. ≥ 150 minutes/week moderate intensity exercise
4. Those with diabetes – may benefit from SGLT2-I
5. Quit smoking
6. Aspirin should not be used routinely
7. Statin should be used in higher risk individuals
8. For those with hypertension, target BP $< 130/80$

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The evaluation of cardiovascular risk – Framingham Risk Score

- Age
- HDL-C
- Total cholesterol
- Systolic blood pressure
- Smoker
- Diabetes

The evaluation of cardiovascular risk

FRAMINGHAM RISK SCORE (FRS) Estimation of 10-year Cardiovascular Disease (CVD) Risk

Date: _____
Patient's Name: _____

Step 1¹

In the "points" column enter the appropriate value according to the patient's age, HDL-C, total cholesterol, systolic blood pressure, and if they smoke or have diabetes. Calculate the total points.

Risk Factor	Risk Points		Points	
	Men	Women		
Age				
30-34	0	0		
35-39	2	2		
40-44	5	4		
45-49	7	5		
50-54	8	7		
55-59	10	8		
60-64	11	9		
65-69	12	10		
70-74	14	11		
75+	15	12		
HDL-C (mmol/L)				
>1.6	-2	-2		
1.3-1.6	-1	-1		
1.2-1.29	0	0		
0.9-1.19	1	1		
<0.9	2	2		
Total Cholesterol				
<4.1	0	0		
4.1-5.19	1	1		
5.2-6.19	2	3		
6.2-7.2	3	4		
>7.2	4	5		
Systolic Blood Pressure (mmHg)	Not Treated	Treated	Not Treated	Treated
<120	-2	0	-3	-1
120-129	0	2	0	2
130-139	1	3	1	3
140-149	2	4	2	5
150-159	2	4	4	6
160+	3	5	5	7
Smoker	Yes	4	3	
No	0	0	0	
Diabetes	Yes	2	4	
No	0	0	0	
Total Points				

Step 2¹

Using the total points from Step 1, determine the 10-year CVD risk* (%).

Total Points	10-Year CVD Risk (%)*	
	Men	Women
-3 or less	<1	<1
-2	1.1	<1
-1	1.4	1.0
0	1.6	1.2
1	1.9	1.5
2	2.3	1.7
3	2.8	2.0
4	3.3	2.4
5	3.9	2.8
6	4.7	3.3
7	5.6	3.9
8	6.7	4.5
9	7.9	5.3
10	9.4	6.3
11	11.2	7.3
12	13.3	8.6
13	15.6	10.0
14	18.4	11.7
15	21.6	13.7
16	25.3	15.9
17	29.4	18.5†
18	>30	21.5
19	>30	24.8
20	>30	27.5
21+	>30	>30

Step 3¹

Using the total points from Step 1, determine heart age (in years).

Heart Age, y	Men	Women
<30	<0	<1
30	0	
31		1
32	1	
34	2	2
36	3	3
38	4	
39		4
40	5	
42	6	5
45	7	6
48	8	7
51	9	8
54	10	
55		9
57	11	
59		10
60	12	
64	13	11
68	14	12
72	15	
73		13
76	16	
79		14
>80	≥17	15*

* Double cardiovascular disease risk percentage for individuals between the ages of 30 and 50 without diabetes if the presence of a positive history of premature cardiovascular disease is present in a first-degree relative before 55 years of age for men and before 65 years of age for women. This is known as the modified Framingham Risk Score.¹

Step 4^{2,3}

Using 10-year CVD risk from Step 2, determine if patient is Low, Moderate or High risk.¹ Indicate Lipid and/or Apo B targets

