

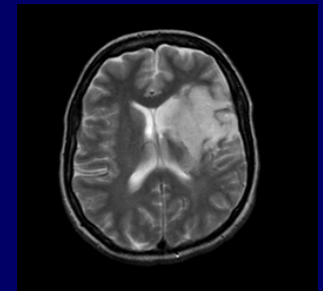
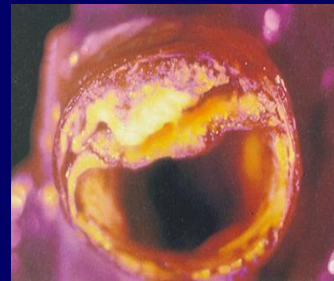
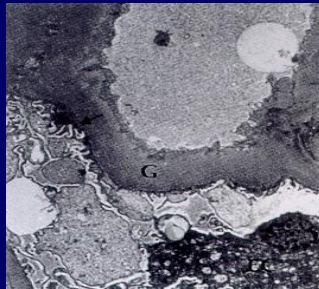
The ABCD Debate:

This house believes that Aspirin resistance in diabetes explains the lack of overall benefit in the primary prevention of vascular complications



Vinod Patel

**Diabetes and Endocrinology Centre,
George Eliot Hospital NHS Trust, Nuneaton,
Institute of Clinical Education
Warwick Medical School**



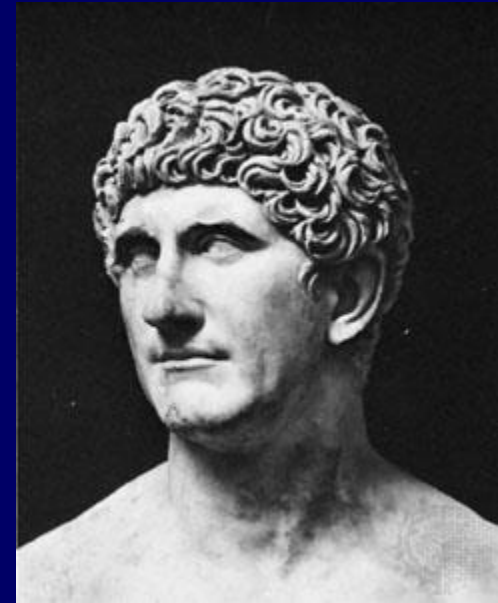
Friends, Romans, countrymen,
lend me your ears;
I come to bury Caesar, not to praise him;

Mark Antony



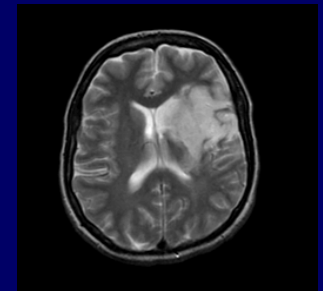
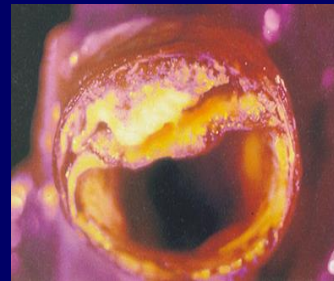
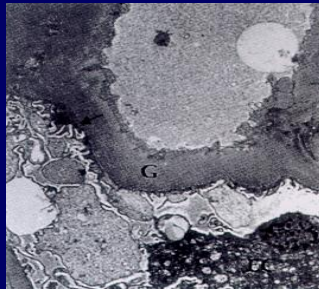
Friends, ABCDers,
lend me your ears;
I come to bury RAMZI,
not to praise him;

Me

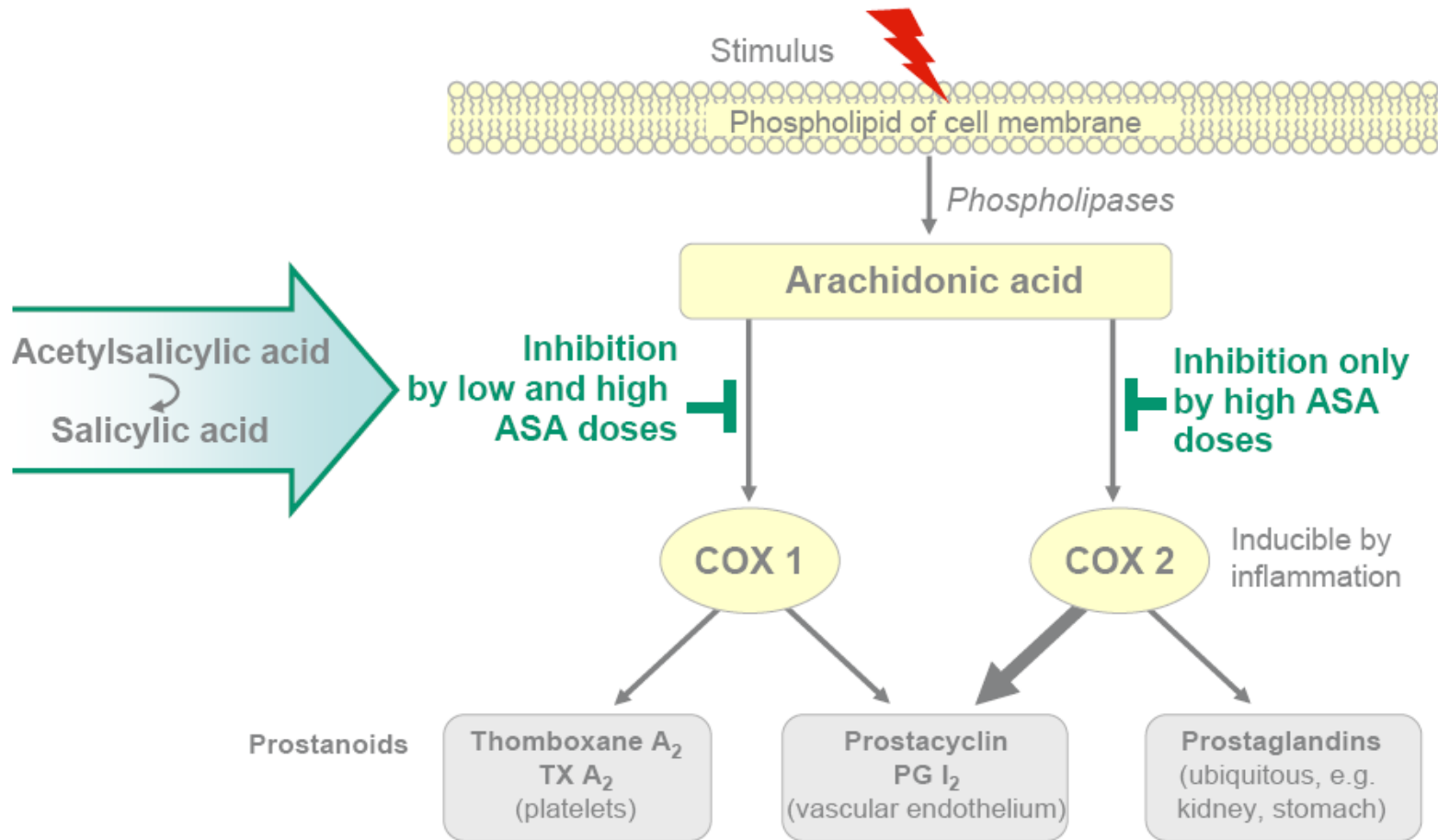


Aspirin Resistance:

- The Need and background, A Poem
- The Polypill Model and Steno-2
- NICE Guidelines
- The Evidence
- Mr Bulsara, the philosopher and possibly Rasputin



Inhibition of the prostanoid biosynthesis by acetylsalicylic acid



Aspirin® Update

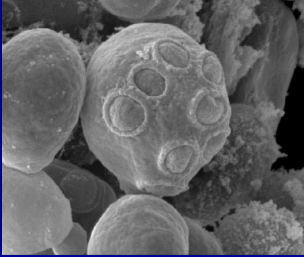
International Press Workshop 2008

I think medicine more art than science...?



Bring me the venom of the pit viper snake !

From bitter goat's rue a potion make



Ferment the juice that fat so hates!

Fetch the spit that shrinks the weight



Extract from offal the magic that cures



Dissolve in blood the bark that spatters!



Raj: lorry driver (now unemployed) aged 56 years, father of 3 children



Overweight, often snacks

Brother recent MI!

Case History:

- Worried!
- HbA1C 8.3%
- BP 154/92 mm/Hg
- Total cholesterol 6.4 mmol/l
- LDL 4.2, HDL 0.9
- Central obesity waist – 40 inches.
- Microalbuminuria positive

• **Current Rx:**

1: Metformin

2: Simvastatin 40mg

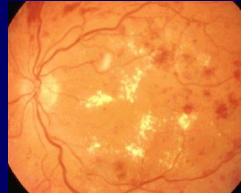
3: Ramipril 10mg

??

Diabetes Care : The Complications

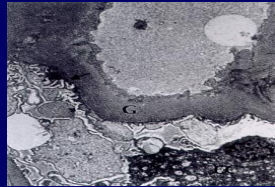
Retinopathy

Most common cause of blindness in people of working age



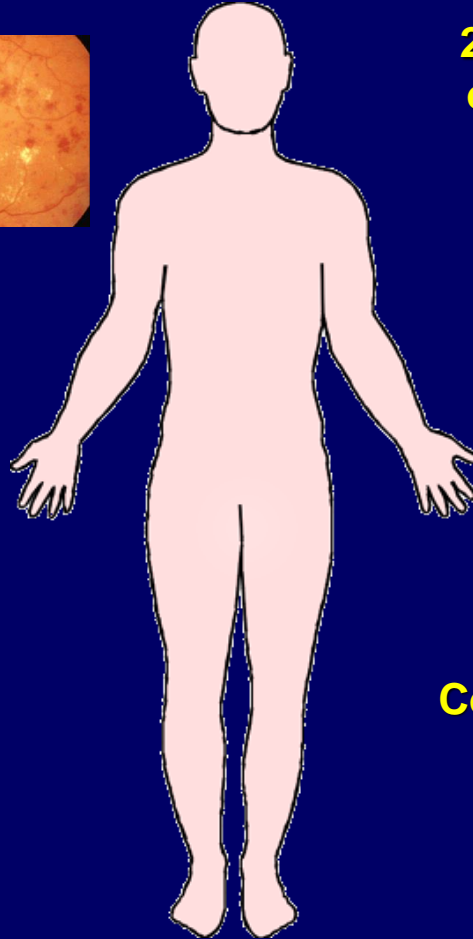
Nephropathy

16% of all new patients needing renal replacement therapy



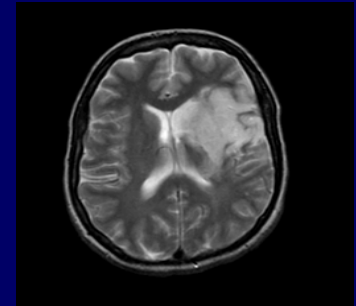
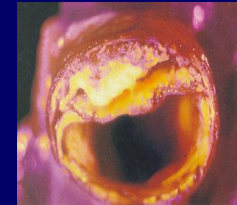
Erectile dysfunction

May affect up to 50% of men with long-standing diabetes



Macrovascular disease

2–4 fold increased risk of coronary heart disease and stroke, 75% have hypertension

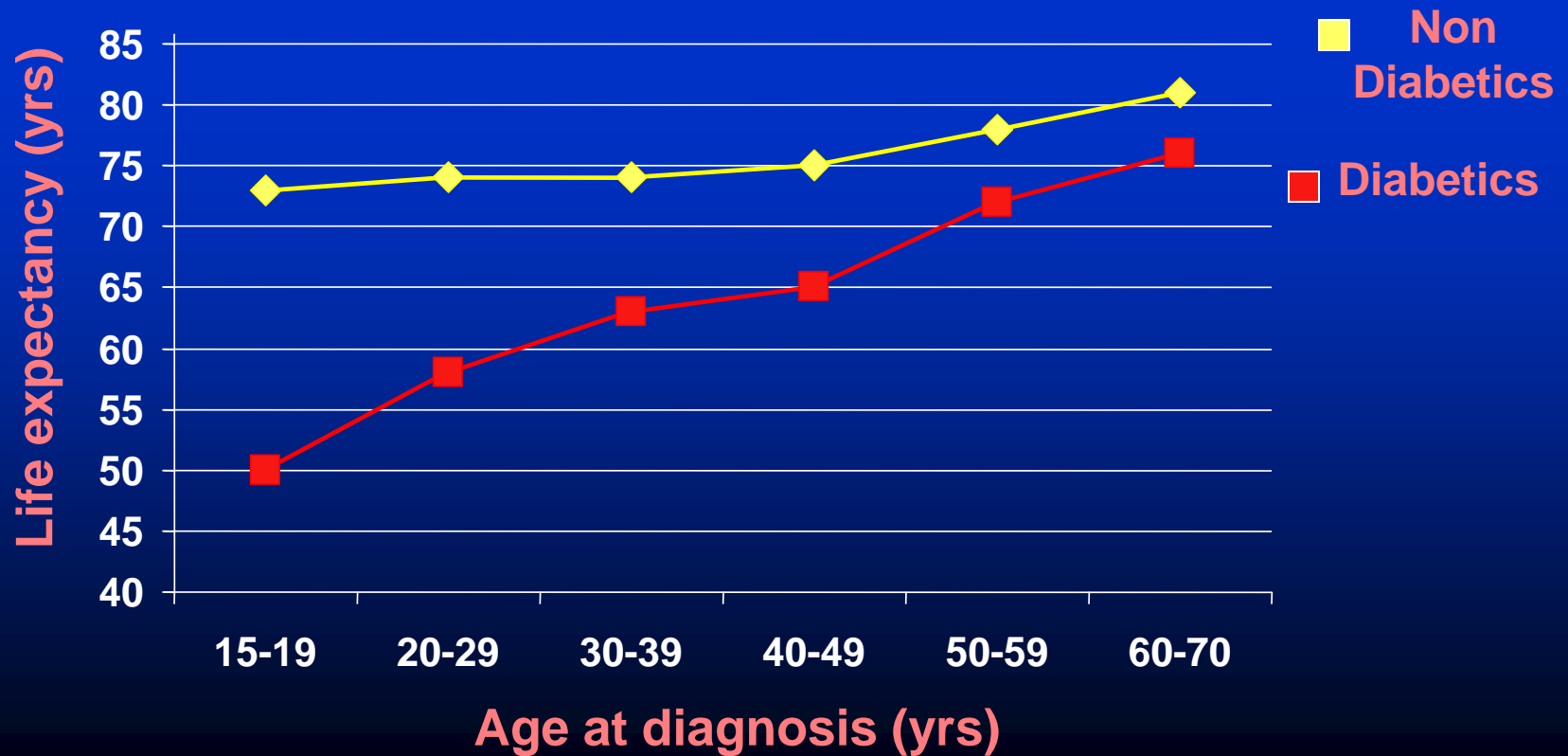


Foot problems

Commonest cause of non-traumatic amputation



Life Expectancy and Diabetes



‘Adults with diabetes have an annual mortality of about 5.4%, double the rate for non-diabetic adults. Life expectancy is decreased by 5–10 years.’

