What's New in Other Risk Management?

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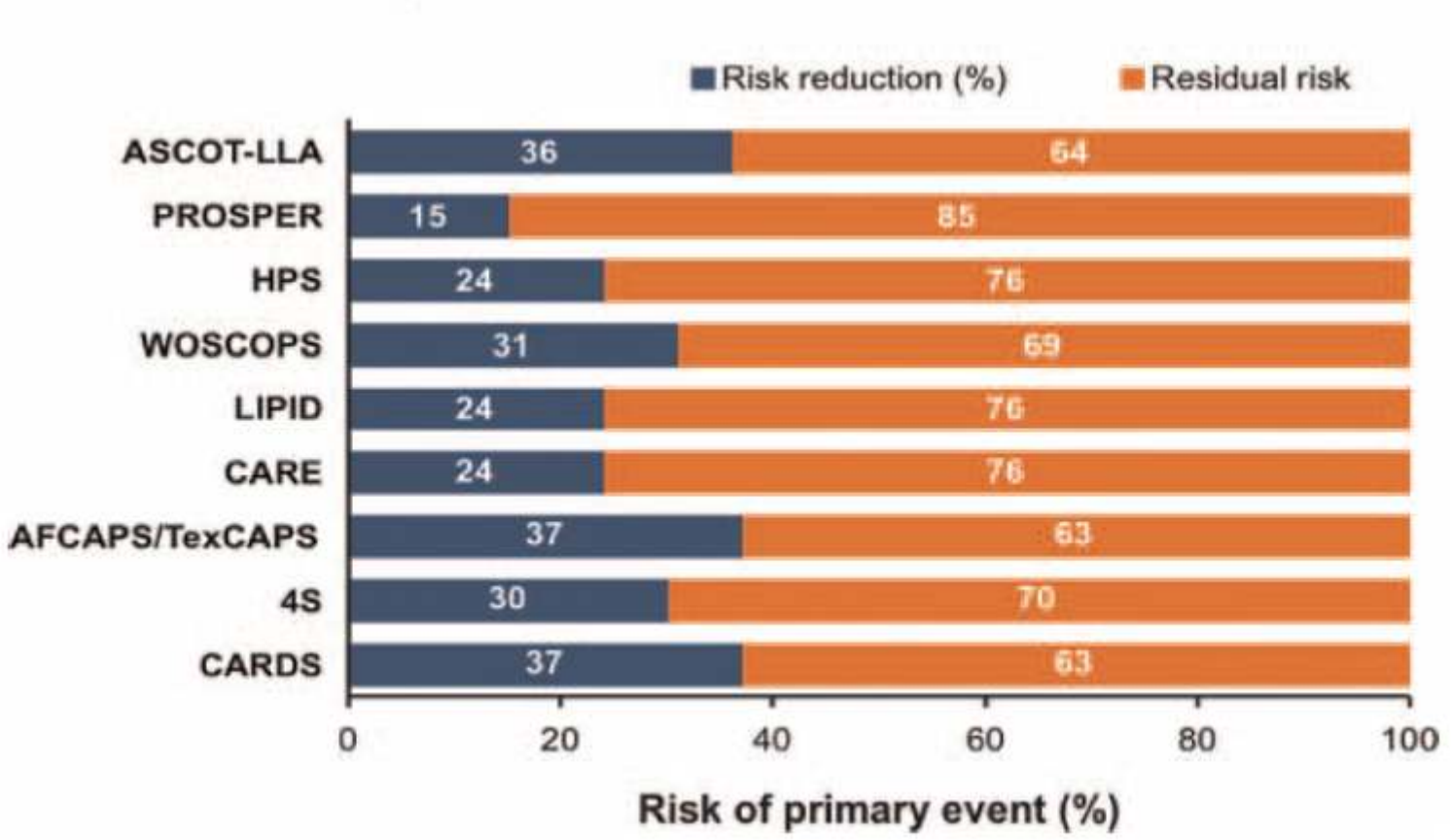
Residual risk after statin treatment in major intervention trials



Rapezzi. Journal of Hypertension. 2010;28:e606-e607

Treating hypertension only reduces CHD risk ≈25%

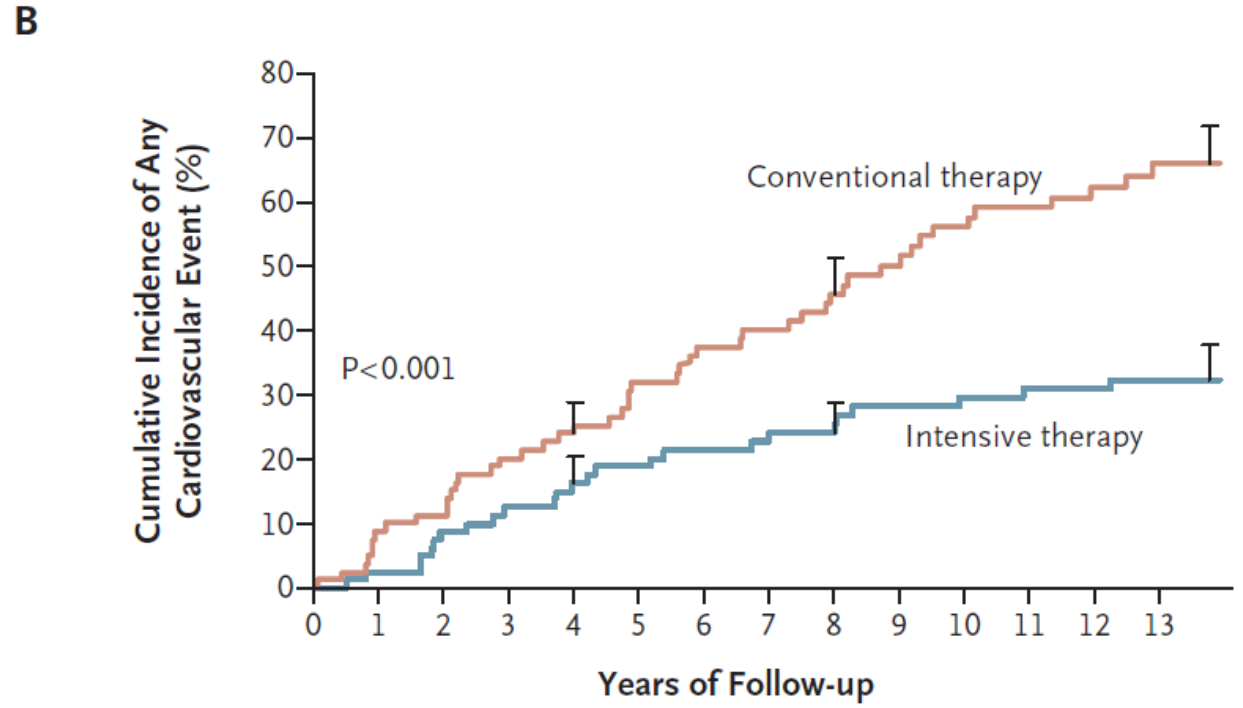
Table 2. Fixed and Random Effects Meta-analysis Comparing any Antihypertensive Drug Treatment vs No Treatment for Each Outcome*

Outcome	No. of Trials	Effects Model	RR (95% CI)	*P* Value for Heterogeneity
Coronary heart disease	24	Fixed	0.86 (0.80-0.93)	.55
		Random	0.87 (0.80-0.94)	.55
Stroke	23	Fixed	0.69 (0.64-0.74)	.004
		Random	0.68 (0.61-0.76)	.004
CHF	7	Fixed	0.54 (0.45-0.66)	.66
		Random	0.60 (0.49-0.74)	.80
Major CVD events	28	Fixed	0.78 (0.74-0.81)	<.001
		Random	0.73 (0.62-0.87)	<.001
CVD mortality	23	Fixed	0.84 (0.78-0.90)	.10
		Random	0.84 (0.78-0.90)	.10
Total mortality	25	Fixed	0.90 (0.85-0.95)	.58
		Random	0.90 (0.85-0.95)	.59

Abbreviations: CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.
*The no treatment comparison group includes placebo-treated controls, participants not treated in open trials, and participants receiving usual care.

Psaty et al. JAMA. 2003;289(19):2534-44.

Effect of a multifactorial intervention on cardiovascular event in type 2 diabetes



No. at Risk								
Intensive therapy	80	72	65	61	56	50	47	31
Conventional therapy	80	70	60	46	38	29	25	14

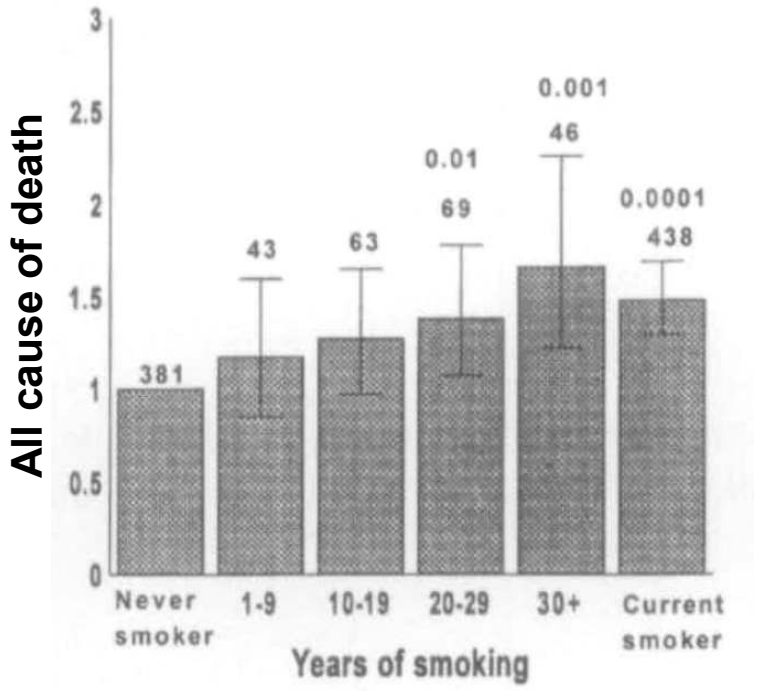
Gaede et al. N Engl J Med. 2008;358(6):580-91.

