

## Epidemiologie

### Intervenční studie – Mendelian randomisation – systematické přehledy literatury

### Cvičení

#### Příklad 1

**Effects of Long-term Vitamin E Supplementation on Cardiovascular Events and Cancer: A Randomized Controlled Trial**

The HOPE and HOPE-TOO Trial Investigators

*JAMA*. 2005;293(11):1338-1347. doi:10.1001/jama.293.11.1338

**Context** Experimental and epidemiological data suggest that vitamin E supplementation may prevent cancer and cardiovascular events. Clinical trials have generally failed to confirm benefits, possibly due to their relatively short duration.

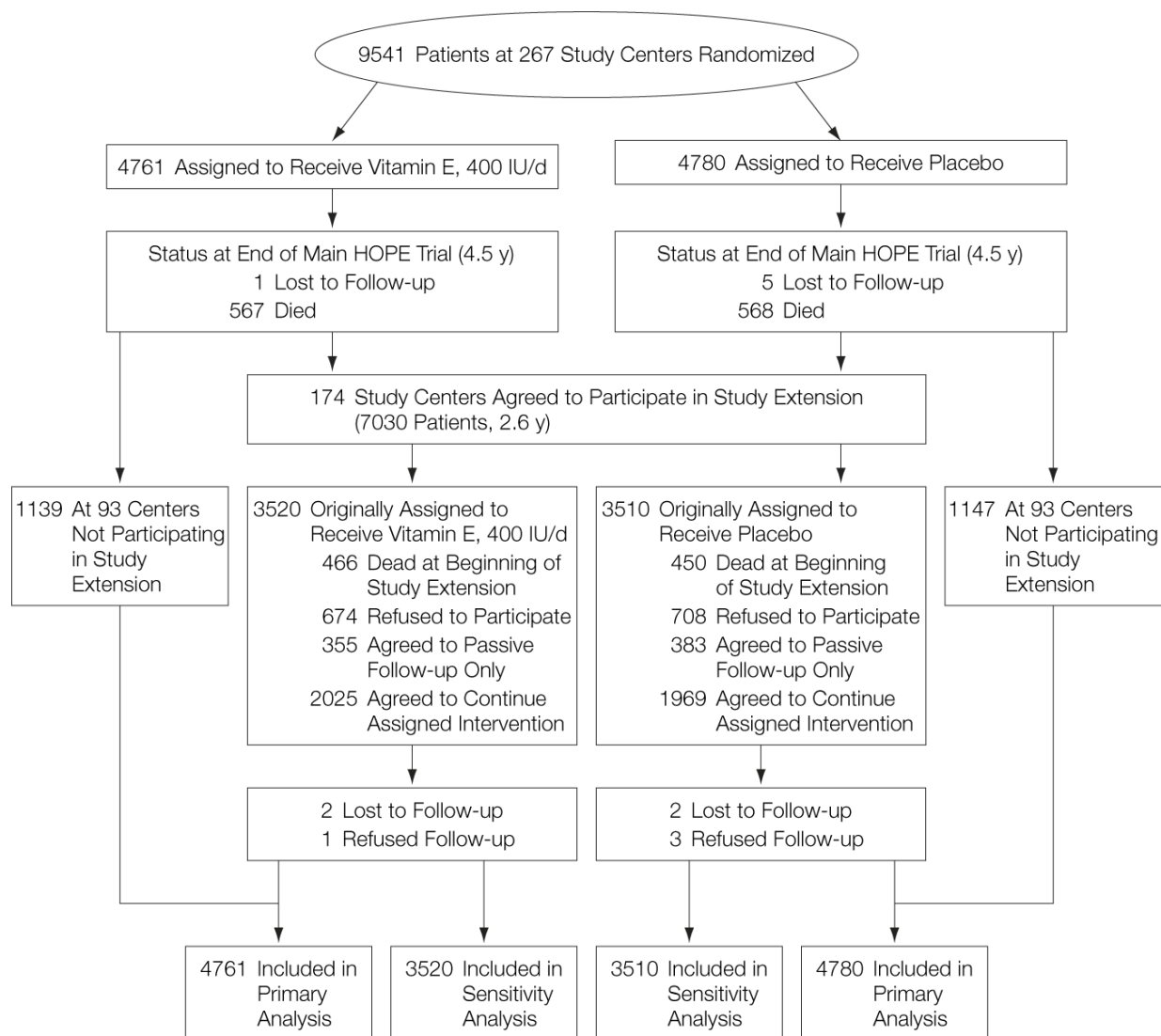
**Objective** To evaluate whether long-term supplementation with vitamin E decreases the risk of cancer, cancer death, and major cardiovascular events.