Goodkin G. Journal of Occupational Medicine 1975;17(11): 716–721.

Donnelly R, et al. British Medical Journal 2000; 320: 1062–1066.

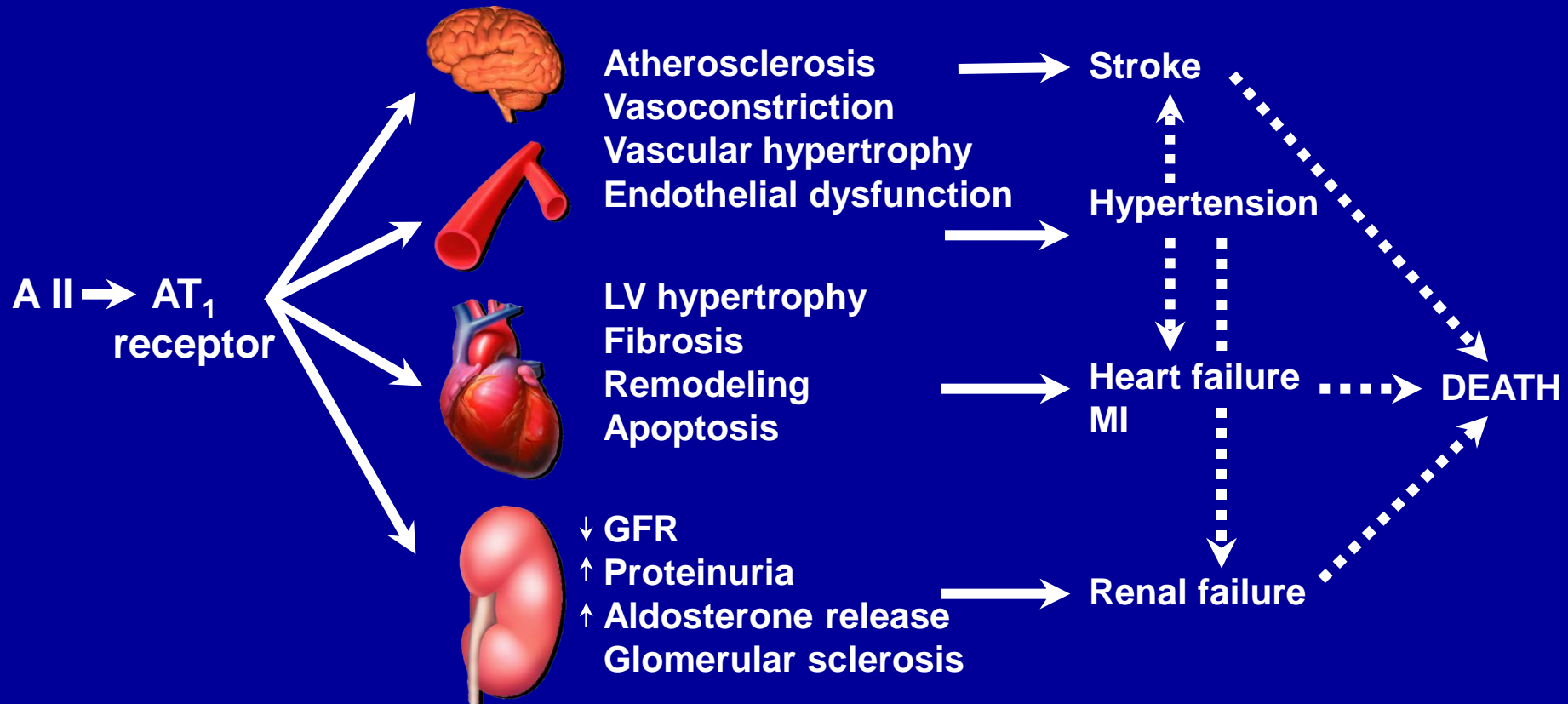
Exhibit 1A



Bring me the venom of the pit viper snake!



Angiotensin II may play a central role in organ damage



LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate

HOPE : stroke rate - ramipril vs placebo in diabetics

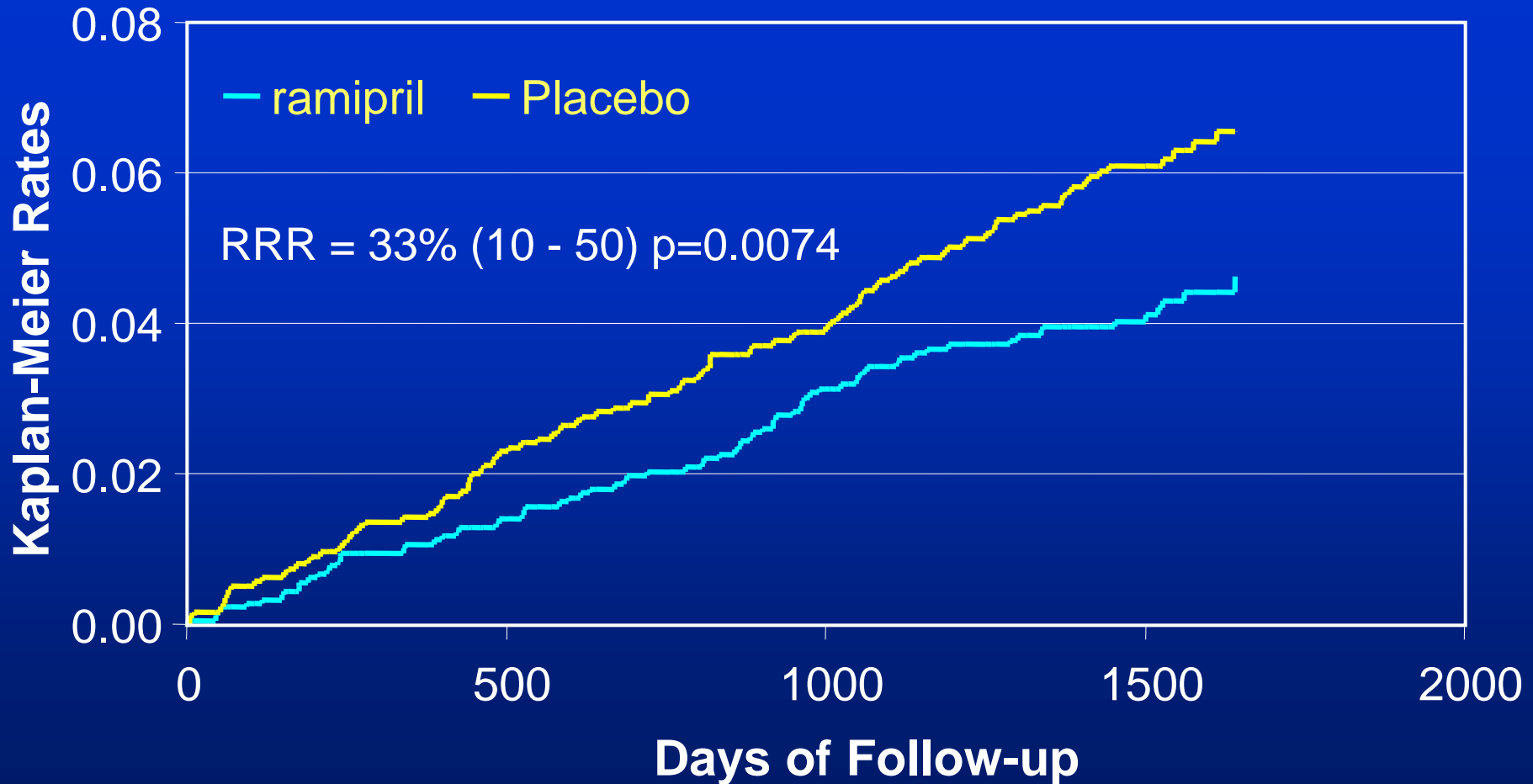
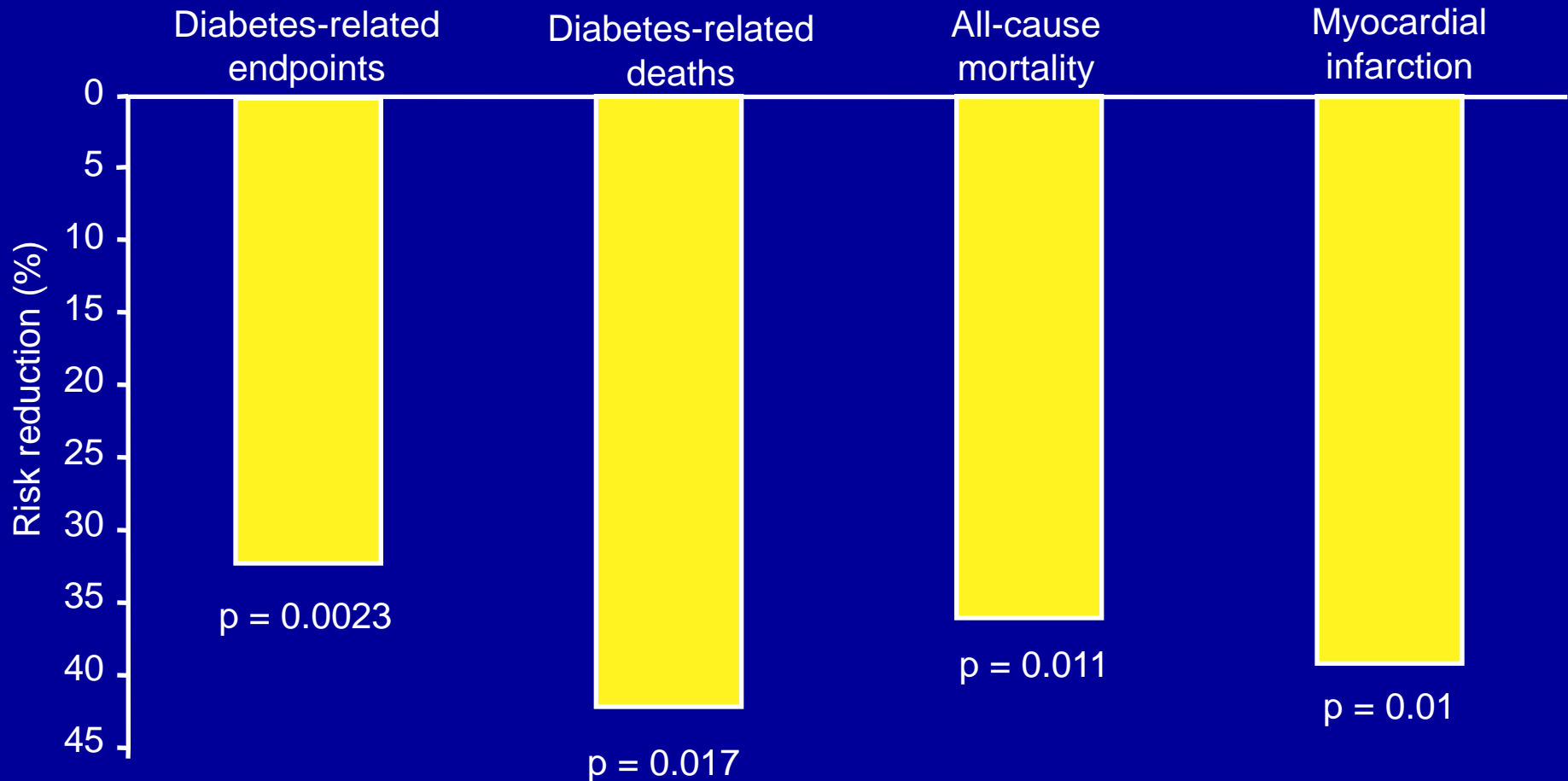


Exhibit 2A



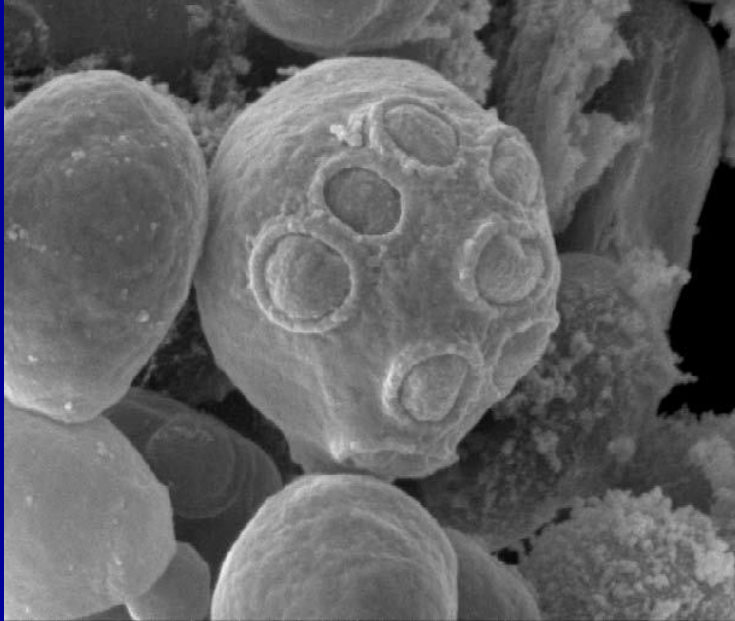
From bitter goat's rue a potion make

UKPDS : metformin in over- weight subjects



p values in comparison to conventional treatment group

Exhibit 3A



Ferment the juice that fat so hates!