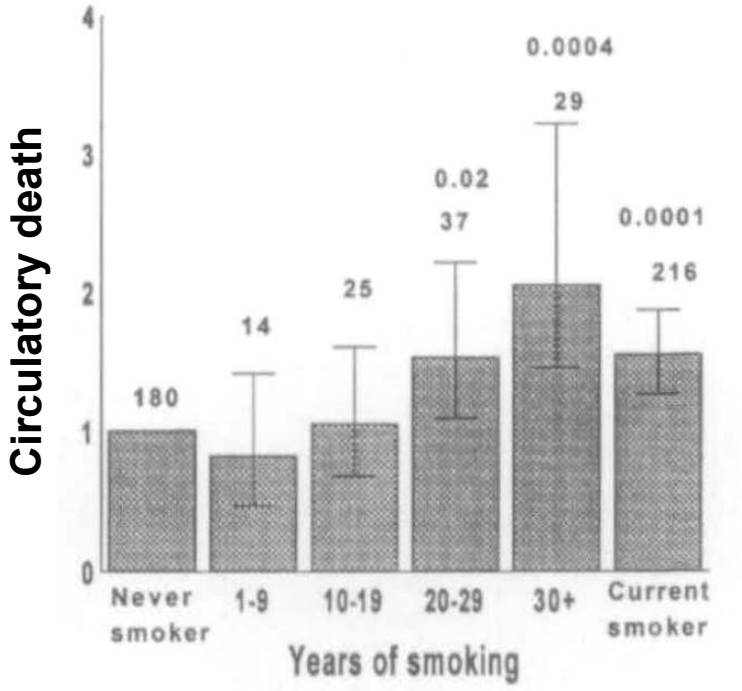
Strategies for Cardiovascular Protection in Patients with Type 2 Diabetes

1. Lipid-modifying therapies
2. Blood pressure control
3. Smoking cessation
4. Antiplatelet therapy
5. Exercise and physical activity
6. Nutrition therapy

Smoking Cessation

Smoking, in individuals with diabetes, is an independent risk factor for all-cause and cardiovascular mortality





Mortality rate ratios, 95% CIs, the number of deaths, and P values for all-cause and cardiovascular deaths for ex-smokers, compared with current smokers and nonsmokers, by the number of years of smoking. All rate ratios were adjusted for age and duration of diabetes

Chaturvedi et al. Diabetes Care. 1997;20(8):1266-72.

Aspirin/Antiplatelet Therapy

In primary prevention without previous CVD, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds

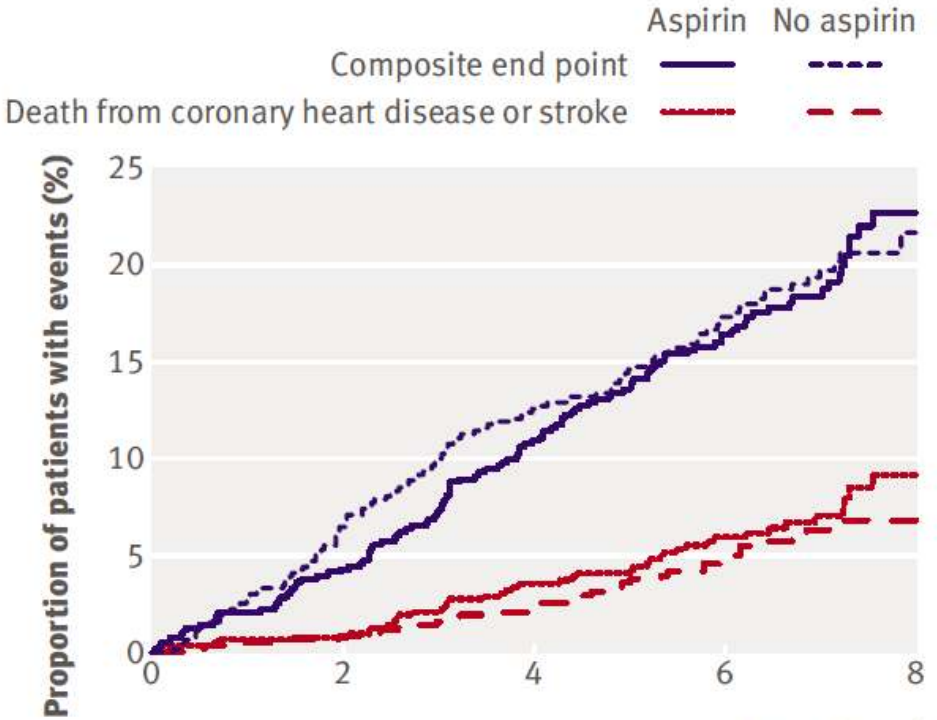
	Number of events (aspirin vs control)		Rate ratio (95% CI) (aspirin vs control)			Yearly absolute difference (% per year)	
	Primary prevention (660 000 person-years)	Secondary prevention (43 000 person-years)	Primary prevention	Secondary prevention	p value for heterogeneity	Primary prevention	Secondary prevention
Major coronary event	934 vs 1115	995 vs 1214	0·82 (0·75–0·90)	0·80 (0·73–0·88)	0·7	−0·06	−1·00*
Non-fatal MI	596 vs 756	357 vs 505	0·77 (0·69–0·86)	0·69 (0·60–0·80)	0·5	−0·05	−0·66
CHD mortality	372 vs 393	614 vs 696	0·95 (0·82–1·10)	0·87 (0·78–0·98)	0·4	−0·01	−0·34
Stroke	655 vs 682	480 vs 580	0·95 (0·85–1·06)	0·81 (0·71–0·92)	0·1	−0·01	−0·46*
Haemorrhagic	116 vs 89	36 vs 19	1·32 (1·00–1·75)	1·67 (0·97–2·90)	0·4	0·01	..†
Ischaemic	317 vs 367	140 vs 176	0·86 (0·74–1·00)	0·78 (0·61–0·99)	0·5	−0·02	..†
Unknown cause	222 vs 226	304 vs 385	0·97 (0·80–1·18)	0·77 (0·66–0·91)	0·1	−0·001	..†
Vascular death	619 vs 637	825 vs 896	0·97 (0·87–1·09)	0·91 (0·82–1·00)	0·4	−0·01	−0·29
Any serious vascular event	1671 vs 1883 (0·51% vs 0·57% per year)	1505 vs 1801 (6·69% vs 8·19% per year)	0·88 (0·82–0·94)	0·81 (0·75–0·87)	0·1	−0·07	−1·49*
Major extracranial bleed	335 vs 219	23 vs 6	1·54 (1·30–1·82)	2·69 (1·25–5·76)	0·2	0·03	..†

MI=myocardial infarction. CHD=coronary heart disease. Non-fatal MI definitions vary; see methods. *Major coronary event rates (percent per year, aspirin vs control) 6·0 vs 7·4 in post-MI trials and 2·4 vs 3·0 in post-cerebral vascular disease trials; corresponding rates of stroke (mainly of unknown cause) 0·6 vs 0·8 in post-MI trials and 3·9 vs 4·7 in post-cerebral vascular disease trials (webappendix pp 14–18). †Stroke causes, and extracranial bleeds, very incompletely reported.

Table 2: **Comparison of proportional and absolute effects of aspirin in primary and secondary prevention trials**

ATT Collaboration. Lancet. 2009;373(9678):1849-60.

Factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease (POPADAD trial)



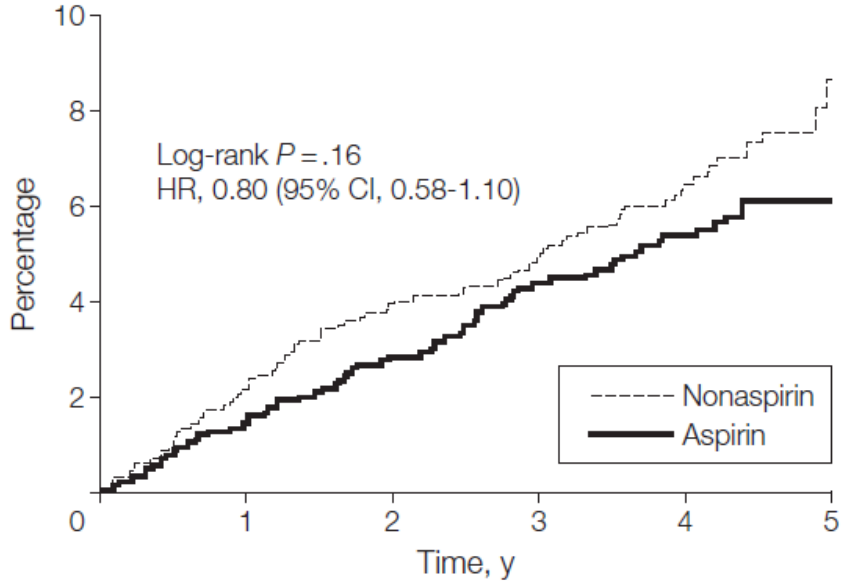
Numbers at risk for composite end point

Aspirin	638	599	543	399	48
No aspirin	638	590	534	381	48

Belch et al. BMJ. 2008;337:a1840

Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes

Figure 2. Total Percentage of Atherosclerotic Events According to Treatment Group



No. at risk						
Nonaspirin	1277	1220	1165	1117	813	135
Aspirin	1262	1210	1159	1095	806	140

CI indicates confidence interval; HR, hazard ratio.