Risk Level ¹	Initiate Treatment If:	Primary Target (LDL-C)	Alternate Target
High FRS ≥20%	• Consider treatment in all (Strong, High)	• ≤2 mmol/L or ≥50% decrease in LDL-C (Strong, Moderate)	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L (Strong, High)
Intermediate FRS 10-19%	• LDL-C ≥3.5 mmol/L (Strong, Moderate) • For LDL-C <3.5 mmol/L consider if: • Apo B ≥1.2 g/L • OR Non-HDL-C ≥4.3 mmol/L (Strong, Moderate) • Men ≥50 and women ≥60 with 1 risk factor: low HDL-C, impaired fasting glucose, high waist circumference, smoker, hypertension	• ≤2 mmol/L or ≥50% decrease in LDL-C (Strong, Moderate)	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L (Strong, Moderate)
Low FRS <10%	• statins generally not indicated	• statins generally not indicated	• statins generally not indicated
Statin-indicated conditions**	• Clinical atherosclerosis* • Abdominal aortic aneurysm • Diabetes mellitus Age ≥ 40 years 15-Year duration for age ≥ 30 years (DM1) Microvascular disease • Chronic kidney disease (age ≥ 50 years) eGFR <60 mL/min/1.73 m ² or ACR > 3 mg/mmol		

Lipid targets LDL-C: _____ or Apo B: _____

¹ Adapted from: D'Agostino RB et al (i). General cardiovascular risk profile for use in primary care: The Framingham Heart Study. Circ 2008;117:743-53.

² Adapted from: Genest J et al (ii). 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult. Can J Cardiol. 2009;25(10):967-979.

³ Adapted from: Anderson T et al (i). 2012 Update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013;29(2):151-167.

* apoB: apolipoprotein B statin. CVD: cardiovascular disease, FRS: Framingham Risk Score, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.

** Statins indicated as initial therapy

** Consider LDL-C < 1.8 mmol/L for subjects with acute coronary syndrome (ACS) within past 3 months

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2. **Healthy diet**
3. ≥ 150 minutes/week moderate intensity exercise
4. Those with diabetes – may benefit from SGLT2-I
5. Quit smoking
6. Aspirin should not be used routinely
7. Statin should be used in higher risk individuals
8. For those with hypertension, target BP $< 130/80$

Healthy Diet

- High fruit, vegetables, nuts, whole grains
- Lower refined carbohydrates and sugary beverages

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For discussion – diabetes management

Metformin	SGLT2-inhibitors (canagliflozin, dapagliflozin, empagliflozin)
Reduces adiposity and improves dysglycemia in ADT recipients	Reduce: <ul style="list-style-type: none">• Cardiovascular death, MI or stroke in patients with diabetes at higher CV risk• Death or severe heart failure in patients with heart failure & reduced ejection fraction• Deterioration in renal function or cardiovascular death in patients with eGFR 25-75ml/min/1.73m² BSA