CARDS : treatment effect on the primary endpoint

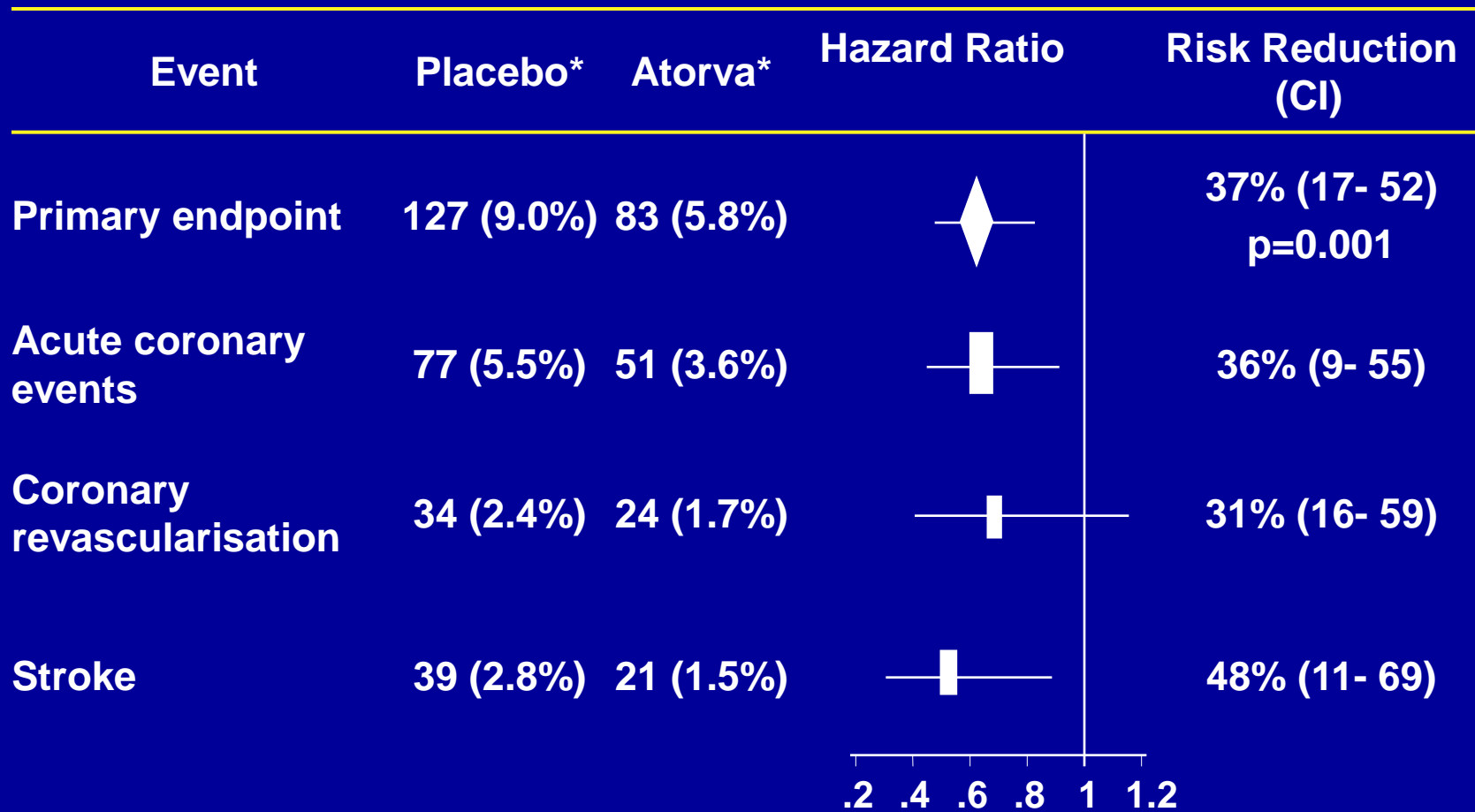


Exhibit 4A



Fetch the spit that shrinks the weight

GLP-1 effects in humans

understanding the natural role of incretins

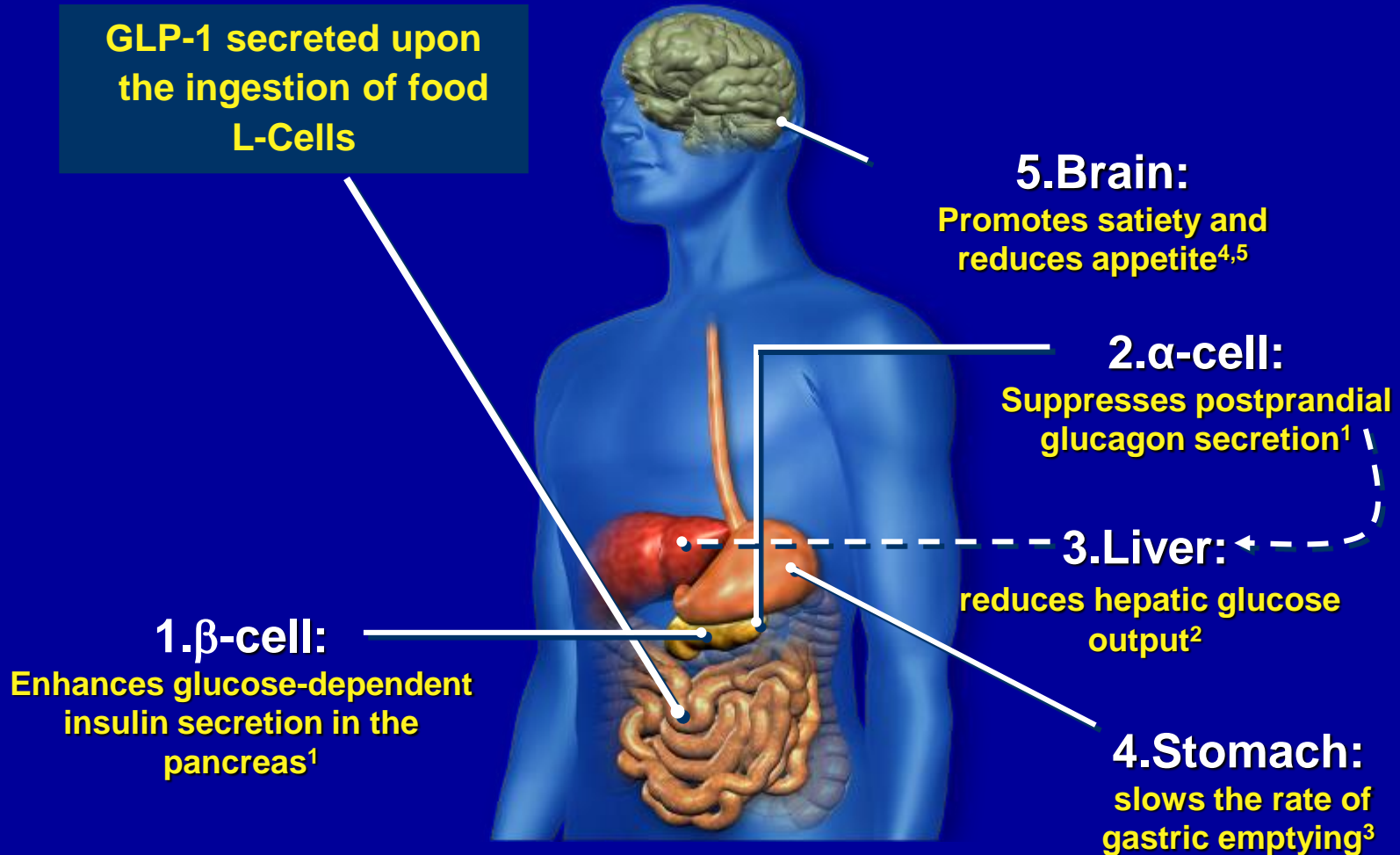


Exhibit 6A



Extract from offal the magic that cures







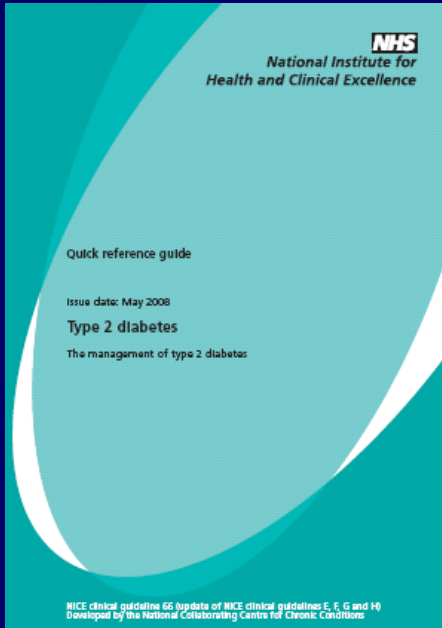
After insulin. "J.L." February 15, 1923,
weight 29 lbs. These spectacular
pictures first appeared in the issue of the
Journal of the American Medical Association
that introduced insulin to the profession.
Eli Lilly and Company Ltd.

Exhibit 5A



Dissolve in blood the bark that spatters!

NICE: Aspirin therapy



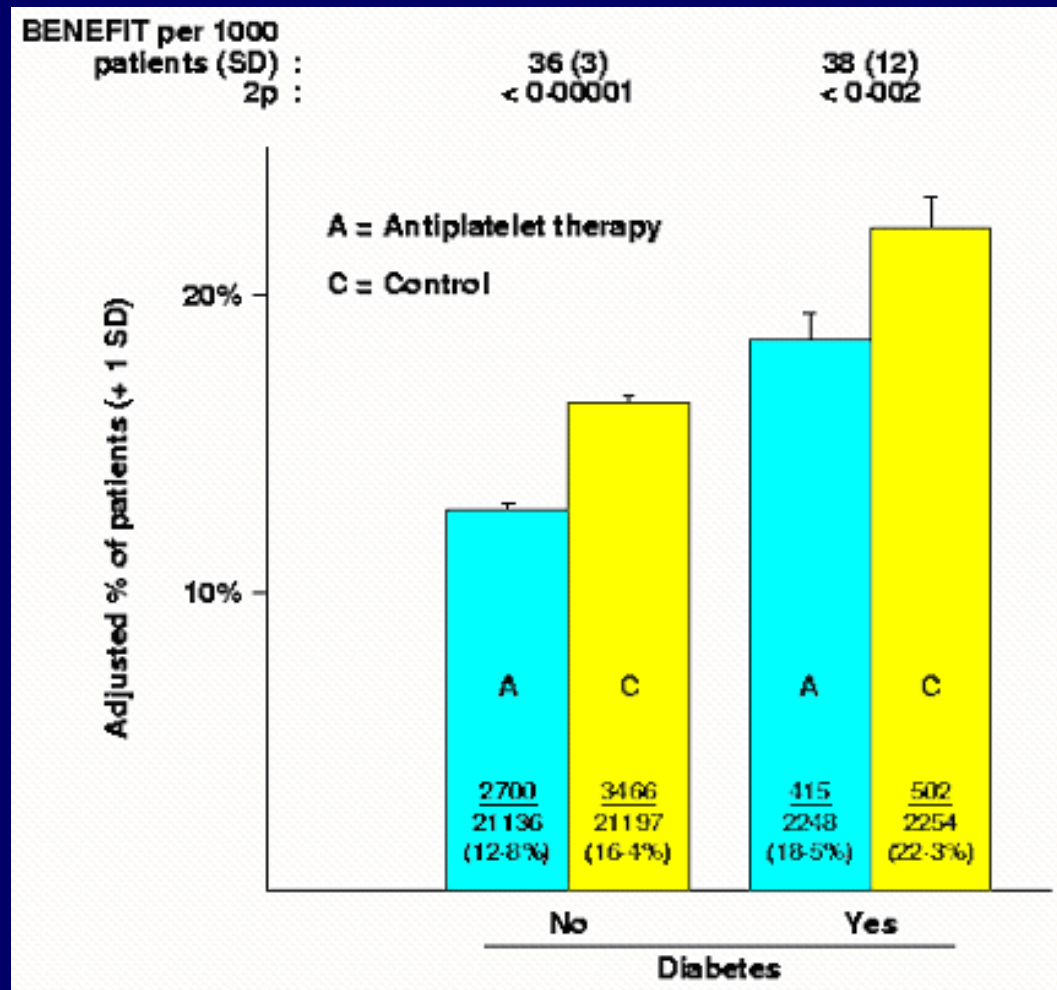
- Offer low-dose aspirin, 75 mg daily, <50 years, if BP <145/90
- Offer low-dose aspirin, if has significant other CVD (metabolic syndrome, strong early FH, CVD, smoking, hypertension, extant cardiovascular disease, microalbuminuria).

Aspirin ?