Ogawa et al. JAMA. 2008;300(18):2134-41

Aspirin partially reduced the development of myocardial infarction in a mixed primary and secondary prevention trial of diabetic patients

Table 7.—Relative Risk of Cardiovascular Events by Study

Study	No. Enrolled	Total Mortality		Myocardial Infarction		Stroke		Important Vascular Events	
		No. of Events	Relative Risk	No. of Events	Relative Risk	No. of Events	Relative Risk	No. of Events	Relative Risk
Early Treatment Diabetic Retinopathy Study									
All follow-up	3711	706	0.91	524	0.83*	170	1.17	729	0.91
First 5 years	3711	476	0.80*	371	0.72†	139	1.16	537	0.82*
Physicians' Health Study[32]									
All enrolled	22071	444	0.96	378	0.56†	217	1.22	677	0.82†
Diabetics	533	NR‡		37	0.39	NR		NR	
Trial of British male doctors[33]	5139	421	0.90§	NR		NR		NR	
Antiplatelet Trialists' Collaboration[35]									
Nondiabetics	63762	NR		NR		NR		6261	0.77‖
Diabetics	4643	NR		NR		NR		885	0.81‖

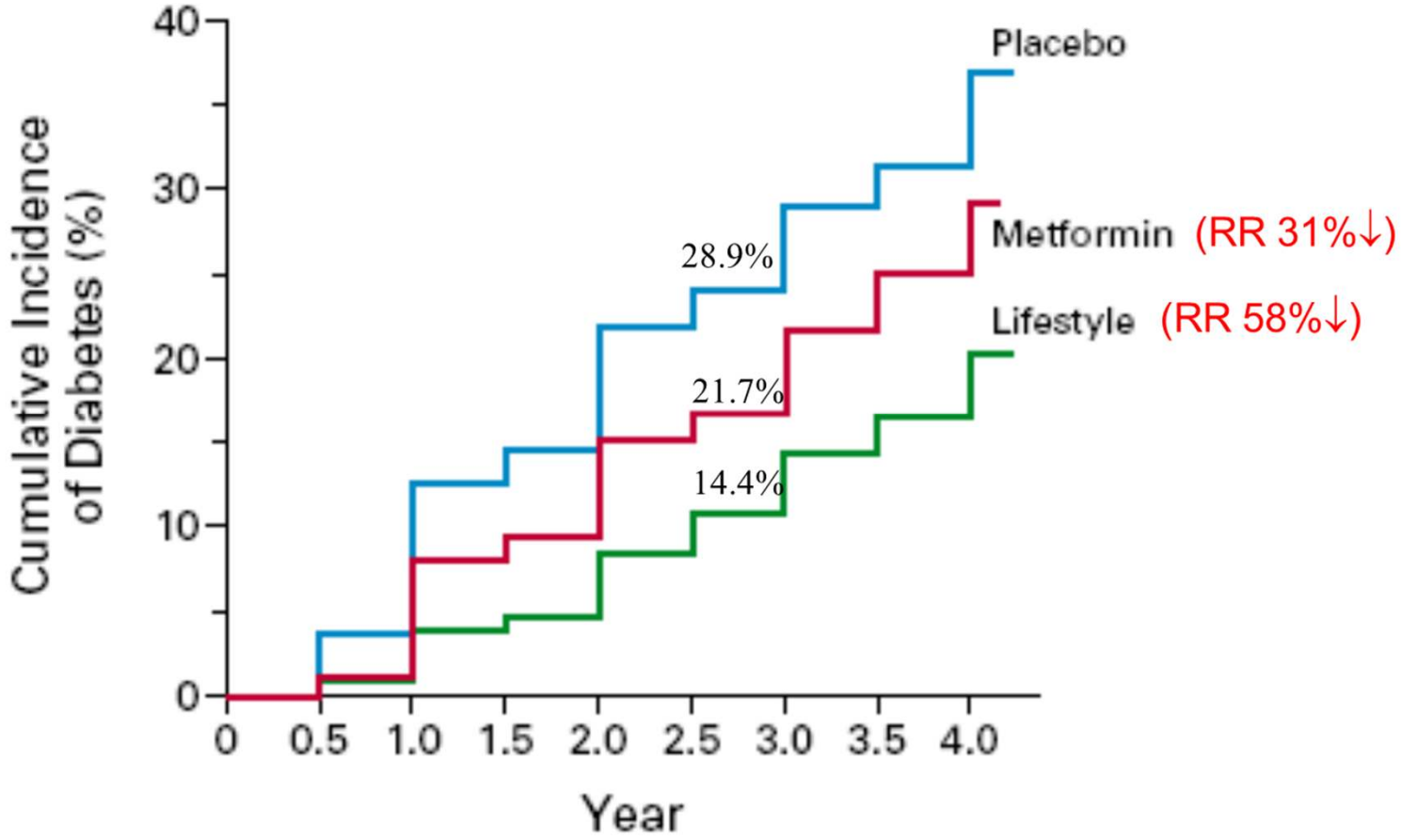
*$P \leq .05$.
†$P \leq .01$.
‡NR indicates not reported.
§Ratio of events to person-years.
‖Odds ratio.

ETDRS Investigators. JAMA 1992;268:1292-300.

Lifestyle Modification

Cumulative Incidence of Diabetes

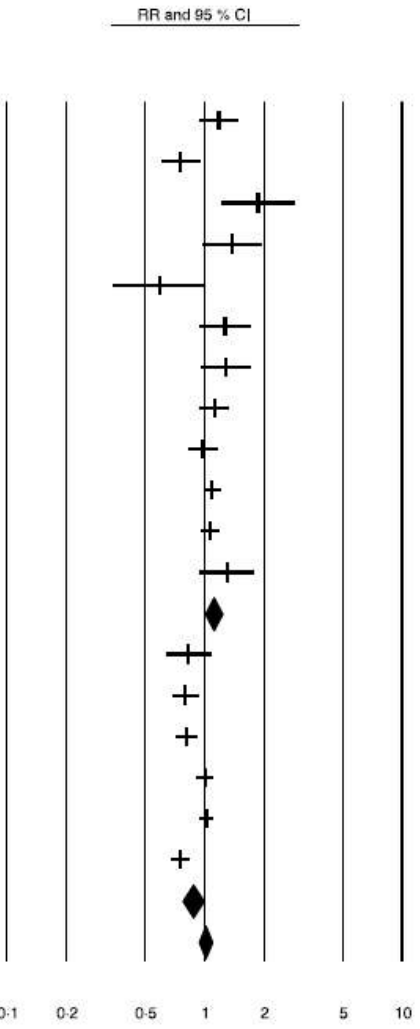
Diabetes Prevention Program



DPP Research Group. N Engl J Med. 2002;346(6):393-403.

Intentional weight loss *per se* had a neutral effect on all-cause mortality

Health status of group	Study name	Statistics for each study			
		RR	Lower limit	Upper limit	*P*
Healthy	French *et al.* (1999)[47]	1·18	0·94	1·48	0·153
Healthy	Gregg *et al.* (2003)[31]	0·76	0·60	0·97	0·025
Healthy	Sørensen *et al.* (2005)[8]	1·87	1·22	2·87	0·004
Healthy	Wannamethee *et al.* (2005)[10]	1·37	0·96	1·95	0·079
Healthy	Wannamethee *et al.* (2005)[10]	0·59	0·34	1·01	0·055
Healthy	Wedick *et al.* (2002)[56]	1·27	0·94	1·71	0·118
Healthy	Wedick *et al.* (2002)[56]	1·28	0·95	1·73	0·107
Healthy	Williamson *et al.* (1995)[45]	1·12	0·94	1·33	0·201
Healthy	Williamson *et al.* (1995)[45]	0·98	0·82	1·17	0·824
Healthy	Williamson *et al.* (1999)[48]	1·09	0·98	1·21	0·109
Healthy	Williamson *et al.* (1999)[48]	1·07	0·96	1·20	0·235
Healthy	Yaari & Goldbourt (1998)[46]	1·30	0·94	1·80	0·116
Healthy		1·11	1·00	1·22	0·050
Unhealthy	Gregg *et al.* (2004)[51]	0·83	0·63	1·09	0·175
Unhealthy	Williamson *et al.* (1995)[45]	0·80	0·68	0·94	0·007
Unhealthy	Williamson *et al.* (1995)[45]	0·81	0·71	0·92	0·001
Unhealthy	Williamson *et al.* (1999)[48]	1·01	0·91	1·12	0·851
Unhealthy	Williamson *et al.* (1999)[48]	1·02	0·94	1·11	0·641
Unhealthy	Williamson *et al.* (2000)[4]	0·75	0·67	0·84	0·000
Unhealthy		0·87	0·77	0·99	0·028
Overall		1·01	0·93	1·09	0·892



Harrington et al. Nutr Res Rev. 2009;22(1):93-108.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

- Does an intensive lifestyle intervention designed to produce weight loss decrease CVD morbidity and mortality in overweight and obese adults with type 2 diabetes?

Wing et al. N Engl J Med. 2013;369(2):145-54.