Zhu, *et al. Urol Int* 2017; 98: 79

Zinman, *et al. NEJM* 2015; 373: 2117

McMurray, *et al. NEJM* 2019; 381: 1995

Heerspink, *et al. NEJM* 2020; 383: 1436

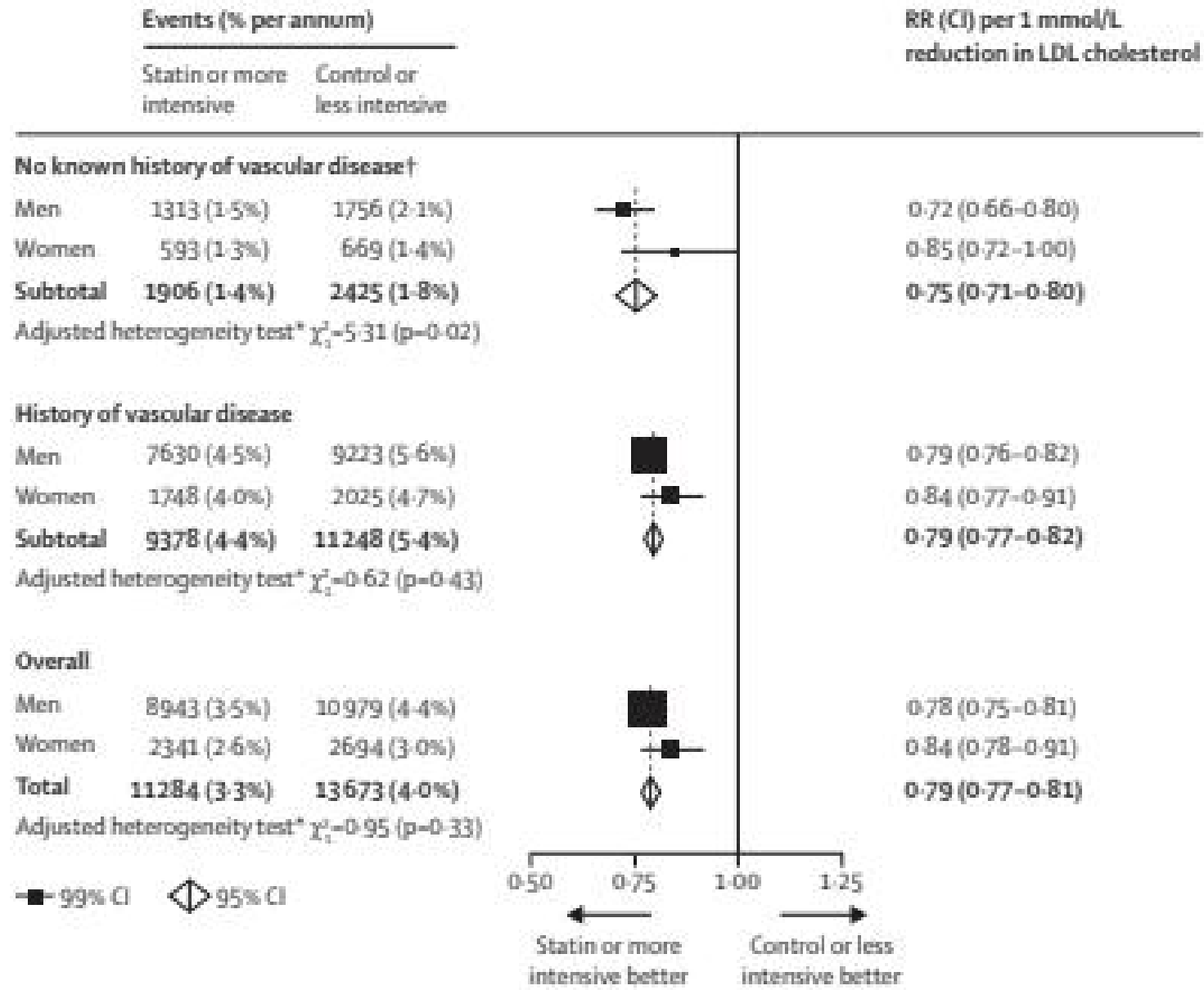