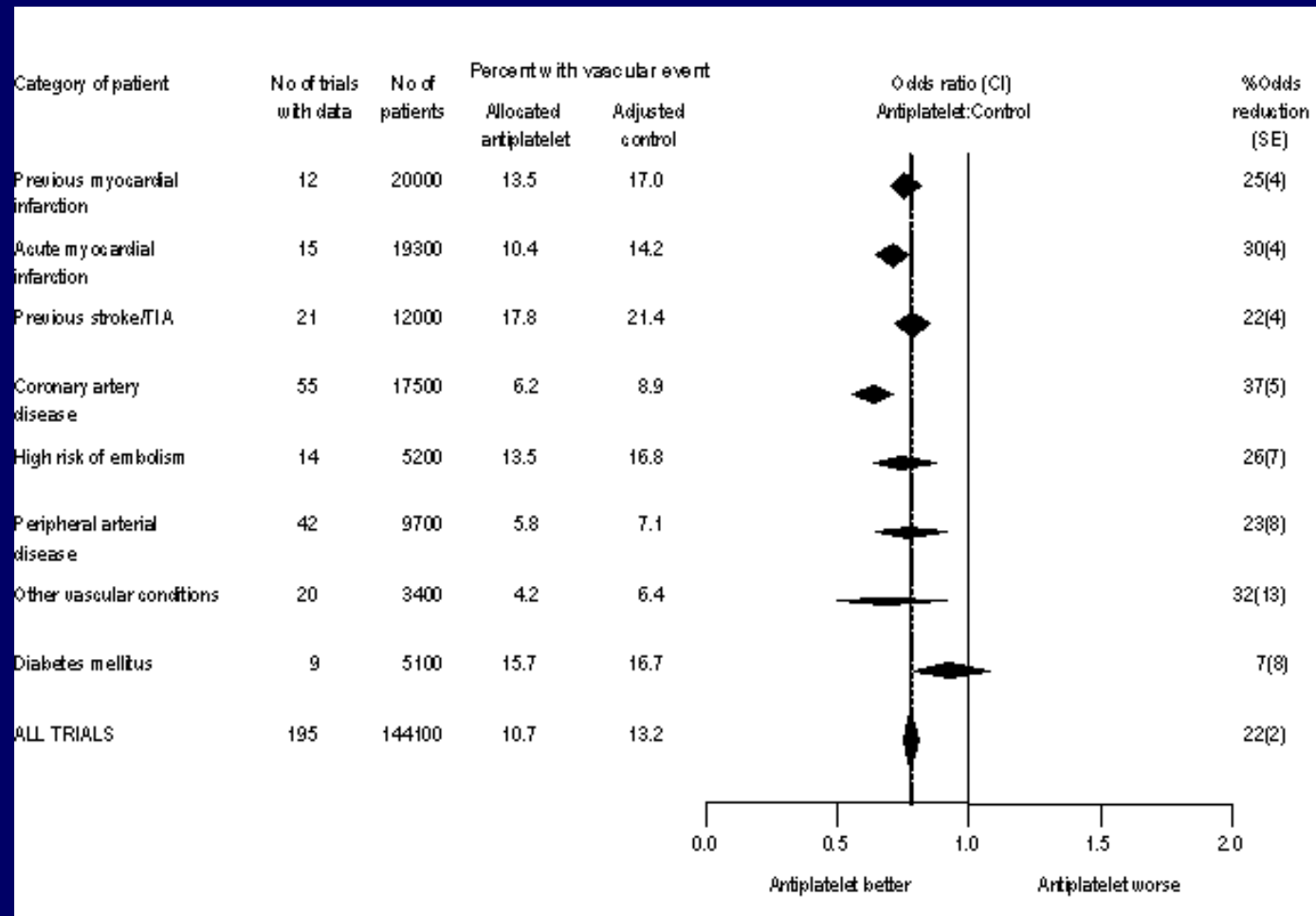
- Role in secondary prevention is well established
- Widely used in accordance with numerous guidelines
- In the HOT study aspirin reduced CV events in hypertensive subjects by 15%
- Evidence for primary prevention in diabetic subjects is still lacking
- ASCEND study awaited : aspirin vs placebo and omega-3 fatty acids vs placebo in 10,000 primary prevention diabetes subjects

Information from the Antiplatelet Trialists' Collaboration

In patients with occlusive arterial disease the figure shows that the proportional benefits of antiplatelet therapy are similar in people with or without diabetes.



Proportional effects of antiplatelet therapy on vascular events in 195 trials among high-risk patients subdivided by disease category



**Effects of aspirin treatment on diabetic retinopathy.
ETDRS report number 8.
Early Treatment Diabetic Retinopathy Study
Research Group.**

- RCT National Eye Institute, 3711 patients with mild-to-severe nonproliferative or early proliferative DR randomly to aspirin (650 mg per day) or placebo.
- Aspirin did not prevent the development of high-risk proliferative DR and did not reduce the risk of visual loss, nor did it increase the risk of vitreous haemorrhage. Reduction in early DR only
- These findings suggest there are no ocular contraindications to aspirin when required for cardiovascular disease or other medical indications.

Effect of aspirin alone ...in early DR. A multicenter RCT The DAMAD Study Group.

- RCT 2 French and two UK, aspirin (330 mg 3 times daily) vs placebo in 475 patients with early DR.
- MAs in the macular field, on fluorescein angiograms, over 3 yr. 420 patients (266 treated with insulin and 154 not treated)
- Placebo group mean yearly increase (1.44 +/- 4.5, n = 133) was higher than in the treated group (P = 0.02).
- Clear relationship between the deterioration in ophthalmological signs and the increase in mean yearly MAs
 - clinically stable, 0.38 +/- 3.96, n = 293;
 - deteriorating, 1.79 +/- 4.89, n = 127; P = (0.002).
- “ We conclude that aspirin ... significantly slows the progression of MA evolution in early diabetic retinopathy”

Aspirin for diabetic retinopathy

The evidence of a beneficial effect is from basic science, not clinical trials

Eva M Kohner, Emeritus Professor, St Thomas's Hospital, London

- DAMAD study less microaneurysms by 1.4 per year!
- ...aspirin may become one of the possible additions to preventive treatment in diabetic retinopathy.

Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Type 2 Diabetes A RCT JPAD

Ogawa H, Nakayama M, Morimoto T et al

- **Context**

- Previous trials have investigated the effects of low-dose aspirin on primary prevention of CVD events, not in T2DM.

- **Objective**

- To examine the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with T2DM.

- **Design, Setting, and Participants**

- Multicenter at 163 institutions throughout Japan, which enrolled 2539 patients with T2DM without a history of CVD disease and had a median follow-up of 4.4 years.

- **Interventions**

- Patients were assigned to the low-dose aspirin group (81 or 100 mg per day) or placebo.

- **Main Outcome Measures**

- Primary: CVD events, including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and PAD.
- Secondary: each primary end point and combinations of primary end points as well as death from any cause.

Results: JPAD

- CVD Events

68 in the aspirin group (13.6 per 1000 person-years)
86 in the nonaspirin group (17.0 per 1000 person-years)
hazard ratio [HR], 0.80; , $P = .16$).

Combined end point of **fatal coronary events and fatal cerebrovascular**
1 patient (stroke) in the aspirin group and 10 patients in placebo
HR, 0.10; 95% CI, 0.01-0.79; **$P = .0037$**)

A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.14; log-rank test, $P = .67$).

The composite of hemorrhagic stroke and significant gastrointestinal bleeding was not significantly different between the aspirin and nonaspirin groups.

- **Conclusion**

- “In this study of patients with type 2 diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.”

Atherosclerotic Events

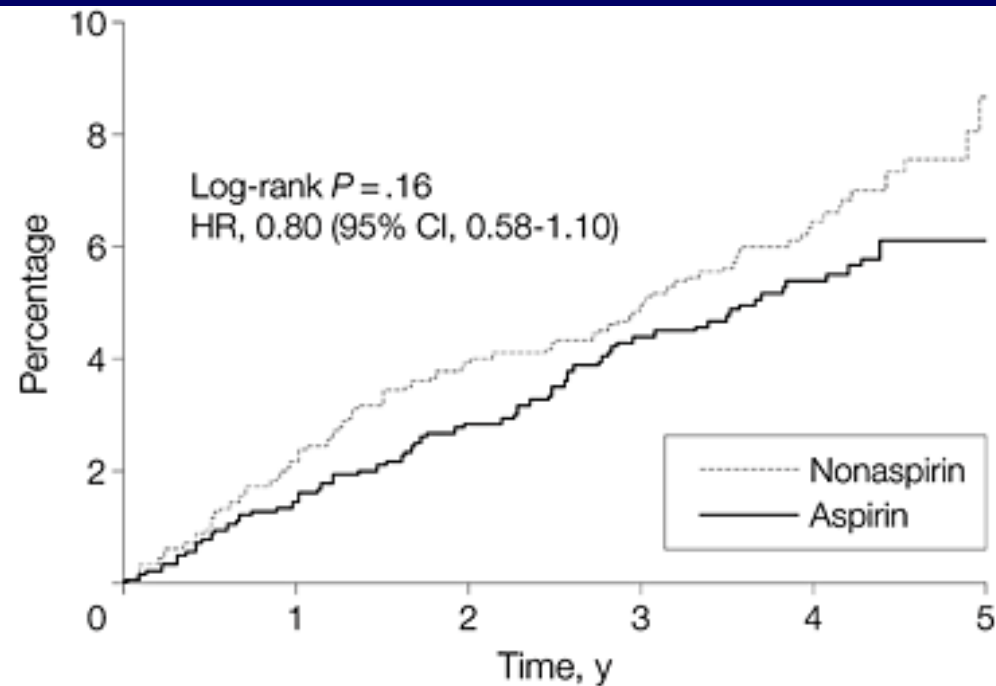
Table 2. Atherosclerotic Events

	Aspirin Group		Nonaspirin Group		Hazard Ratio (95% CI)	P Value
	No. (%)	No. per 1000 Person-Years	No. (%)	No. per 1000 Person-Years		
Primary end point: all atherosclerotic events	68 (5.4)	13.6	86 (6.7)	17.0	0.80 (0.58-1.10)	.16
Coronary and cerebrovascular mortality	1 (0.08)	0.2	10 (0.8)	2.0	0.10 (0.01-0.79)	.0037
CHD events (fatal + nonfatal)	28 (2.2)	5.6	35 (2.7)	6.9	0.81 (0.49-1.33)	.40
Fatal MI	0	0	5 (0.4)	1.0		
Nonfatal MI	12 (1.0)	2.4	9 (0.7)	1.8	1.34 (0.57-3.19)	.50
Unstable angina	4 (0.3)	0.8	10 (0.8)	2.0	0.40 (0.13-1.29)	.13
Stable angina	12 (1.0)	2.4	11 (0.9)	2.2	1.10 (0.49-2.50)	.82
Cerebrovascular disease (fatal + nonfatal)	28 (2.2)	5.6	32 (2.5)	6.3	0.84 (0.53-1.32)	.44
Fatal stroke	1 (0.08)	0.2	5 (0.4)	1.0	0.20 (0.024-1.74)	.15
Nonfatal stroke						
Ischemic	22 (1.7)	4.4	24 (1.9)	4.6	0.93 (0.52-1.66)	.80
Hemorrhagic	5 (0.4)	1.0	3 (0.2)	0.6	1.68 (0.40-7.04)	.48
Transient ischemic attack	5 (0.4)	1.0	8 (0.6)	1.6	0.63 (0.21-1.93)	.42
Peripheral artery disease ^a	7 (0.6)	1.4	11 (0.9)	2.2	0.64 (0.25-1.65)	.35

Abbreviations: CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.

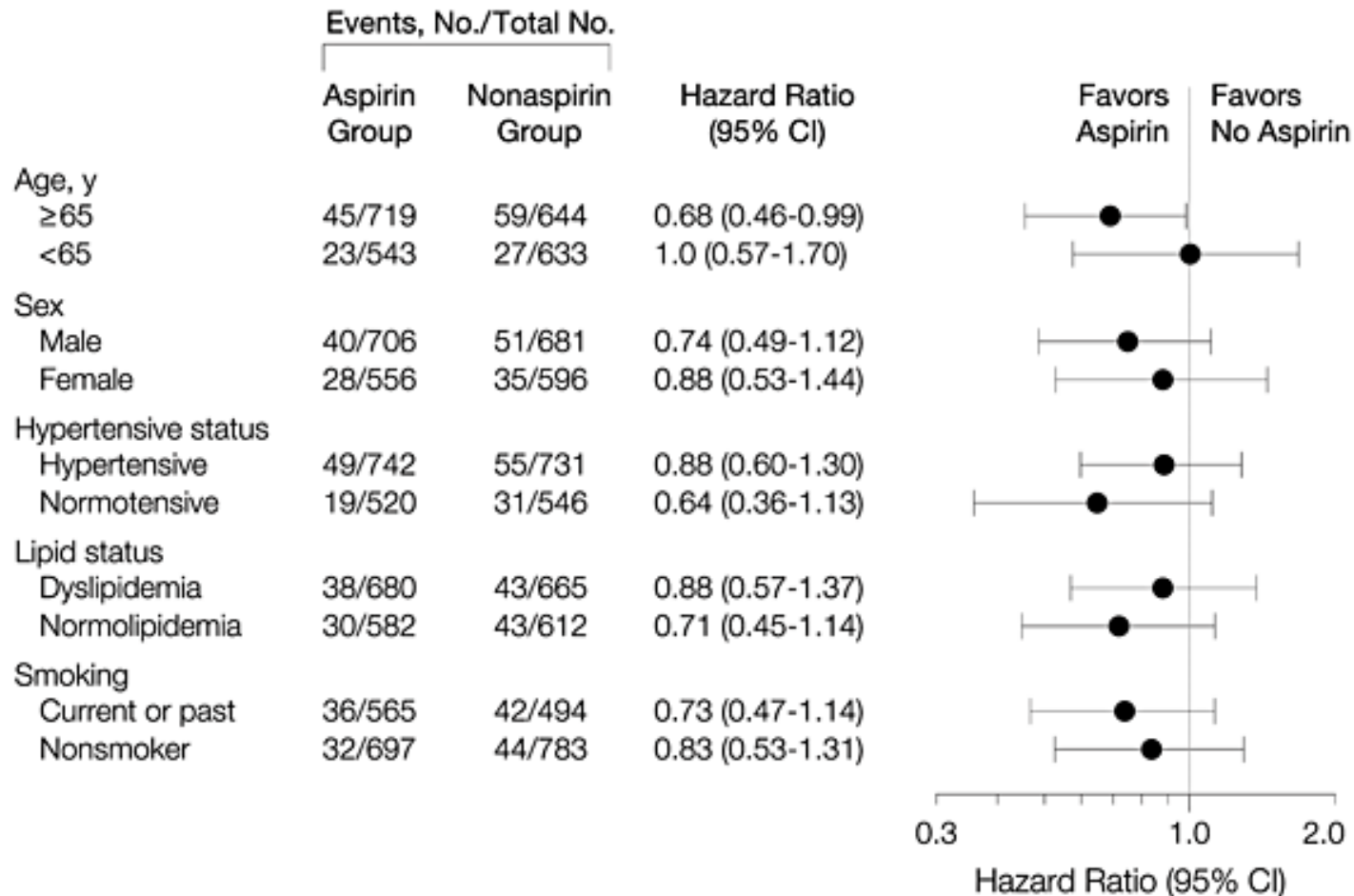
^aArteriosclerosis obliterans (5 in aspirin group and 8 in nonaspirin group); aortic dissection (2 fatal in the aspirin group and 1 nonfatal in the nonaspirin group); mesenteric artery thrombosis (1 in the nonaspirin group), and retinal artery thrombosis (1 in the nonaspirin group).