Look AHEAD: Study design

N = 5145
45-74 years with T2DM, BMI ≥25 kg/m^2 (≥27 kg/m^2 if taking insulin)

Usual medical care + diabetes support and education for 4 years	a planned maximum F/U of 13.5 years	Usual medical care + lifestyle intervention* for 4 years, with maintenance counseling thereafter

Primary endpoint: **CV death, nonfatal MI, nonfatal stroke, hospitalization for angina**

- *≥7% mean weight loss with hypocaloric diet ± pharmacologic therapy + ≥175 min/week moderate physical activity
- Diet = 1200-1500 kcal/day (<250 lbs) or 1500-1800 kcal/day (≥250 lbs)

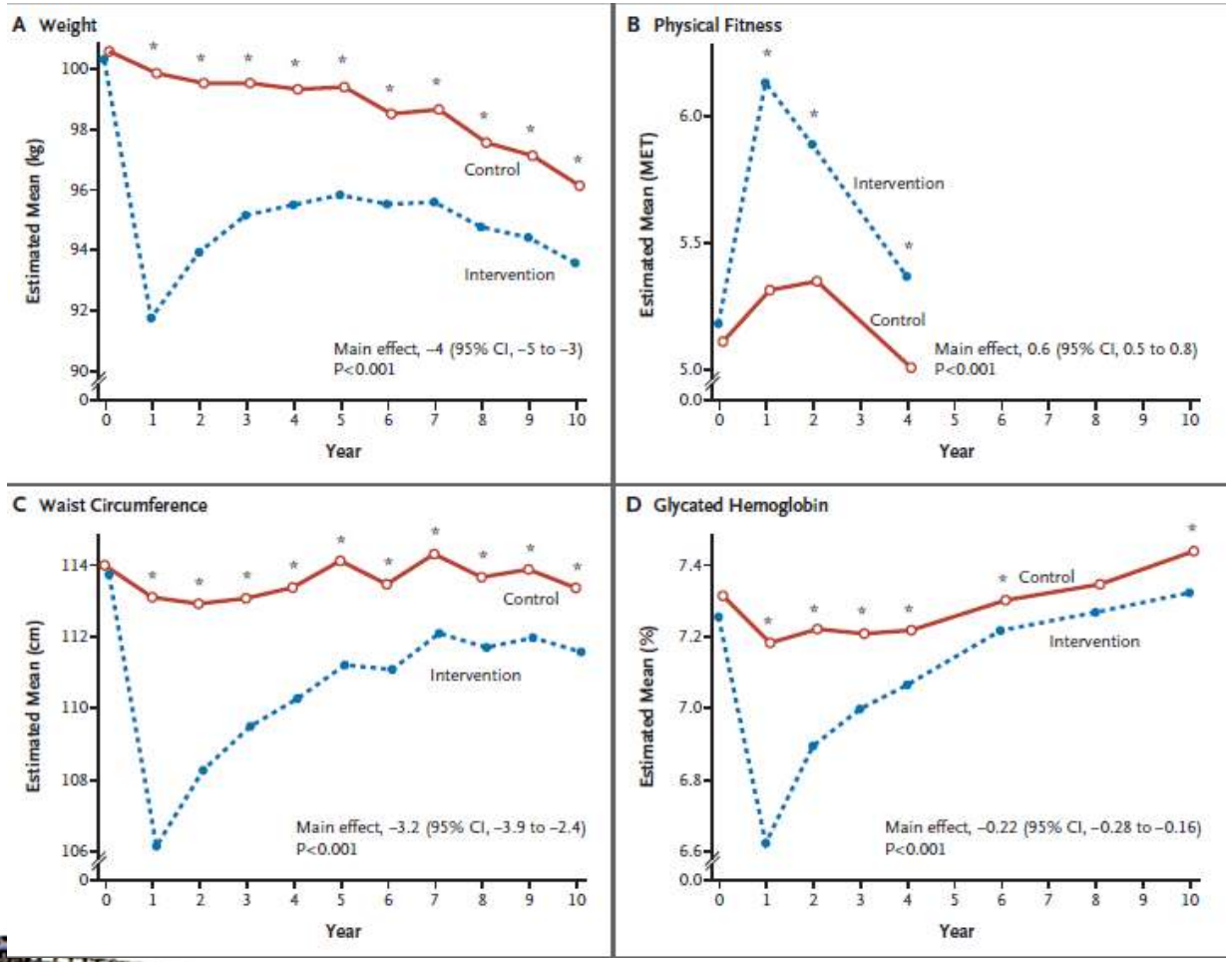
Look AHEAD Research Group. *Control Clin Trials*. 2003;24:610-28; *Obesity*. 2006;14:737-52.

Characteristics of the patients at baseline-Look AHEAD

Variable	Control Group (N=2575)	Intervention Group (N=2570)
Age — yr	58.9±6.9	58.6±6.8
Female sex — no. (%)	1537 (59.7)	1526 (59.4)
Race or ethnic group — no. (%)†		
Black	404 (15.7)	400 (15.6)
Native American	128 (5.0)	130 (5.1)
Asian or Pacific Islander	21 (0.8)	29 (1.1)
White	1631 (63.3)	1621 (63.1)
Hispanic	340 (13.2)	340 (13.2)
Other	51 (2.0)	50 (1.9)
History of cardiovascular disease — no. (%)‡	348 (13.5)	366 (14.2)
Use of insulin — no. (%)§	410 (16.5)	382 (15.4)
Current smoking — no. (%)	110 (4.3)	117 (4.6)
Median duration of diabetes (interquartile range) — yr	5.0 (2.0–10)	5.0 (2.0–10)
Weight — kg	101±19	101±20

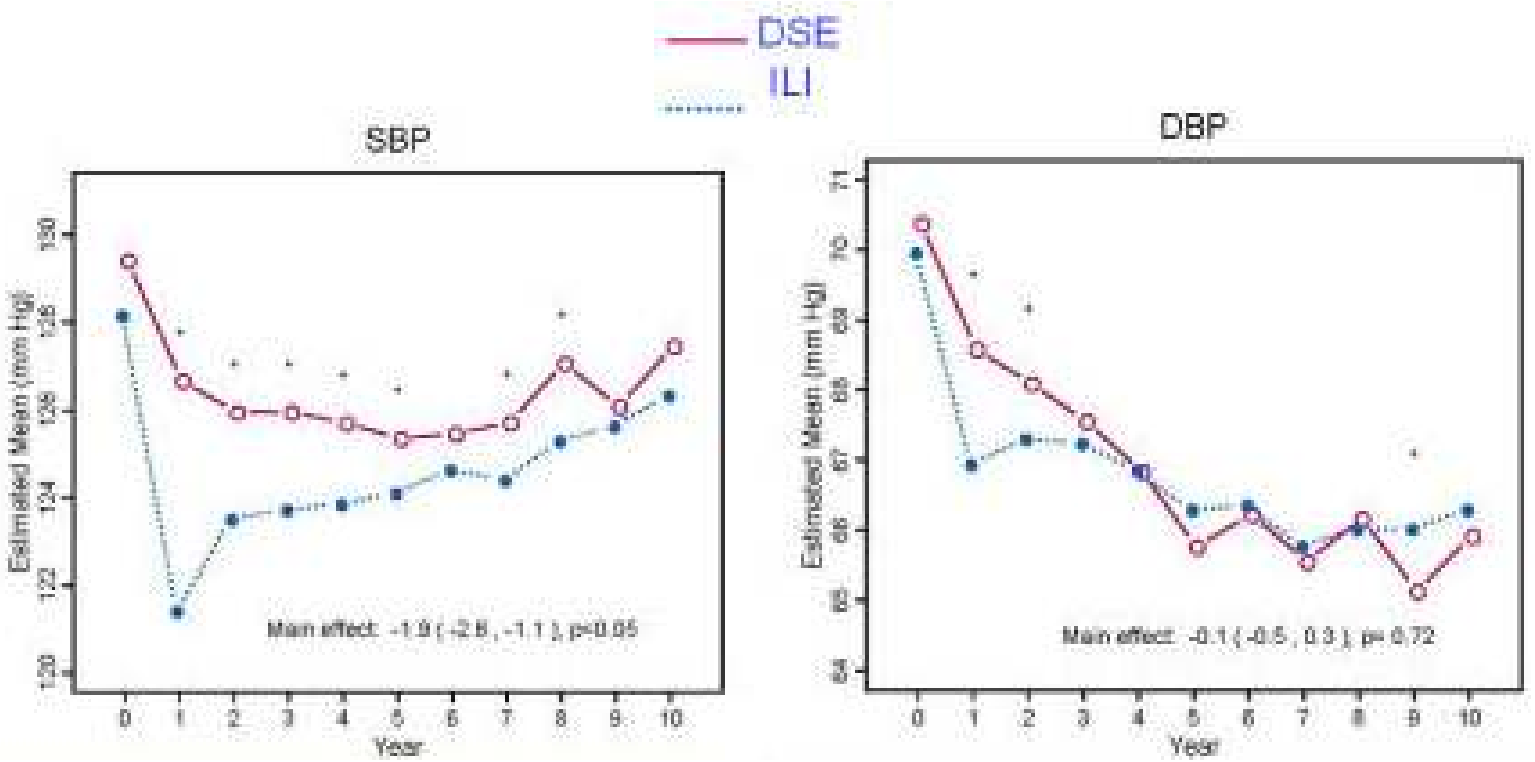
369(2):145-54.

Changes in weight, physical fitness, waist circumference, and glycated hemoglobin levels during 10 years of follow-up-Look AHEAD



Wing et al. N Engl J Med. 2013;369(2):145-54.