**Design, Setting, and Patients** A randomized, double-blind, placebo-controlled international trial (the initial Heart Outcomes Prevention Evaluation [HOPE] trial conducted between December 21, 1993, and April 15, 1999) of patients at least 55 years old with vascular disease or diabetes mellitus was extended (HOPE–The Ongoing Outcomes [HOPE-TOO]) between April 16, 1999, and May 26, 2003. Of the initial 267 HOPE centers that had enrolled 9541 patients, 174 centers participated in the HOPE-TOO trial. Of 7030 patients enrolled at these centers, 916 were deceased at the beginning of the extension, 1382 refused participation, 3994 continued to take the study intervention, and 738 agreed to passive follow-up. Median duration of follow-up was 7.0 years.

**Intervention** Daily dose of natural source vitamin E (400 IU) or matching placebo.

**Main Outcome Measures** Primary outcomes included cancer incidence, cancer deaths, and major cardiovascular events (myocardial infarction, stroke, and cardiovascular death). Secondary outcomes included heart failure, unstable angina, and revascularizations.

Figure 1



**Table 4.** Incidence and Relative Risks of Major Vascular Events, Deaths, and Secondary Cardiovascular Outcomes

	No. (%) of Patients		Relative Risk (95% Confidence Interval)	P Value*
	Received Vitamin E	Received Placebo		
<b>Primary Analysis (All HOPE Study Patients, N = 9541)</b>				
Major vascular events and deaths				
Myocardial infarction, stroke, or death from cardiovascular causes	1022 (21.5)	985 (20.6)		
Myocardial infarction	724 (15.2)	686 (14.4)		
Stroke	270 (5.7)	246 (5.1)		
Death from cardiovascular causes	482 (10.1)	475 (9.9)		
Death from any cause	799 (16.8)	801 (16.8)		
Secondary cardiovascular outcomes				
Hospitalization for unstable angina	712 (15.0)	698 (14.6)		
Revascularization and limb amputation	1082 (22.7)	1013 (21.3)		
All heart failure	641 (13.5)	578 (12.1)		
Hospitalization for heart failure	236 (5.0)	196 (4.1)		
<b>Sensitivity Analysis (Patients at Centers Contin in the HOPE-TOO Trial Extension, N = 7030)</b>				
Major vascular events and deaths				
Myocardial infarction, stroke, or death from cardiovascular causes	807 (22.9)	769 (21.9)		
Myocardial infarction	580 (16.5)	534 (15.2)		
Stroke	208 (5.9)	191 (5.4)		
Death from cardiovascular causes	364 (10.3)	361 (10.3)		
Death from any cause	620 (17.6)	604 (17.2)		
Secondary cardiovascular outcomes				
Hospitalization for unstable angina	565 (16.1)	547 (15.6)		
Revascularization and limb amputation	882 (25.1)	822 (23.4)		
All heart failure	519 (14.7)	443 (12.6)		
Hospitalization for heart failure	203 (5.8)	146 (4.2)		