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

Subgroup Analysis of Incidence of Atherosclerotic Events



JPAD Trial Quote

- “The JPAD trial indicates that among these medications, aspirin is well tolerated for primary prevention and may provide an additional low-cost option.”
- (POPADAD: is secondary prevention study in PAD)

ASCEND Study Aims

- Determine whether 100mg daily aspirin and/or supplementation 1 gm 90% omega-3 fatty acids prevents CVD events in DM
- 10,000 patients with T2DM & no clinical evidence of occlusive CVD allocated 100mg aspirin or placebo and 1g omega-3 fatty acids or placebo for 5 years.
- A study of this size should have excellent power to detect a 20% proportional reduction in the cardiovascular event rate among such patients.

Factorial design of ASCEND

	Aspirin Tablets	Placebo Tablets	
Omega-3 FA capsules	2500 Aspirin + Omega-3 FA	2500 Omega-3 FA	Subtotal 1: 5000 Omega-3 FA
Placebo capsules	2500 Aspirin	2500 Neither	Subtotal 2: 5000 Placebo
	Subtotal A: 5000 Aspirin	Subtotal B: 5000 Placebo	

Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins

Giorgia De Berardis, Michele Sacco, Virgilio Evangelista, Alessandro Filippi, Carlo B Giorda, Gianni Tognoni, Umberto Valentini, Antonio Nicolucci, and ACCEPT-D Study Group

Introduction

- The radical Polypill Concept proposes that improvement of cardiovascular risk factors by polypharmacy can reduce the risk of events by 80%¹.
- The argument is theoretical and based on meta-analyses of the extensive existing evidence-base.
- Although the mathematical logic appears irrefutable, it seems scarcely credible that such dramatic results could be achieved in real clinical practice.
- However, in our view, considerable support for the Polypill Concept is provided by the results of the Steno-2 Study².

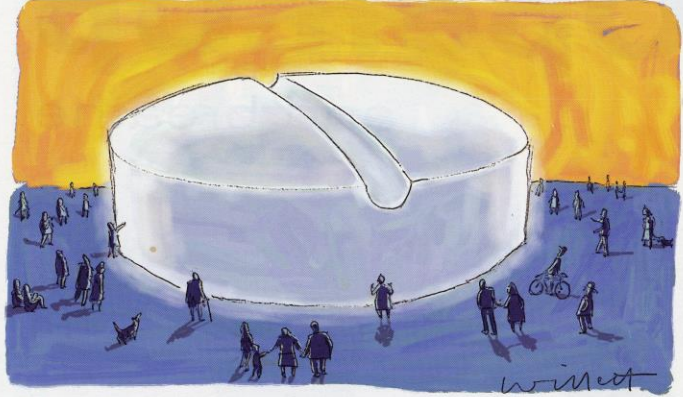
The Poly-pill Concept:

“The Polypill Concept proposes treating BP, LDL-cholesterol, homocysteine and platelet dysfunction by administration of three antihypertensive agents, a statin, folic acid and aspirin will reduce cardiovascular disease by more than 80%”

28 June 2003

BMJ

Aspostatinopitololazide Folate



326 1407-468 No 704 28 JUNE 2003 Clinical research ISSN 0959-8138

A pill to prevent 80% of heart attacks

Polypill would contain a statin, three antihypertensives, folic acid, and aspirin [pp1407, 1419, 1423, 1427]

↓ CM At+ PC an to PM pvan

Managing chronic pain in children p1408
Molecular epidemiology can help in Chagas' disease p1444
Positron emission tomography p1449
How consultants value aspects of their work p1432
The return of Questions and Answers p1412

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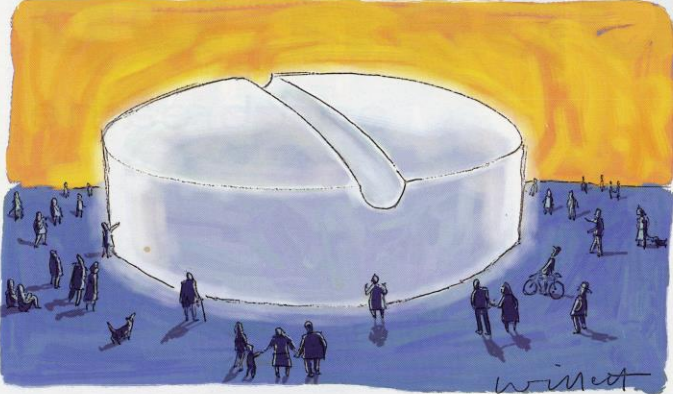
The Diabetes Polypill?

X?
Y?
Z?
A?
B?

28 June 2003

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The Diabetes Polypill?

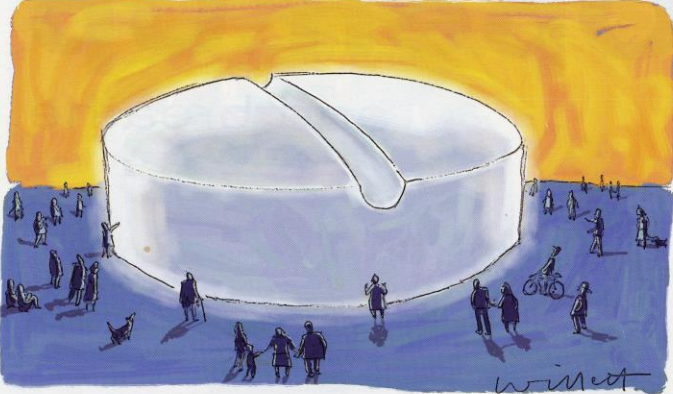
Statin
Aspirin
Metformin
Thiazide
ACE-I or ARB

Indolinguistically: “equality” ie in terms of reducing morbidity and mortality esp. CVD

28 June 2003

BMJ

Aspostatinopitololazide Folate



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Polypill Concept in reducing Cardiovascular Events

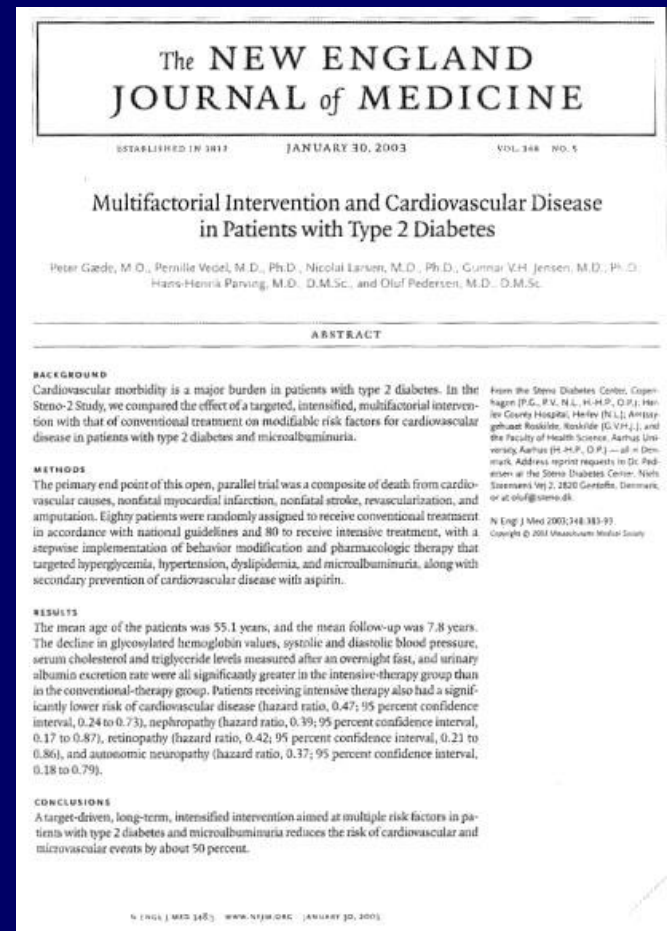
	Polypill proposal ¹		
Risk Factor	Reduction in risk factor	% Reduction in Cardiac Events	Relative risk reduction in CVD events
LDL-C	-1.8 mmol/l	61%	0.39
Diastolic BP	-11 mmHg	46%	0.54
Aspirin effect	100% treated	32%	0.68
Serum Homocysteine	-3 umol/l	16%	0.84
Combined Effect	-	88% Reduction in CVD events	0.12

Table 1:

The Steno-2 Study : A Summary

Steno Diabetes Centre
Copenhagen, Denmark

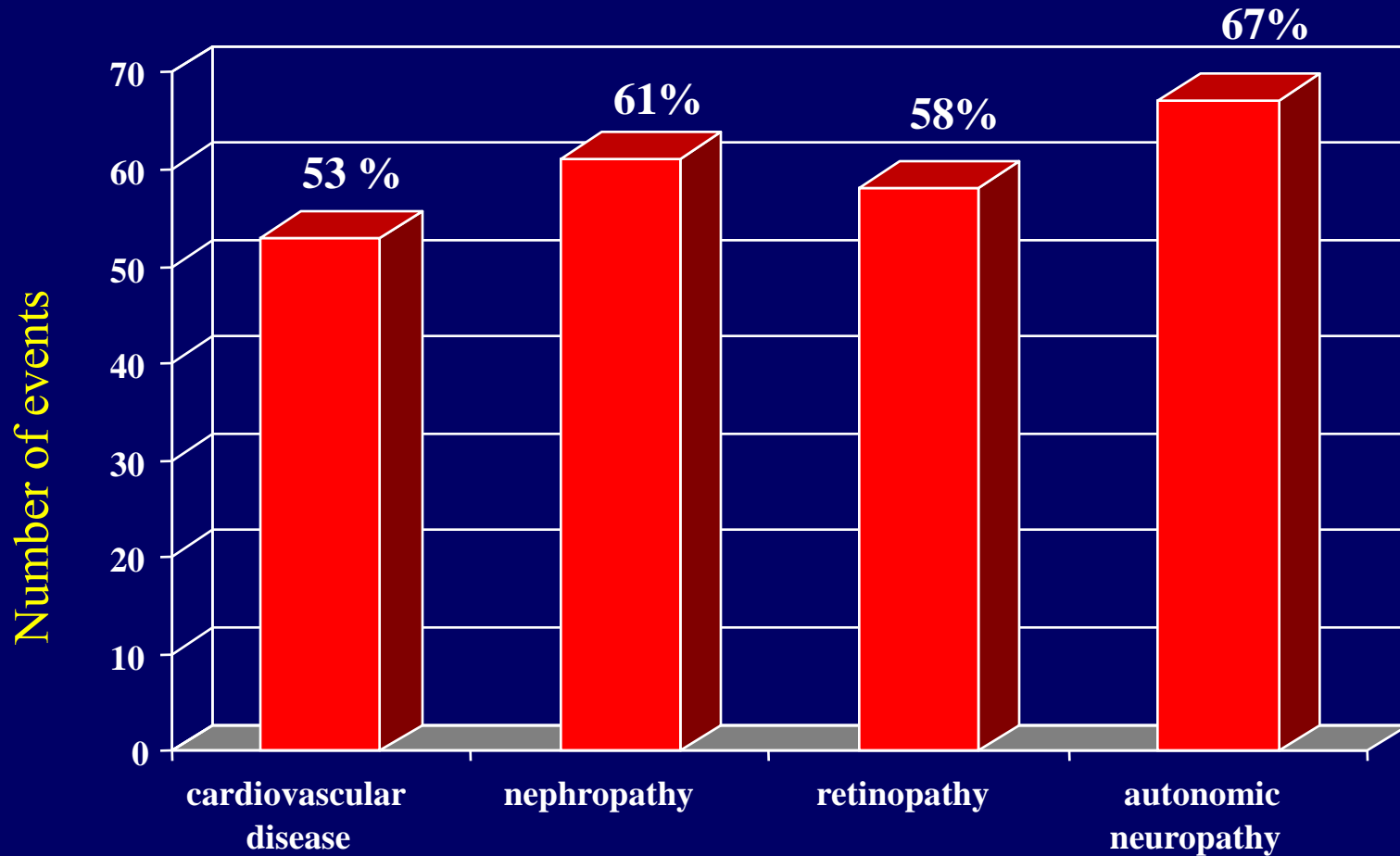
- 160 with T2D and microalbuminuria
- 80 allocated to conventional treatment
- 80 allocated to intensive treatment
- Mean age 55.1 years
- Mean follow-up 7.8 years



Steno-2 Targets Achieved

	Intensive	Conventional
Advice	Standard	Standard
Blood Pressure	131 / 73	146/78
Cholesterol	TC 3.5 mmol/l LDL 1.8 mmol/l	5mmol/l
Diabetes Control : HbA1c%	7.9%	9%
Eyes	Annually	Annually
Feet	Annually	Annually
Guardians : aspirin, ACEI / AIIA	All on ACE-I	
Statins and Aspirin	85%, 100%	22%

Steno 2: Event Reduction



Steno-2 : CVD Event Reduction

Event	Conventional	Intensive
Cardiovascular Death	7 ...died earlier!	7
MI : non-fatal	17	5
CABG	10	5
PCI	5	0
Stroke : non-fatal	20	3
Amputations	14	7
Revascularisation for PVD	12	6
<i>P<0.002</i>	85 events in 35 patients 44% overall	33 events in 19 patients 24% overall

Steno-2 : CVD Deaths at 13 years

Event	Conventional Mortality 30%	Intensive Mortality 50%
Cardiovascular Deaths	Reduced by 57%!	
<i>P</i> <0.05		

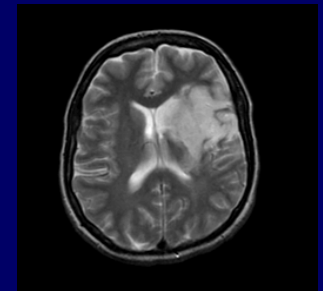
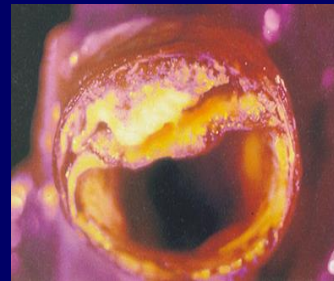
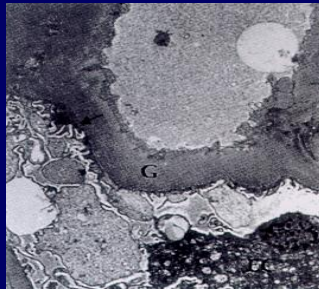
Steno-2 : 13 years follow up data

Event	Reduction in Intensive Group
All Deaths	46%
Cardiovascular Deaths	57%
Cardiovascular events	59%
End Stage Renal Failure	1 versus 6 patients
Retinal Laser Rx	55%
Aspirin Effect	32% of above total effect
<i>P<0.05</i>	

Absolute risk reduction for ESRD was 6.3%

Steno-2 : Conclusion

“ A target driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria reduces the risk of cardiovascular and microvascular events by about 50%. ”



Steno-2 Study:

Estimated baseline Cardiac Risk and Observed Cardiac event rates

Event	Steno-2 conventional intervention cohort	Steno-2 intensive intervention cohort
UKPDS estimated events for 100 subjects over 10 years		
UKPDS Cardiac Event Rate	39.8	36.2
Steno-2* Expected Cardiac Event Rate	79.6	72.4
Observed events during Steno-2 study		
Cardiovascular deaths	7	7
Nonfatal myocardial infraction	17	5
Total events	24	12
× 1.25 to obtain event rate over 10 years from 7.8 yrs in the study , then: × 1.25 to obtain event rate for 100 subjects from 80 in the study		
Predicted event rate for 100 subjects over	37.5	18.8

10 yrs

Table 2: This table compares the observed cardiac event rates in Steno-2 with the UKPDS risk engine baseline estimates. *x 2 for microalbuminuria⁴. **Steno-2 followed 80 subjects for an average of 7.8 years: to enable comparison, the event rates need to be adjusted upwards to obtain the equivalents for 100 subjects over 10 years.