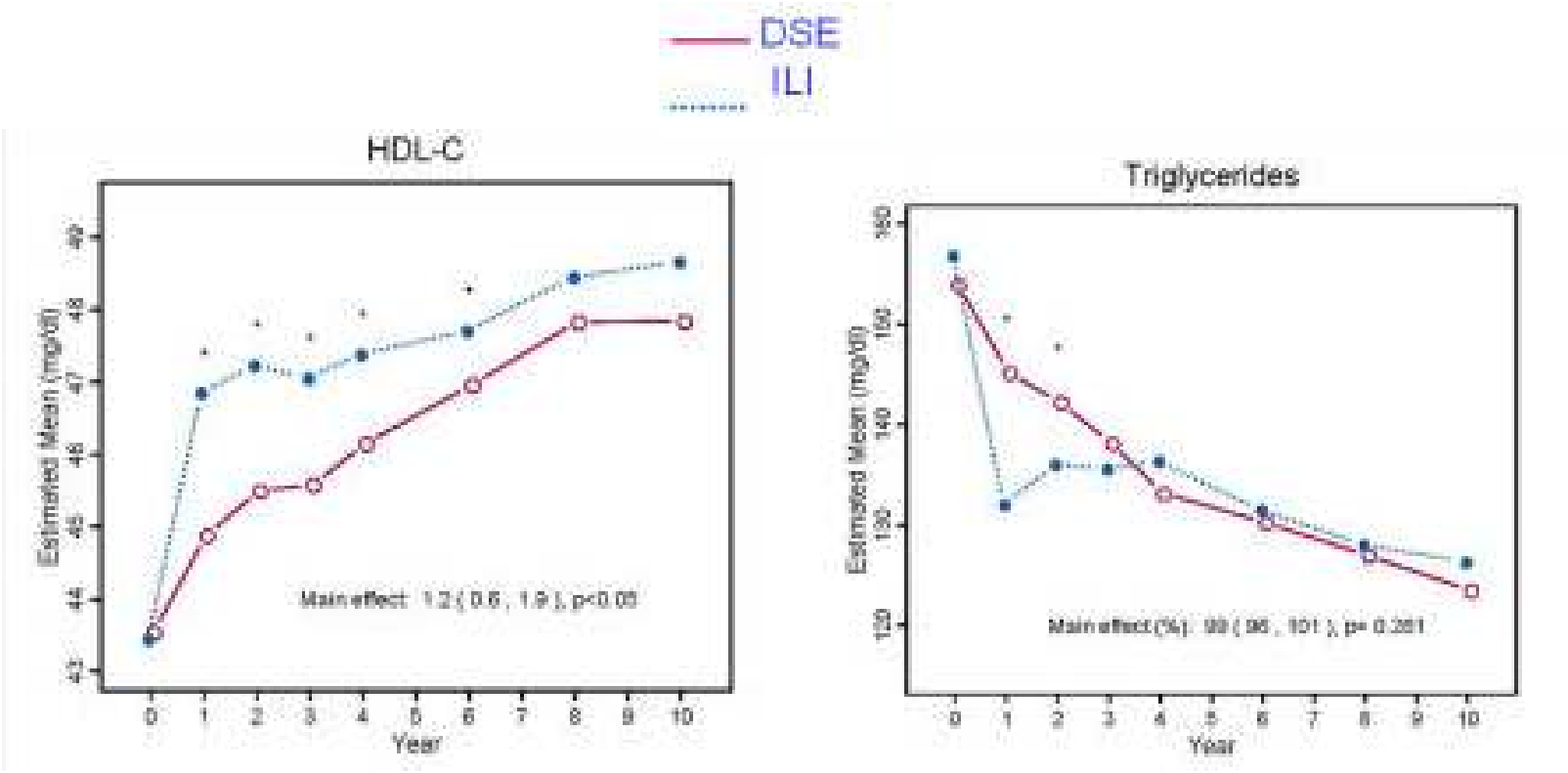
Changes in blood pressures



ILI: intensive lifestyle intervention (intervention group)
DSE: diabetes support and education (control group)

Wing et al. N Engl J Med. 2013;369(2):145-54.

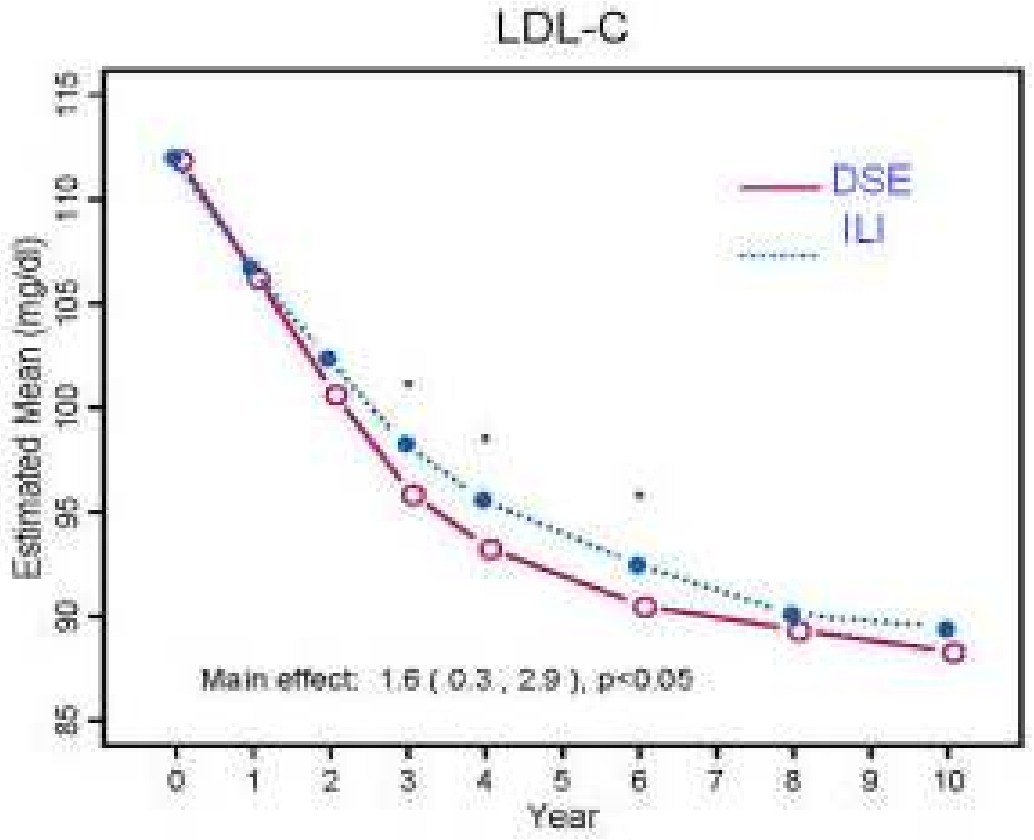
HDL-C and Triglyeride



ILI: intensive lifestyle intervention (intervention group)
DSE: diabetes support and education (control group)

Wing et al. N Engl J Med. 2013;369(2):145-54.

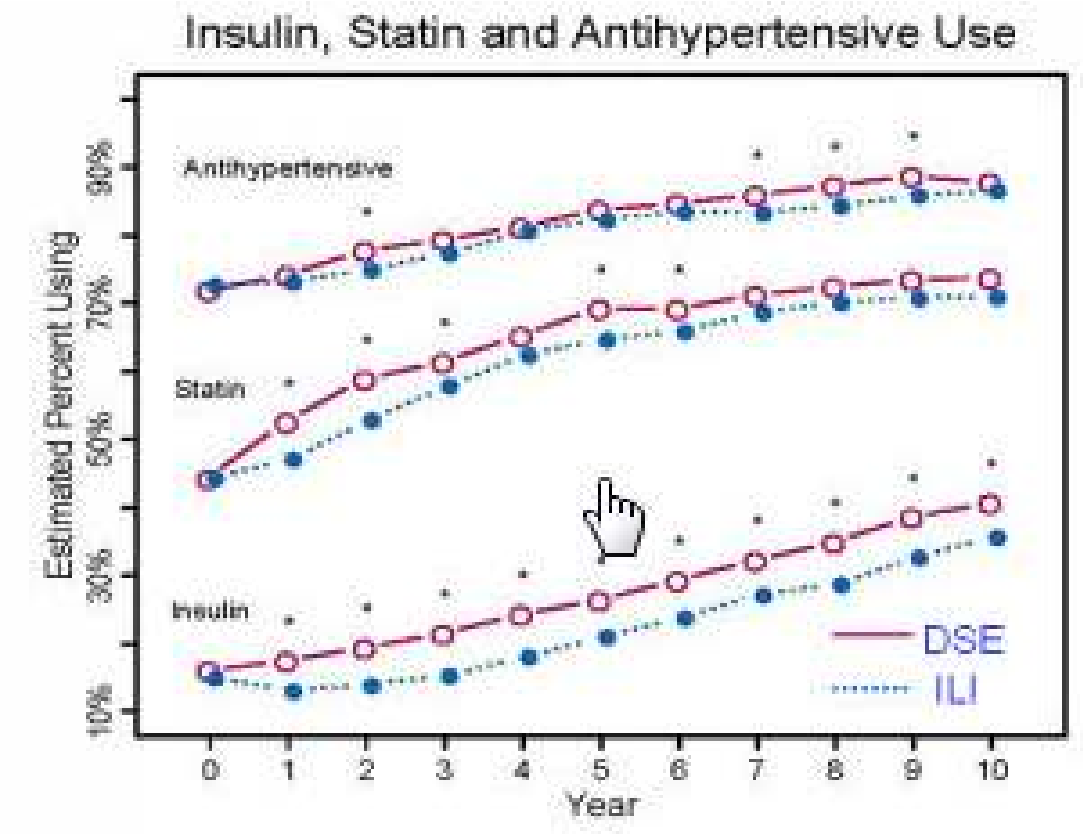
DSE had significantly greater reductions in LDL cholesterol than ILI



ILI: intensive lifestyle intervention (intervention group)
DSE: diabetes support and education (control group)

Wing et al. N Engl J Med. 2013;369(2):145-54.