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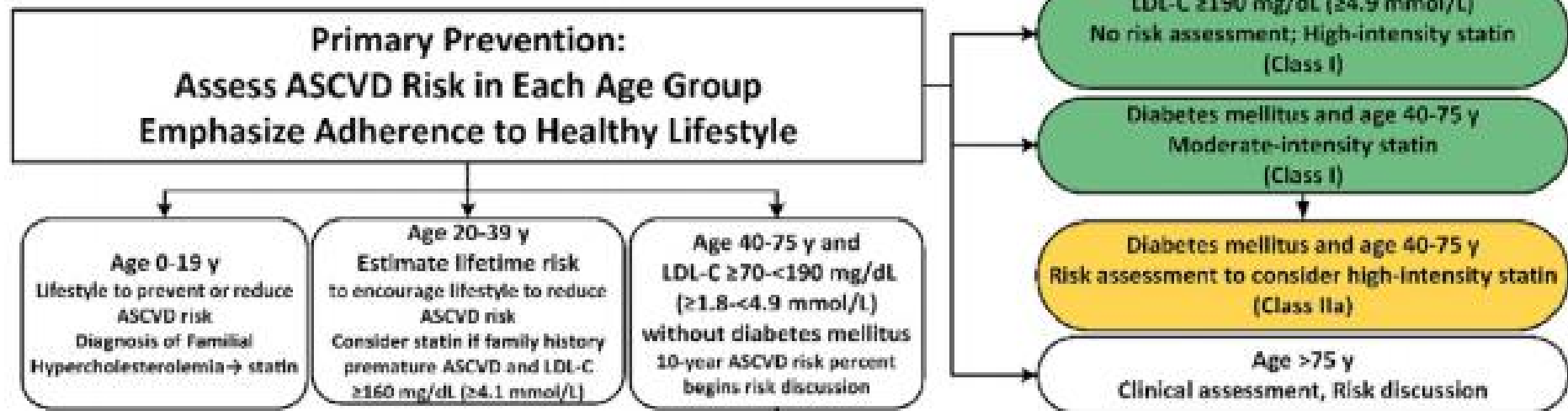
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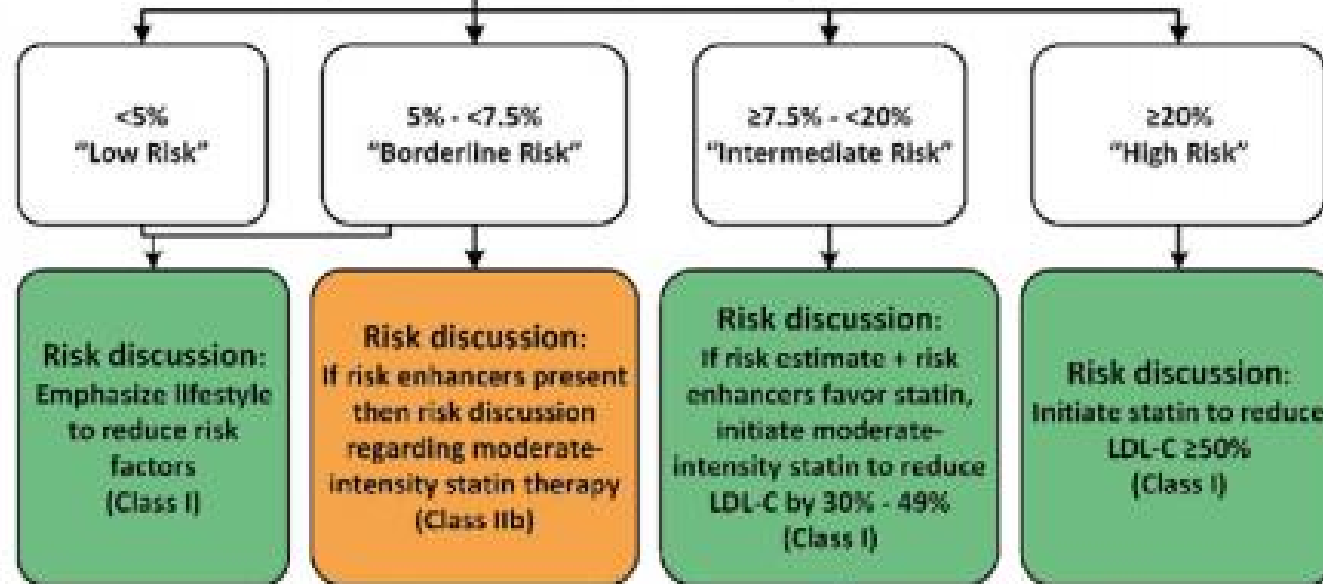
Statin effects on major cardiovascular events