Polypill predicted benefits of risk factor reductions in the Steno-2 Study

Risk Factor	Polypill Concept factors that apply in Steno-2		Steno-2 Conventional intervention cohort		Steno-2 Intensive intervention cohort	
	Reduction in risk factor	Relative risk	Reduction in risk factor	Relative risk	Reduction in risk factor	Relative risk
LDL-Cholesterol	-1.8 mmol/l	0.39	-0.336 mmol/l	0.89	-1.215 mmol/l	0.59***
Diastolic BP	-11 mmHg	0.54	-8 mmHg	0.67	-12 mmHg	0.50
Aspirin effect	100% treated	0.68	43.8% treated	0.86	72.5% treated	0.77
All three interventions	-	0.143	-	0.513	-	0.227
% reduction Cardiac risk Predicted	-	85.7%	-	48.7%	-	77.3%

Table 5:

Observed outcomes in Steno-2 compared with Polypill Concept predictions

	Steno-2 Conventional intervention cohort	Steno-2 Intensive intervention cohort
UKPDS estimated events adjusted for microalbuminuria (from Table 2)	79.6	72.4
% reduction in risk predicted by Polypill effect (from Table 3)	48.7%	77.3%
Event rate predicted by Polypill effect per 100 patients/10 years	40.8	16.4
Steno-2 observed event rate (from Table 2)	37.5	18.8
Steno-2 event rate reduction from baseline estimate	52.9%	74.0%

Table 4: The % reduction in Cardiac events predicted by the Polypill Concept are remarkably similar to the Steno-2 event rate reduction, similarly the event rate predicted by the Polypill Concept is also similar to the Steno-2 observed event rate.

Conclusion

- CVD reduction predicted Polypill Concept is remarkably similar to the Steno-2 event rate reduction:

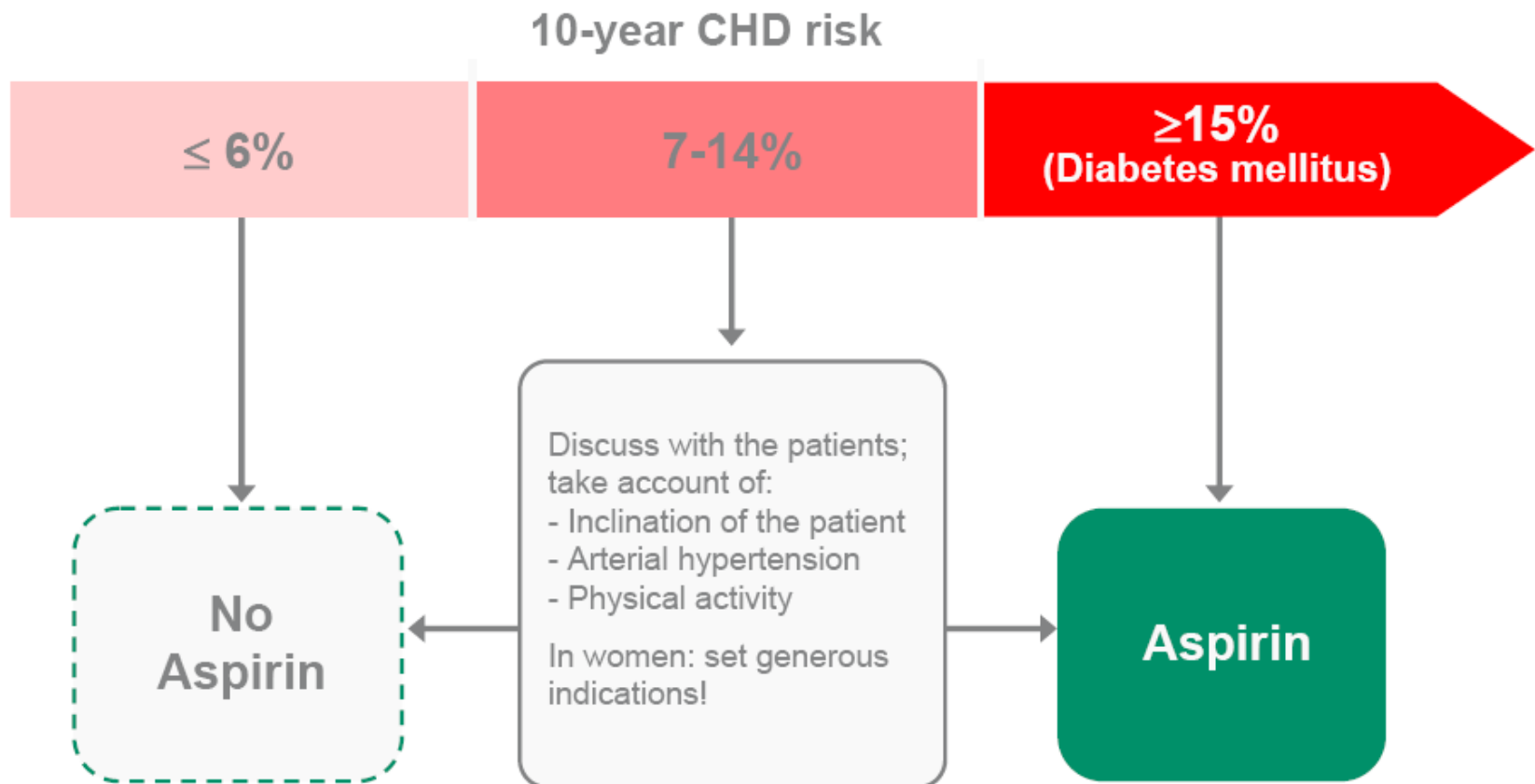
Conventional: 48.7% vs 52.9%, Intensive: 77.3% vs 74.0%

Similarly, event rate predicted by the Polypill Concept is also similar to the Steno-2 observed event rate:

Conventional: 40.8 vs 37.5, Intensive: 16.4 vs 18.8

- Aspirin an essential component of this strategy!







Aspirin in primary prevention: summary of international recommendations



Aspirin® Update

International Press Workshop 2008

Six completed primary prevention studies with Aspirin

Study	n	Mean follow-up (years)*	Aspirin [®] dose per day (mg)	Control group	Patients		
					Age (years)	Risk factors	10-year risk for a first cardiovascular event
WHS 2005	39,876	10	100 every 2 days	Placebo	> 45	Healthy women	 2.5%
HOT 1998	18,790	4	75	Placebo	50-80	Men + women with hypertension	 3.6%
PPP 1994-2001	4,495	3.6	100	No medication	>50	Men + women with ≥ 1 risk-factor for CHD	 4.3%
PHS 1982-1988	22,071	5	325 every 2 days	Placebo	40-84	Healthy male doctors	 4.8%
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TPT 1998	5,499	5	75	Placebo	45-69	Men with high CV risk	 12.4%

WHS – Women’s Health Study: N Engl J Med 2005; 352: 1293-1304

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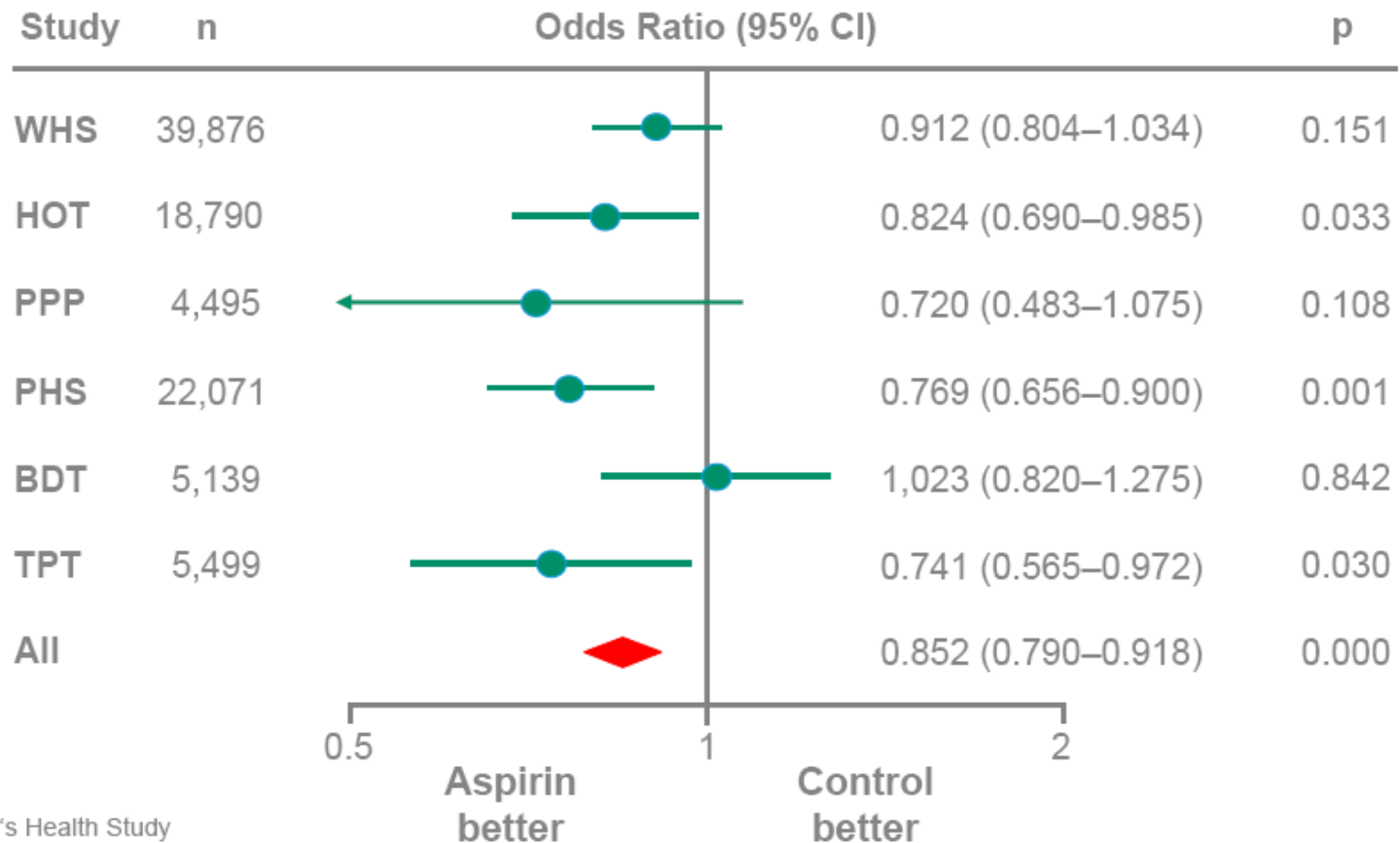
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Aspirin[®] Update

International Press Workshop 2008

Meta-analysis of the six primary prevention studies with Aspirin



WHS – Women's Health Study
 HOT – Hypertension Optimal Treatment trial
 PPP – Primary Prevention Project
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 TPT – Thrombosis Prevention Trial



Aspirin® Update

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A Quote from the Indian Philosopher

Farrokh Bulsara (1946 -1991)

- Farrokh Bulsara, on the island of Zanzibar
- Bomi and Jer Bulsara were ethnic Parsis from the Gujarat, India
- From the town of Bulsar (also known as Valsad) in southern Gujarat.
- At 8, St. Peter's School, a boarding school for boys in Panchgani near Mumbai, India.
- At the age of 17, the family moved into a small house in Feltham, London
- He also held a job at Heathrow airport (catering).

A Quote from the Indian Philosopher

Farrokh Bulsara (1946 -1991)

Open your eyes,
Look up to the skies and see,

A Quote from the Indian Philosopher Farrokh Bulsara (1946 -1991)

No escape from reality

Open your eyes, Look up to the skies and see,
....a poor boy, I need no sympathy,

“Galileo figaro
Magnifico I'm just a poor boy and nobody loves me...