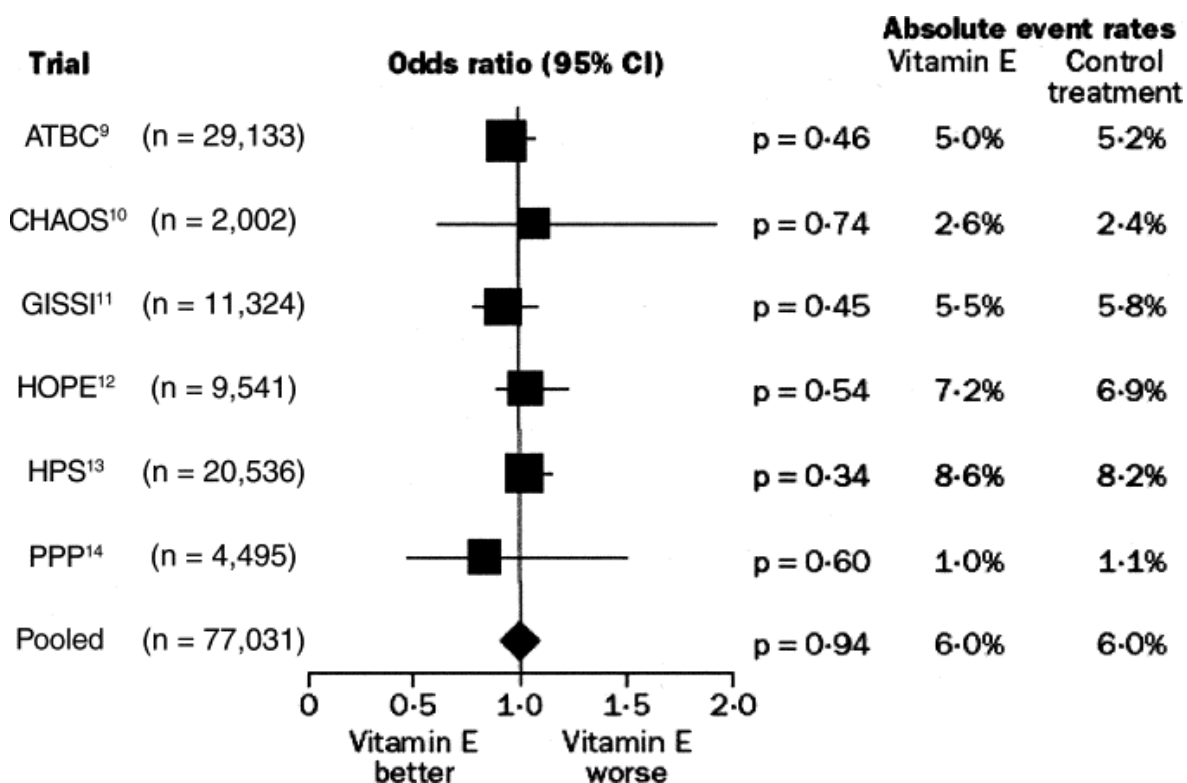
Abbreviations: HOPE, Heart Outcomes Prevention Evaluation Study; HOPE-TOO, HOPE-TOO Trial Extension. \*Log-rank test.

**Otázky:**

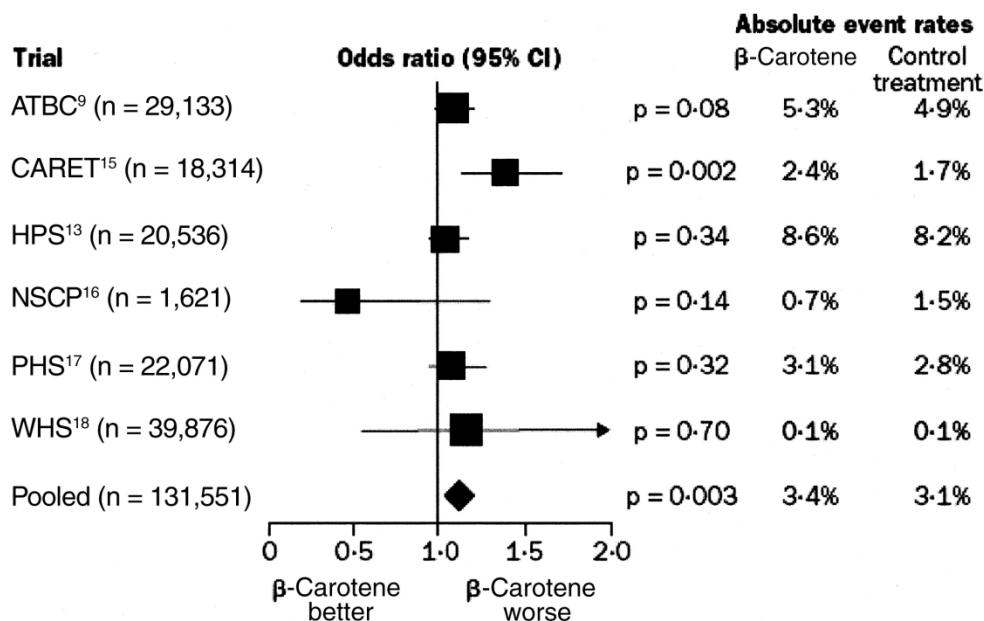
1. Popište stručně cíle této studie
2. Co byla expozice?
3. Co byla hlavní závislá proměnná?
4. Jaká byla studovaná populace a kritéria pro vstup participantů do studie?
5. Jaká byla účast pozvaných?
6. Co soudíte o velikosti této studie?
7. Jaké jsou rozdíly v úbytku participantů mezi oběma větvemi studie (Figure 1)?
8. Table 4: Bez počítání – co soudíte o vlivu suplementace vitamínem 4 na riziko KVO?
9. Spočítejte relativní rizika pro major vascular events in the primary analysis (Table 4)
10. Myslíte, že tato relativní rizika jsou statisticky významná?