Lancet 2015;
385: 1397



- ASCVD Risk Enhancers:**
- Family history of premature ASCVD
 - Persistently elevated LDL-C ≥ 160 mg/dL (≥ 4.1 mmol/L)
 - Chronic kidney disease
 - Metabolic syndrome
 - Conditions specific to women (e.g., preeclampsia, premature menopause)
 - Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
 - Ethnicity (e.g., South Asian ancestry)
- Lipid/Biomarkers:**
- Persistently elevated triglycerides (≥ 175 mg/dL, (≥ 2.0 mmol/L))
- In selected individuals if measured:**
- hs-CRP ≥ 2.0 mg/L
 - Lp(a) levels > 50 mg/dL or > 125 nmol/L
 - apoB ≥ 130 mg/dL
 - Ankle-brachial index (ABI) < 0.9



**If risk decision is uncertain:
Consider measuring CAC in selected adults:**

CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)

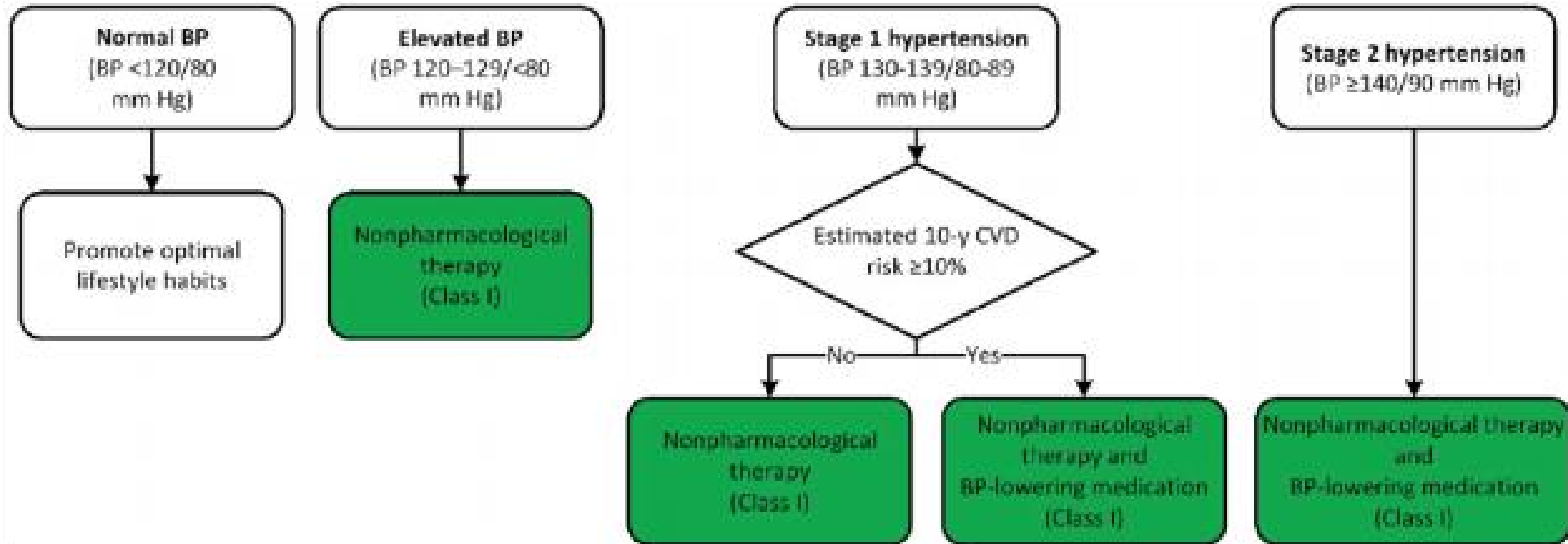
CAC = 1-99 favors statin (especially after age 55)

CAC = 100+ and/or ≥ 75 th percentile, initiate statin therapy

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Blood pressure control



Conclusion

- To have your cake (i.e. no PC treatment-related complications with active surveillance) and eat it too (i.e. avoid dying from competing risks, like CVD), preventing CVD is of high importance