Spare him his life from this monstrosity

A Quote from the Indian Philosopher

Farrokh Bulsara (1946 -1991)

Freddie Mercury: Queen - Bohemian Rhapsody

No escape from reality

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DEMAND



ASPIRIN

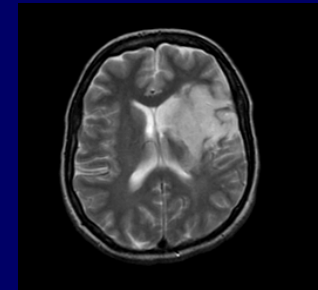
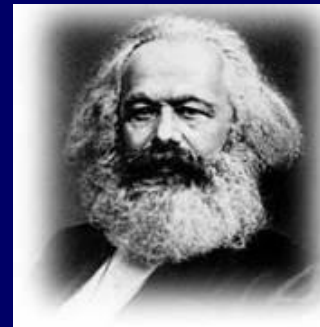
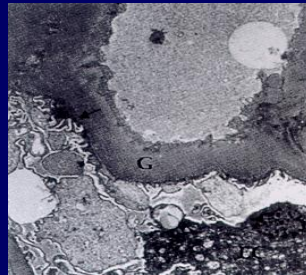
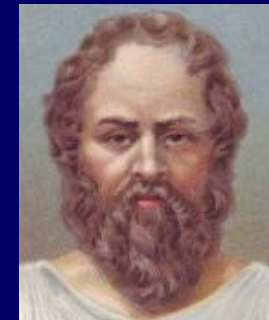
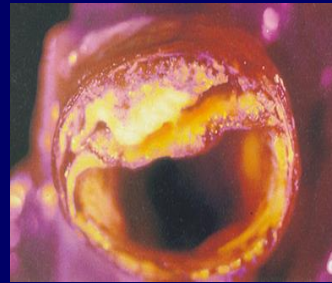
Unless you see the "Bayer Cross" on package or on tablets you are not getting the genuine Bayer Aspirin proved safe by millions and prescribed by physicians over twenty-seven years for

Colds	Headache
Neuritis	Lumbago
Toothache	Rheumatism
Neuralgia	Pain, Pain

DOES NOT AFFECT THE HEART

Aspirin Resistance:

“ A condition defined as the inability of clinicians, whether pogonophobic or not, to consider aspirin for their patients with diabetes despite evidence indicating its use in the high risk patient”



A World Class NHS: Our Vision

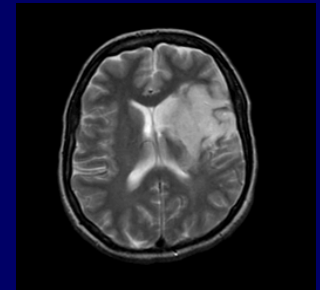
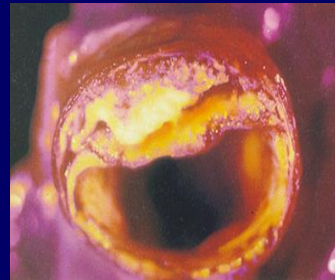
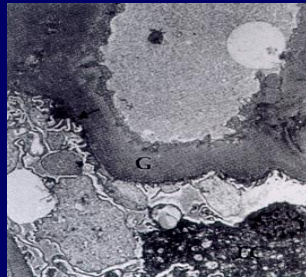


- **Fair** – equally available to all, taking full account of personal circumstances and diversity
- **Personalised** – tailored to the needs and wants of each individual, especially the most vulnerable and those in greatest need, providing access to services at the time and place of their choice
- **Effective** – focused on delivering outcomes for patients that are among the best in the world
- **Safe** – as safe as it possibly can be, giving patients and the public the confidence they need in the care they receive.



Aspirin Resistance:

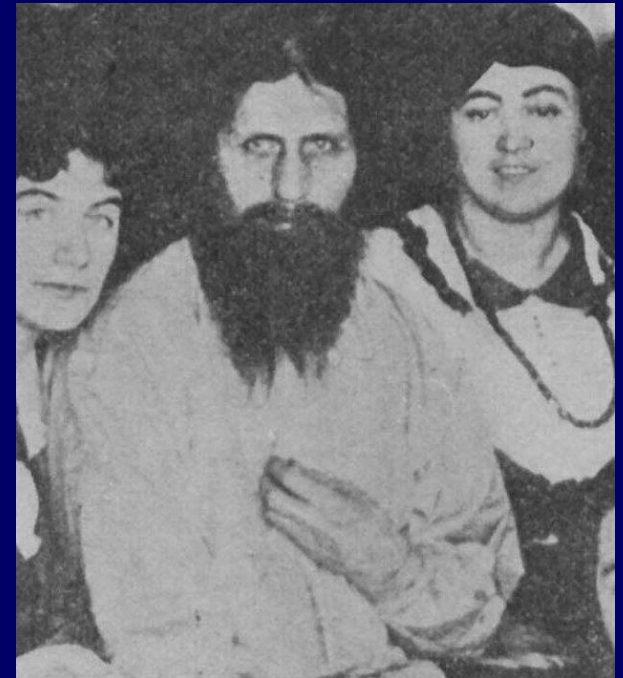
“ A condition defined as the inability of clinicians, to consider aspirin for their patients with diabetes despite evidence indicating its use the high risk patient”



Who is this ?

How did aspirin contribute to his success ?

Name 3 contraindications.

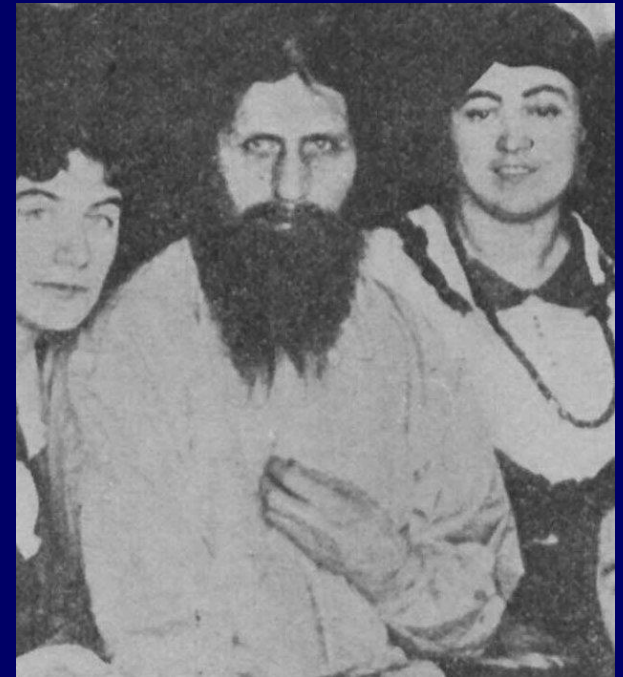


Who is this ?

How did aspirin contribute to his success ?

Name 3 contraindications.

- **Rasputin**
- **Uncontrolled hypertension, active peptic ulceration, < 16 years, breast feeding, bleeding disorder, allergy or intolerance**



Raj: lorry driver (now unemployed) aged 56 years, father of 3 children



Overweight, often snacks

Brother recent MI!

Case History:

- Worried!
- HbA1c 8.3%
- BP 154/92 mm/Hg
- Total cholesterol 6.4 mmol/l
- LDL 4.2, HDL 0.9
- Central obesity waist – 40 inches.
- Microalbuminuria positive

• Current Rx:

1: Metformin

2: Simvastatin 40mg

3: Ramipril 10mg

??

**Would you put
him on Aspirin?**

*You can see 6 different cards.
Think on one.
Just think on it.*

I will find the card on your mind

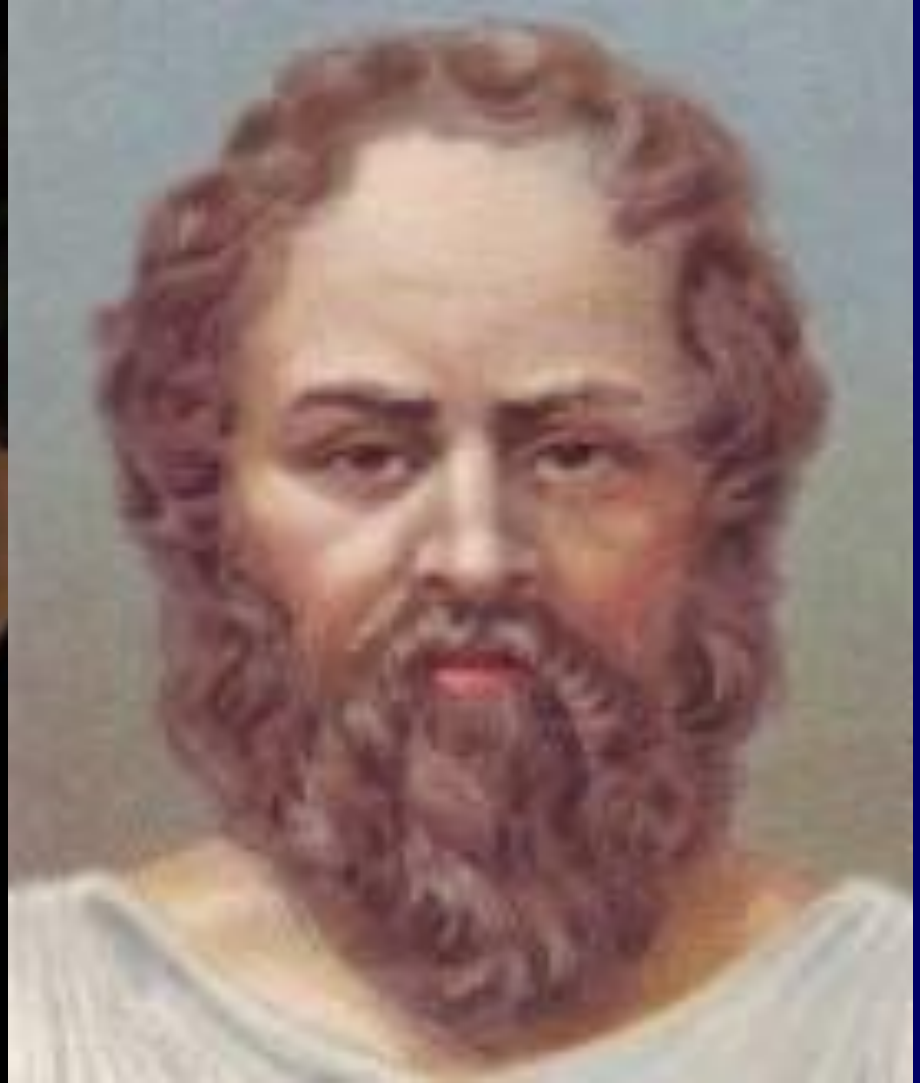


Just choose one card,

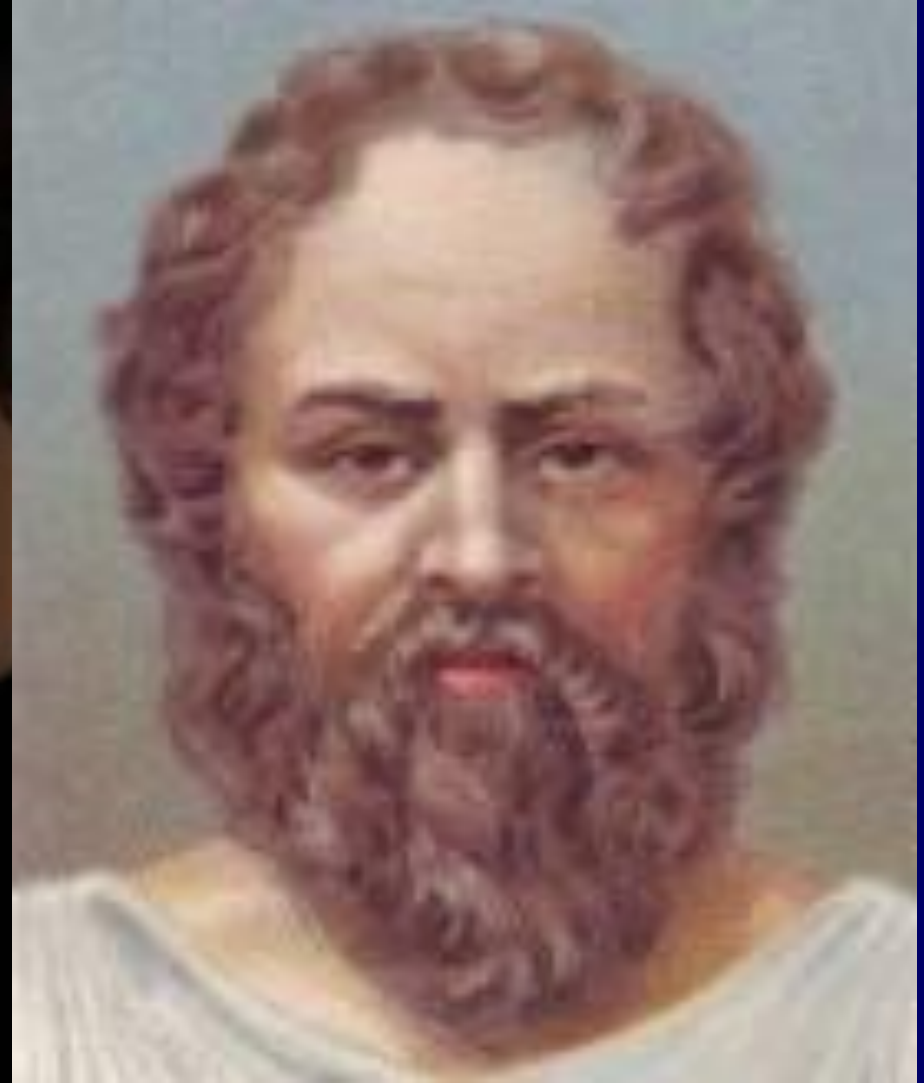
If artist you be,

If aspirin you think fine,

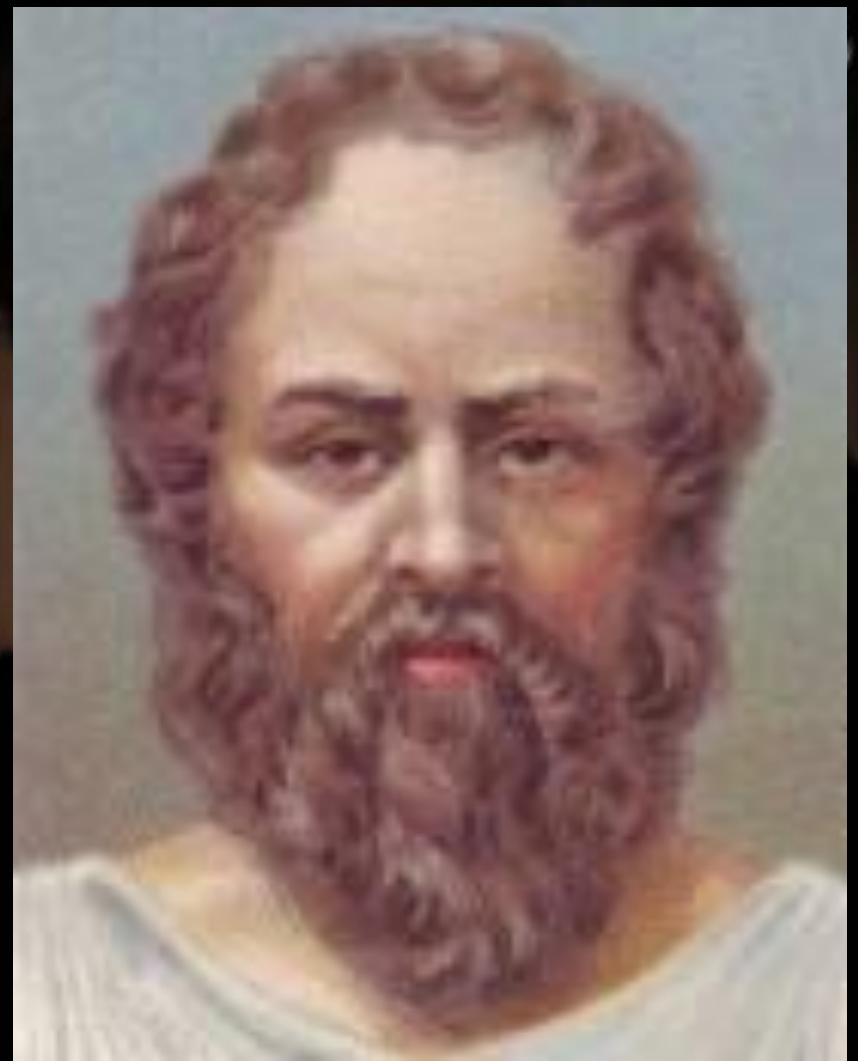
This test will reveal!