## Příklad 2

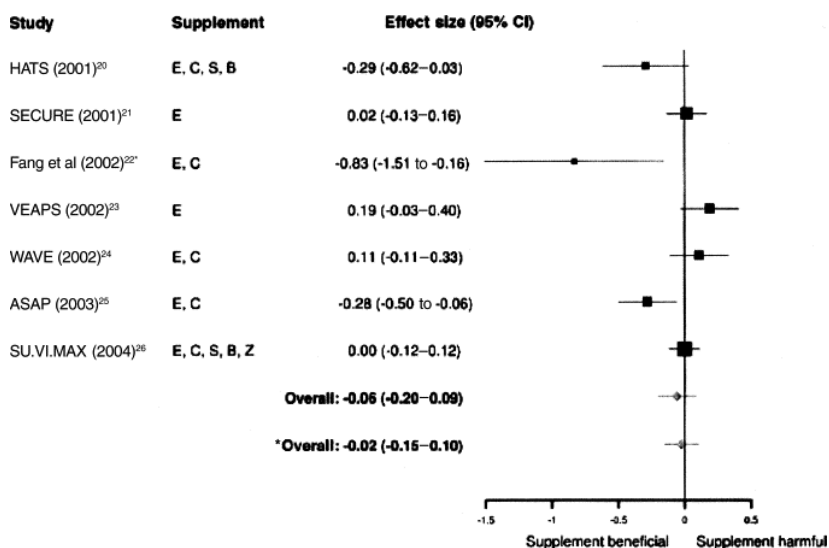
**Figure 2.** Meta-analysis of 7 randomized trials involving 81,788 patients comparing the risk of cardiovascular death among those randomized to placebo or vitamin E (Breslow-Day test,  $p = 0.73$ ). ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention trial; CHAOS = Cambridge Heart Antioxidant Study; CI = confidence interval; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto; HOPE = Heart Outcomes Prevention Evaluation; HPS = Heart Protection Study; PPP = Primary Prevention Project.



**Figure 3.** Meta-analysis of 8 randomized trials involving 138,113 patients comparing the risk of cardiovascular death among those randomized to placebo or  $\beta$ -carotene (Breslow-Day test,  $p = 0.12$ ).



**Figure 4.** Meta-analysis of 7 antioxidant trials (N = 3,130) studying atherosclerotic disease progression using imaging techniques. ASAP = Antioxidant Supplementation in Atherosclerosis Prevention; HATS = HDL Atherosclerosis Treatment Study; SECURE = Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E; SU.VI.MAX = The Supplémentation en Vitamines et Minéraux Antioxydants; VEAPS = Vitamin E Atherosclerosis Prevention Study; WAVE = Women's Angiographic Vitamin and Estrogen.



### Otázky:

1. O jaký typ studií se jedná?
2. Popište výsledky v grafech 2-4
3. Jaký je vliv suplementace vitamíny na riziko KVO?

### Příklad 3

#### Otázky:

1. Jaké jsou principy Mendelovské randomizace?

1. Dovedete si představit Mendelovskou randomizaci na vztah antioxidantních vitamínů a rizika KVO? Jak by taková studie asi vypadala?

3. Jaké informace/data by byly k takové studii potřeba?

4. Podívejte se na obrázek níže (týká se beta-karotenu a diabetu). Dokázali byste tento graf interpretovat? (z Perry et al., 2009)