DSE participants had significantly greater use of medications than ILI



ILI: intensive lifestyle intervention (intervention group)
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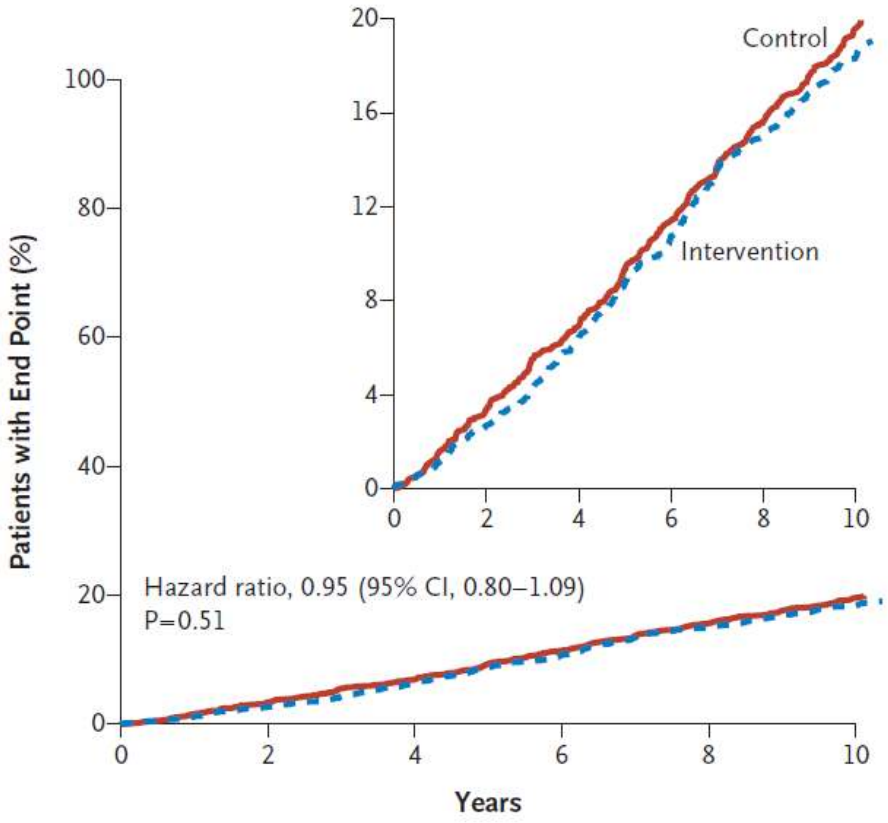
Wing et al. N Engl J Med. 2013;369(2):145-54.

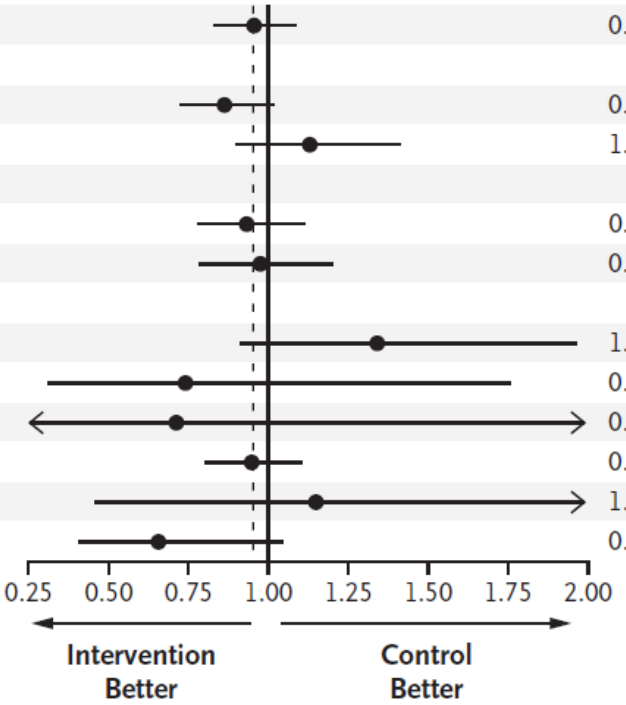
Cumulative hazard curves for the primary composite end point-Look AHEAD



Wing et al. N Engl J Med. 2013;369(2):145-54.

Primary outcome in prespecified subgroups-Look AHEAD

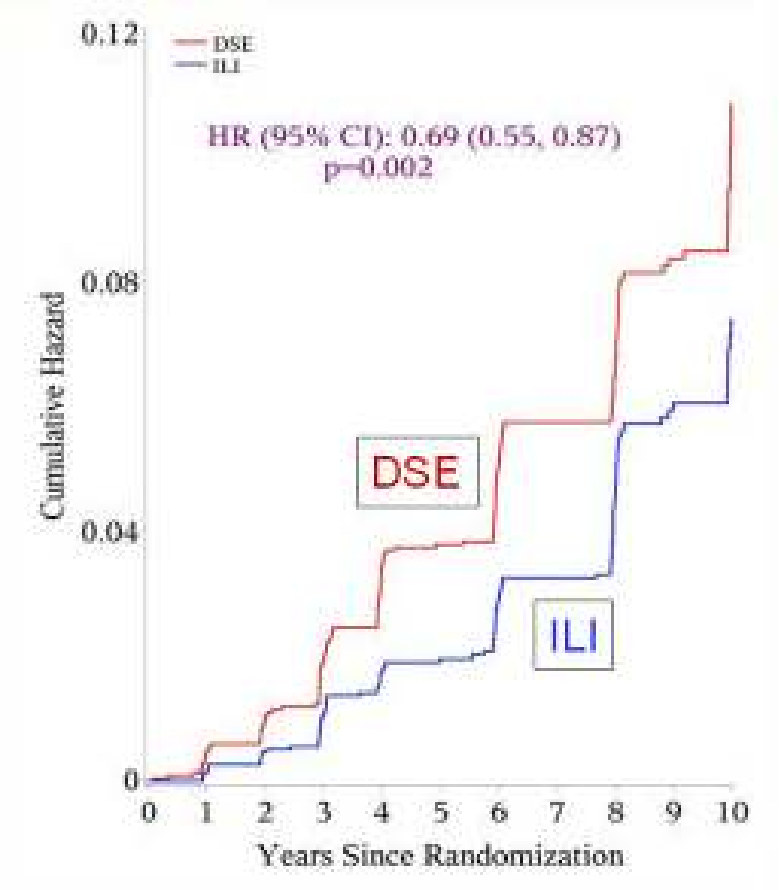
Subgroup	Control	Intervention	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events (rate/100 person-yr)			
Overall	418 (1.92)	403 (1.83)	0.95 (0.83–1.09)	
Cardiovascular disease at baseline				0.06
No	274 (1.42)	240 (1.23)	0.86 (0.72–1.02)	
Yes	144 (5.92)	163 (6.56)	1.13 (0.90–1.42)	
Sex				0.73
Male	245 (2.94)	232 (2.72)	0.93 (0.78–1.11)	
Female	173 (1.29)	171 (1.26)	0.97 (0.79–1.20)	
Race or ethnic group				0.17
Black	46 (1.32)	63 (1.82)	1.34 (0.91–1.96)	
Native American	13 (1.18)	10 (0.86)	0.74 (0.31–1.76)	
Asian or Pacific Islander	3 (1.67)	1 (0.38)	0.71 (0.06–8.28)	
White	303 (2.19)	286 (2.06)	0.94 (0.80–1.11)	
Other	10 (2.35)	12 (2.96)	1.15 (0.45–2.89)	
Hispanic	43 (1.54)	31 (1.06)	0.66 (0.41–1.05)	



Wing et al. N Engl J Med. 2013;369(2):145-54.

Cumulative hazard of very-high-risk CKD

ILI: intensive lifestyle intervention (intervention group)
DSE: diabetes support and education (control group)



73rd scientific session of ADA. 2013

Conclusions-Look AHEAD

- Intensive lifestyle intervention program did not reduce the risk of cardiovascular morbidity and mortality compared with a control program in overweight and obese participants with type 2 diabetes
  - Explanations considered for lack of significant differences in CVD event rates
    - ✓ CVD was developed less than anticipated
    - ✓ Small and non-sustained differences in body weight between groups
    - ✓ Greater use of statins in control group

- Modest glycemic improvement through intensive lifestyle modification could reduce the development of diabetic nephropathy

Wing et al. N Engl J Med. 2013;369(2):145-54.

Omega-3 Fatty Acids

Meta-analysis of RCTs showed that supplementation with the marine n−3 fatty acids reduced the rate of death from CHD

Study	No with event/ No in group: Fish oil	No with event/ No in group: Placebo	Odds ratio (random) (95% CI)	Weight (%)	Odds ratio (random) (95% CI)
Sacks et al 1995[w10]	0/41	1/39		0.20	0.31 (0.01 to 7.82)
Singh et al 1997[w11]	14/122	26/118		4.10	0.46 (0.23 to 0.93)
GISSI-Prevenzione 1999[w1]	291/5666	348/5658		79.77	0.83 (0.70 to 0.97)
Johansen et al 1999[w8]	1/250	3/250		0.40	0.33 (0.03 to 3.20)
Von Shacky et al 1999[w12]	0/111	1/112		0.20	0.33 (0.01 to 8.27)
Durrington et al 2001[w7]	0/30	1/29		0.20	0.31 (0.01 to 7.96)
Nilsen et al 2001[w9]	8/150	8/150		2.02	1.00 (0.37 to 2.74)
Leaf et al 2005[w3]	9/200	9/202		2.29	1.01 (0.39 to 2.60)
Raitt et al 2005[w2]	2/100	5/100		0.74	0.39 (0.07 to 2.05)
Brouwer et al 2006[w4]	6/273	13/273		2.12	0.45 (0.17 to 1.20)
JELIS 2007[w5]	29/9326	31/9319		7.96	0.93 (0.56 to 1.55)
Total (95% CI)	16 269	16 250		100.00	0.80 (0.69 to 0.92)

Total events: 360 (fish oil), 446 (placebo)

Test for heterogeneity: χ^2=6.90, df=10, P=0.74, I^2=0%

Test for overall effect: z=3.08, P=0.002

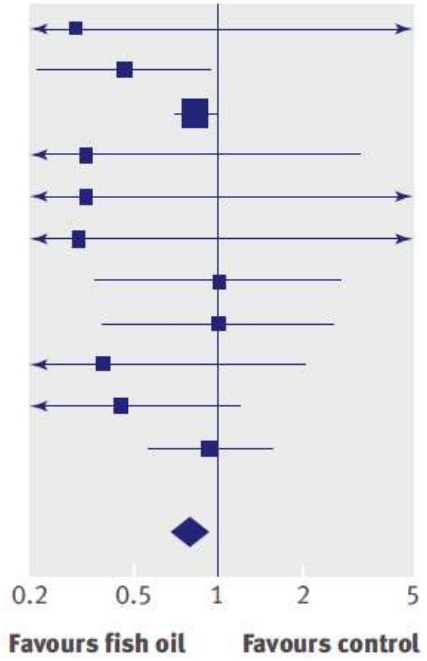
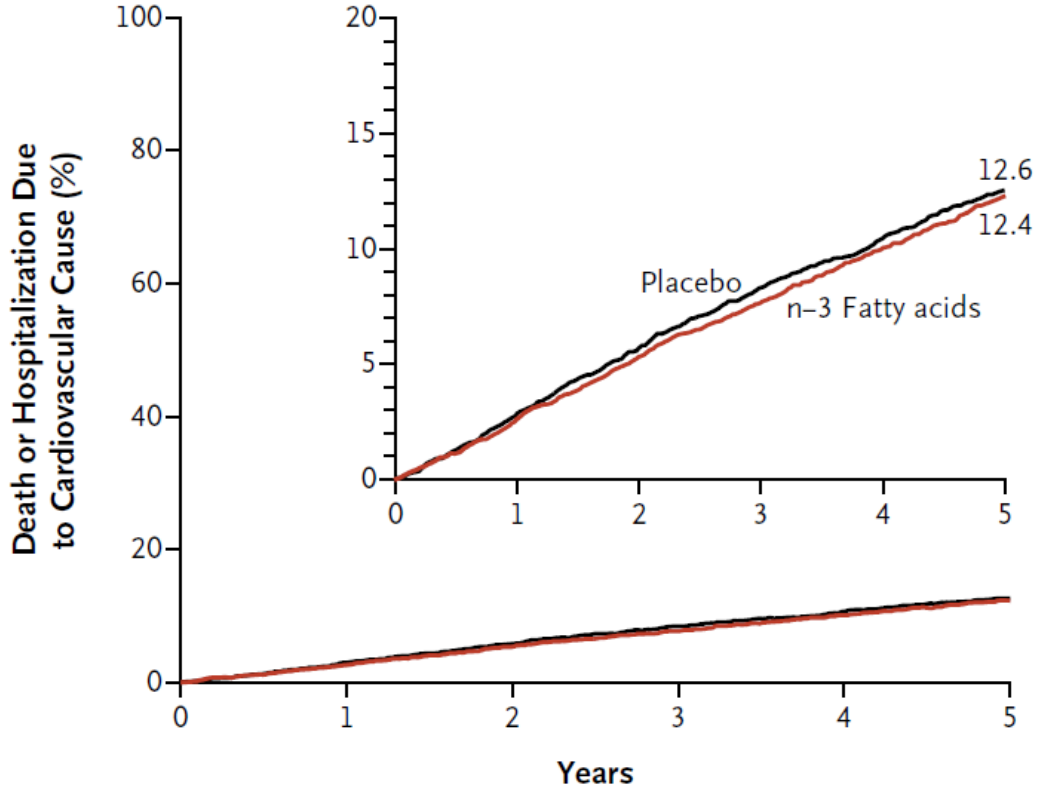


Fig 3 | Effect of fish oil on death from cardiac causes

León et al. BMJ. 2008;337:a2931.

In a large general-practice cohort of patients with multiple cardiovascular risk factors, daily treatment with n-3 fatty acids did not reduce cardiovascular mortality and morbidity



No. at Risk

n–3 Fatty acids	6239	5910	5566	5216	4863	2992
Placebo	6266	5908	5528	5137	4780	2926

Risk and Prevention Study. N Engl J Med. 2013;368(19):1800-8.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

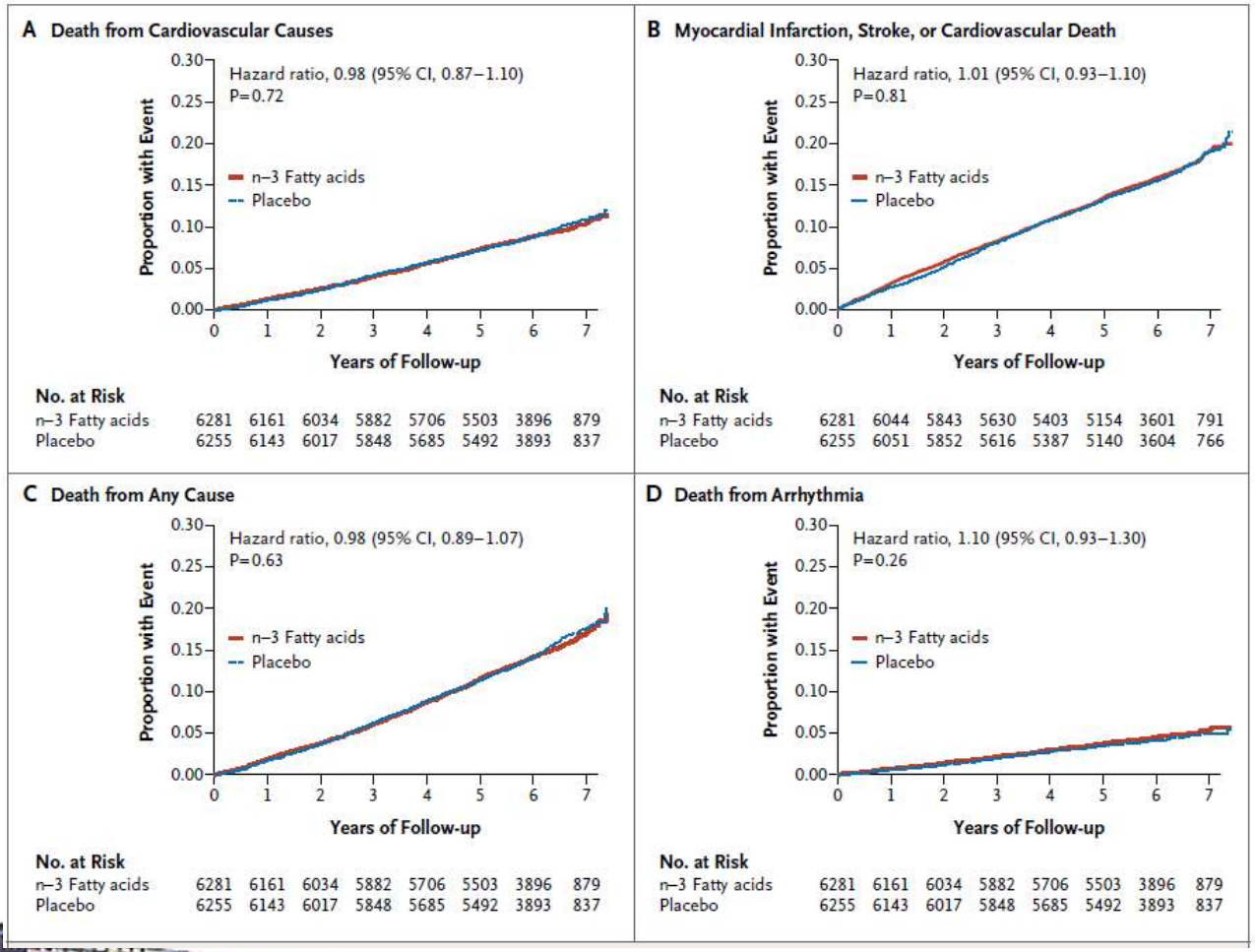
n–3 Fatty Acids and Cardiovascular Outcomes in Patients with Dysglycemia

The ORIGIN Trial Investigators*

- We tested the hypothesis that long-term supplementation with 1 g of n–3 fatty acids would reduce the rate of cardiovascular events in patients with T2DM, IGT and IFG

ORIGIN Trial. N Engl J Med. 2012;367(4):309-18.

Daily supplementation with 1 g of n–3 fatty acids did not reduce the rate of cardiovascular events in dysglycemic patients at high risk for cardiovascular events



ORIGIN Trial. N Engl J Med. 2012;367(4):309-18.

CONCLUSIONS

- What's New in Other Risk Management? -

- To date, many measures have been developed and they've been attempted for CV protection
  - But CVD still remains the main cause of death in people with diabetes

- Recent clinical trials showed that traditional CV protective methods were less effective than we expected
  - Therefore, innovative measures are required for a noticeable reduction in CV risk in diabetic patients

Thank you for your attention

Back-up Slides

A review and meta-analysis of the effect of weight loss on all-cause mortality risk

Harrington et al. Nutr Res Rev. 2009 Jun;22(1):93-108.

Reasons for intentional weight loss, unintentional weight loss, and mortality in older men

Table 2. Adjusted Relative Risks of Mortality From All Causes and CVD and Non-CVD Causes by Perceived Weight Change Categories and by Reasons for Intentional Weight Loss

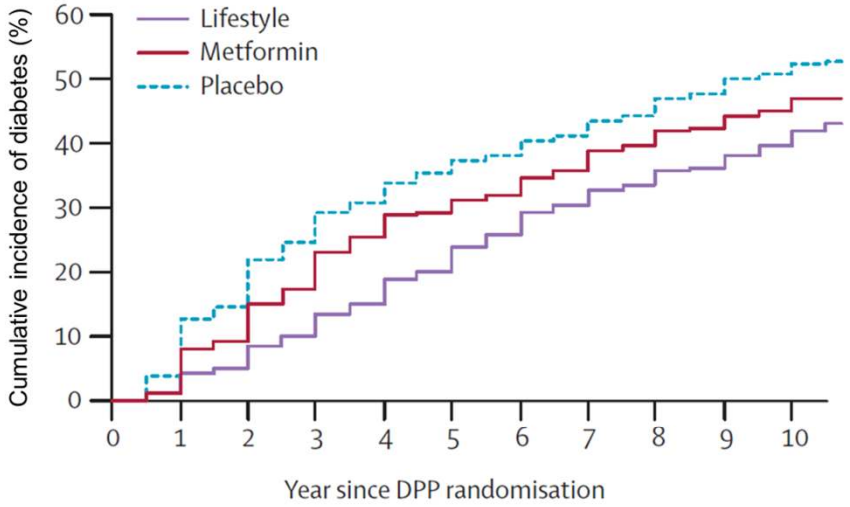
Mortality	No Change (n = 2539)	Weight Gain (n = 1378)	Unintentional Weight Loss (n = 527)	Intentional Weight Loss		
				All (n = 342)	Personal Reason (n = 178)	Physician's Advice/Ill Health (n = 164)
Total mortality						
No. of deaths	414	200	191	53	16	37
Adjusted RR (95% CI)*	1.00 (Referent)	0.95 (0.71-1.18)	1.88 (1.47-2.40)	1.04 (0.94-1.14)	0.62 (0.36-1.05)	1.63 (1.15-2.30)
Adjusted RR (95% CI) + disease†	1.00 (Referent)	0.86 (0.69-1.08)	1.71 (1.33-2.19)	1.00 (0.91-1.10)	0.59 (0.34-1.00)	1.37 (0.96-1.94)
CVD mortality						
No. of deaths	183	98	76	24	10	14
Adjusted RR (95% CI)*	1.00 (Referent)	1.06 (0.91-1.23)	1.68 (1.09-2.30)	1.05 (0.91-1.21)	0.95 (0.48-1.86)	1.31 (0.75-2.29)
Adjusted RR + disease (95% CI)†	1.00 (Referent)	0.94 (0.68-1.30)	1.63 (1.16-2.43)	0.98 (0.85-1.14)	0.90 (0.46-1.78)	0.98 (0.55-1.72)
Non-CVD mortality‡						
No. of deaths	231	102	115	29	6§	23
Adjusted RR (95% CI)*	1.00 (Referent)	0.86 (0.63-1.17)	2.06 (1.41-2.72)	1.03 (0.90-1.17)	0.38 (0.16-0.92)	1.85 (1.19-2.88)
Adjusted RR (95% CI) + disease†	1.00 (Referent)	0.79 (0.58-1.25)	1.79 (1.28-2.49)	1.01 (0.89-1.16)	0.36 (0.15-0.87)	1.74 (1.11-2.73)

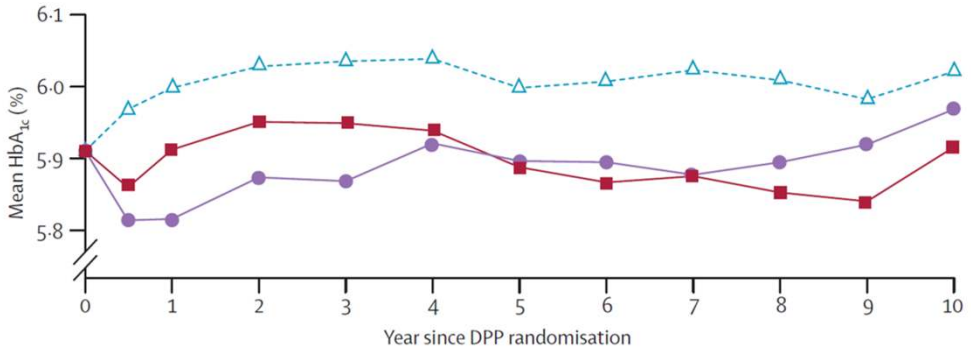
Wannamethee et al. Arch Intern Med. 2005 May 9;165(9):1035-40.

Weight loss and mortality in persons with type-2 diabetes mellitus

Williamson. Exp Clin Endocrinol Diabetes. 1998;106 Suppl 2:14-21.

10-year follow-up of diabetes incidence in the Diabetes Prevention Program Outcomes Study





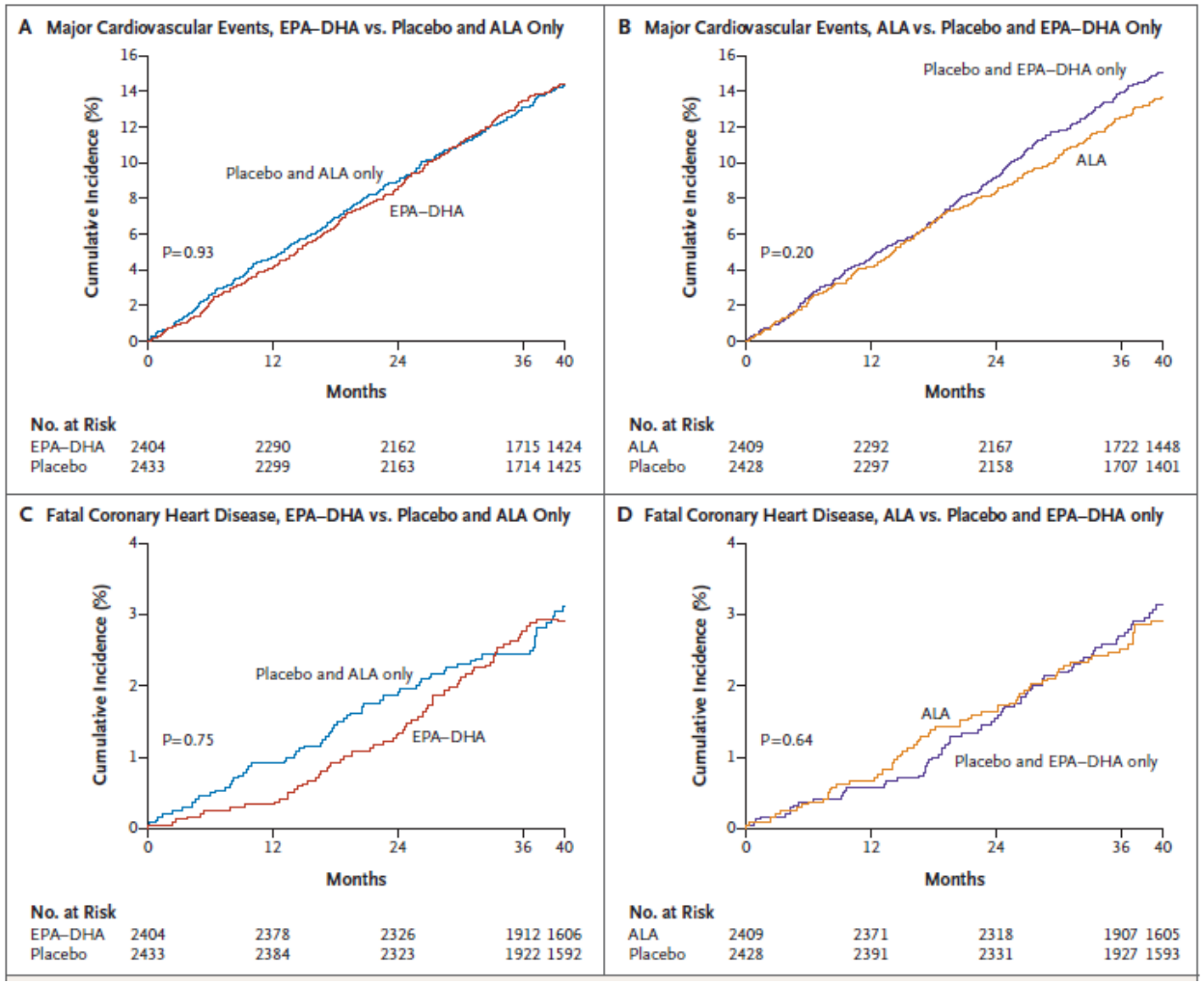
DPP Research Group. Lancet. 2009;374(9702):1677-86.

Primary outcome-Look AHEAD

- the first occurrence of a composite cardiovascular outcome
  - death from cardiovascular causes
  - nonfatal myocardial infarction
  - nonfatal stroke
  - hospitalization for angina

Low-dose supplementation with EPA–DHA or ALA did not significantly reduce the rate of major cardiovascular events among patients who had had a MI

EPA: eicosapentaenoic acid
DHA: docosahexaenoic acid
ALA: alpha-linolenic acid



Alpha Omega Trial. N Engl J Med. 2010;363(21):2015-26.

Conclusions-Look AHEAD

- Individuals with diabetes can successfully lose weight and maintain modest weight losses long-term
- Intensive lifestyle interventions improve CVD risk factors
- Intensive lifestyle intervention improved glycemic control relative to DSE

- Look AHEAD found that an intensive lifestyle intervention program did not reduce the risk of cardiovascular morbidity and mortality compared with a control program of diabetes support and education in overweight and obese participants with type 2 diabetes

Wing et al. N Engl J Med. 2013;369(2):145-54.