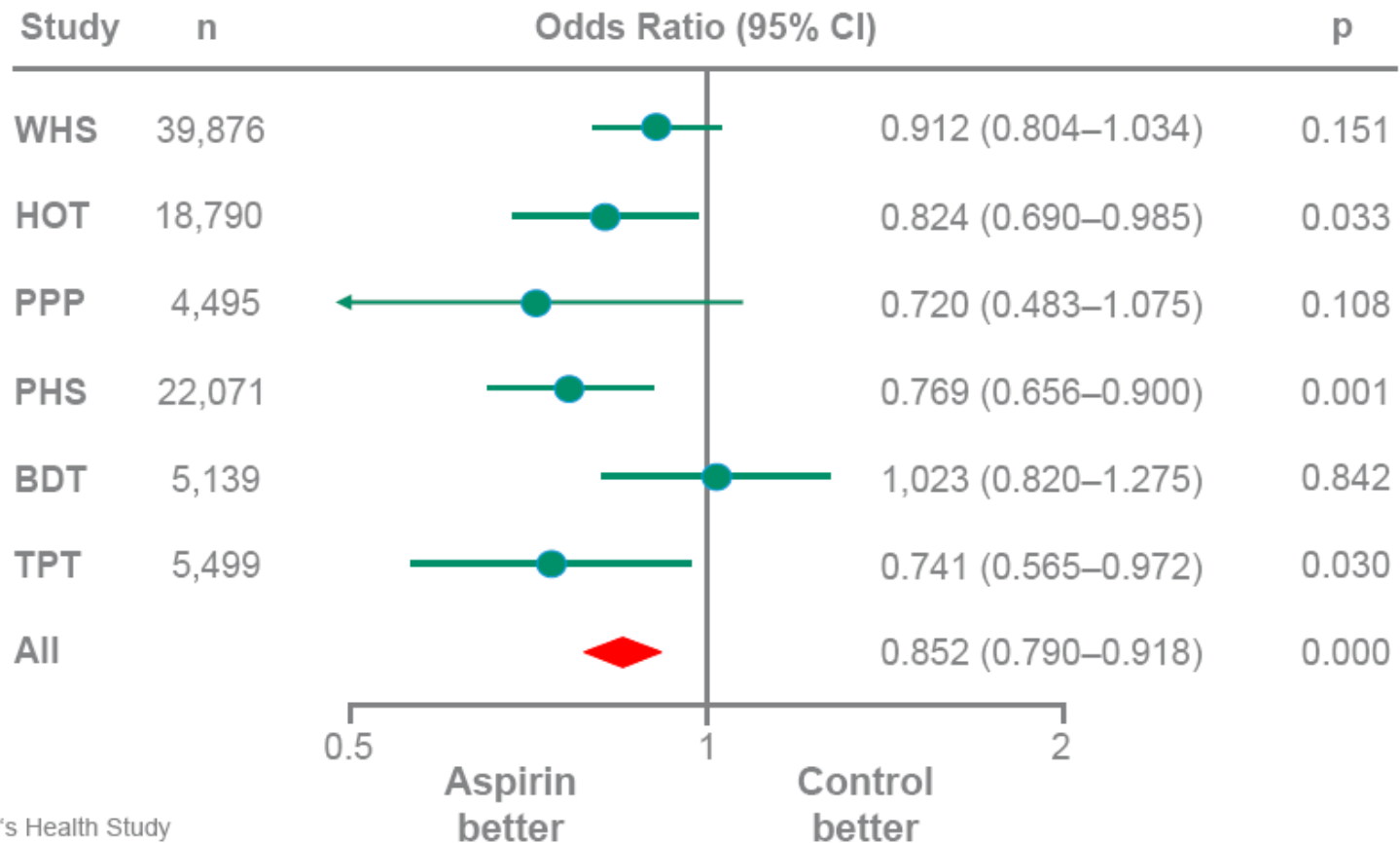
*You can see 6 different cards.
Think on one.
Just think on it.
Do not touch it
Do not click on it.
I will find the card on your mind*



*¡Look!
¡¡ Your card is
gone!!*



Meta-analysis of the six primary prevention studies with Aspirin



WHS – Women's Health Study
 HOT – Hypertension Optimal Treatment trial
 PPP – Primary Prevention Project
 PHS – Physicians' Health Study
 BDT – British Doctors' Trial
 TPT – Thrombosis Prevention Trial



Aspirin® Update

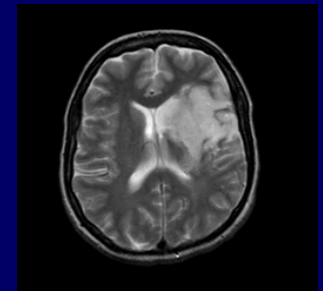
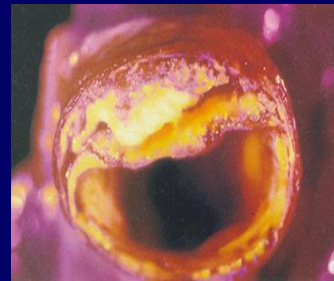
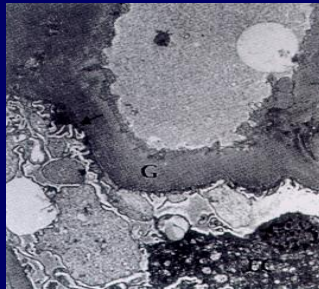
International Press Workshop 2008

Aspirin Resistance?:

“ A condition defined as the inability of clinicians, to consider aspirin for their patients with diabetes despite evidence indicating its use in high risk patient”

“that is not you as the scientist and the artist!”

Thank You!

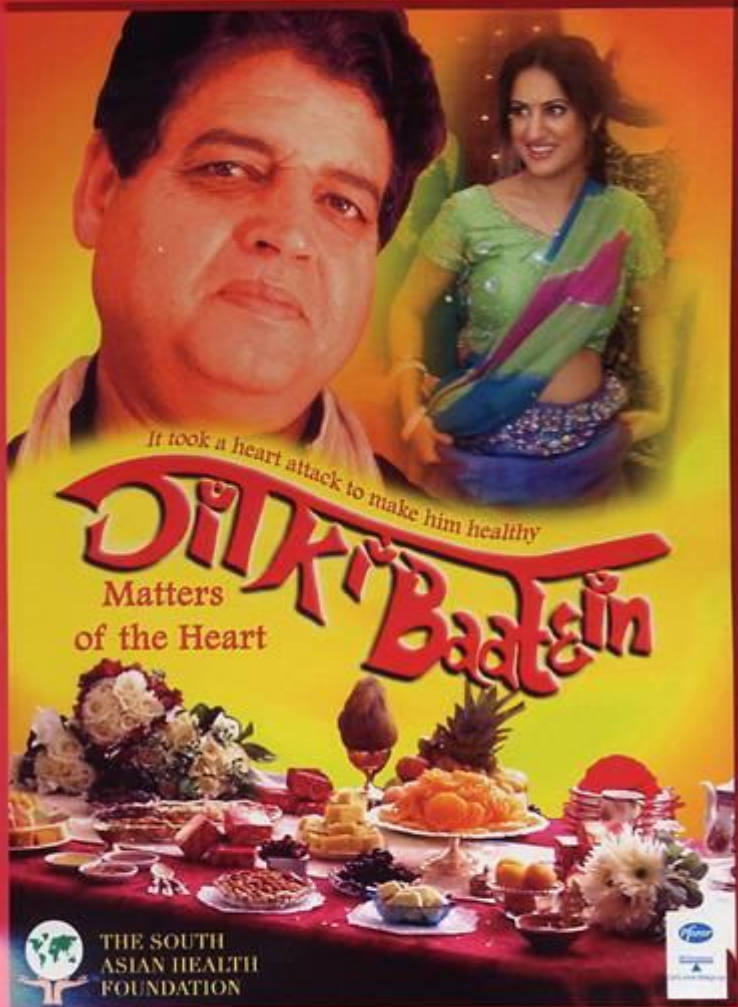


Pink Sequin Productions presents

DiLKi BaatEin Matters of the Heart

THE SOUTH ASIAN HEALTH FOUNDATION
S.A.H.F.

Pink Sequin Productions presents



It took a heart attack to make him healthy

DiLKi BaatEin

Matters of the Heart



THE SOUTH ASIAN HEALTH FOUNDATION

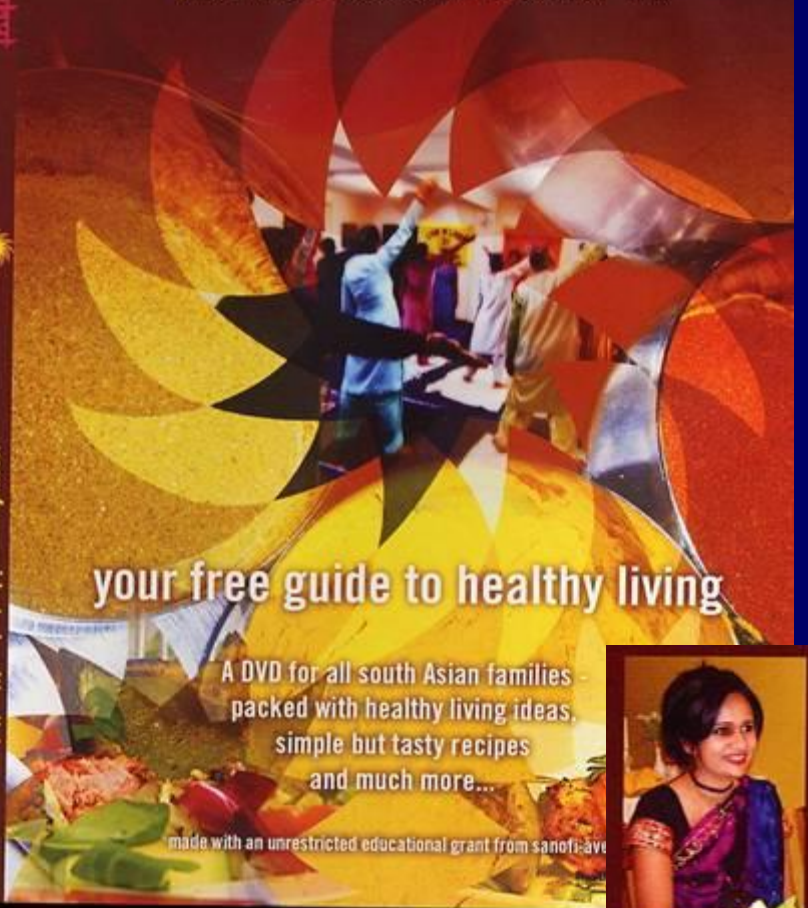
A heart health education film

आपके सेहत

Your free guide to healthy living

आपके सेहत

Healthy choices for a better life



your free guide to healthy living

A DVD for all south Asian families - packed with healthy living ideas, simple but tasty recipes and much more...

made with an unrestricted educational grant from sanofi-ave



- But, most younger and middle-aged people with diabetes do not have manifest arterial disease - although they are still at significant cardiovascular risk - and yet the available randomised evidence for the use of antiplatelet therapy in such individuals is sparse.
- As a result, there is major uncertainty about the role of antiplatelet therapy for the primary prevention of cardiovascular events among people with diabetes, and only a small minority receives it.
- Surveys from around the world indicate that in general less than 20% of patients with diabetes and no vascular disease take regular aspirin.
- The main randomised evidence currently available on the effects of antiplatelet therapy in such patients with diabetes comes from 9 trials involving a total of about 5000 patients, and a meta-analysis of their results indicates a much smaller proportional reduction in cardiovascular events than has been found in the secondary prevention setting (just 7% compared with about 20-25%:
- Even in aggregate, however, those studies in diabetics involved relatively few events, and the confidence interval for the estimated effect is wide, ranging from a 23% risk reduction to an 8% hazard.

- Given the consistency of the beneficial effect in other high-risk settings (including patients with diabetes and arterial disease), it seems likely that the true effect of antiplatelet therapy in people with diabetes alone is similar to the reduction of about one-quarter seen overall in high-risk patients as, for example, has been shown with cholesterol-lowering[3] and anti-hypertensive therapies[4].

Eligibility

Inclusion Criteria:

- Men and women with diabetes (Type 1 or 2)
- Age \geq 40 years with no previous history of vascular disease
- No clear contra-indication to aspirin
- No other predominant life-threatening medical problem (e.g. cancer)

Exclusion Criteria:

- Definite history of myocardial infarction, stroke or arterial revascularisation procedure
- Currently prescribed aspirin, warfarin or any other blood thinning medication

Cardiovascular Prevention in Focus

Professor Dr. Harald Darius
Department of Internal Medicine – Cardiology &
Intensive Care Medicine,
Vivantes Berlin-Neukölln Medical Center,
Germany

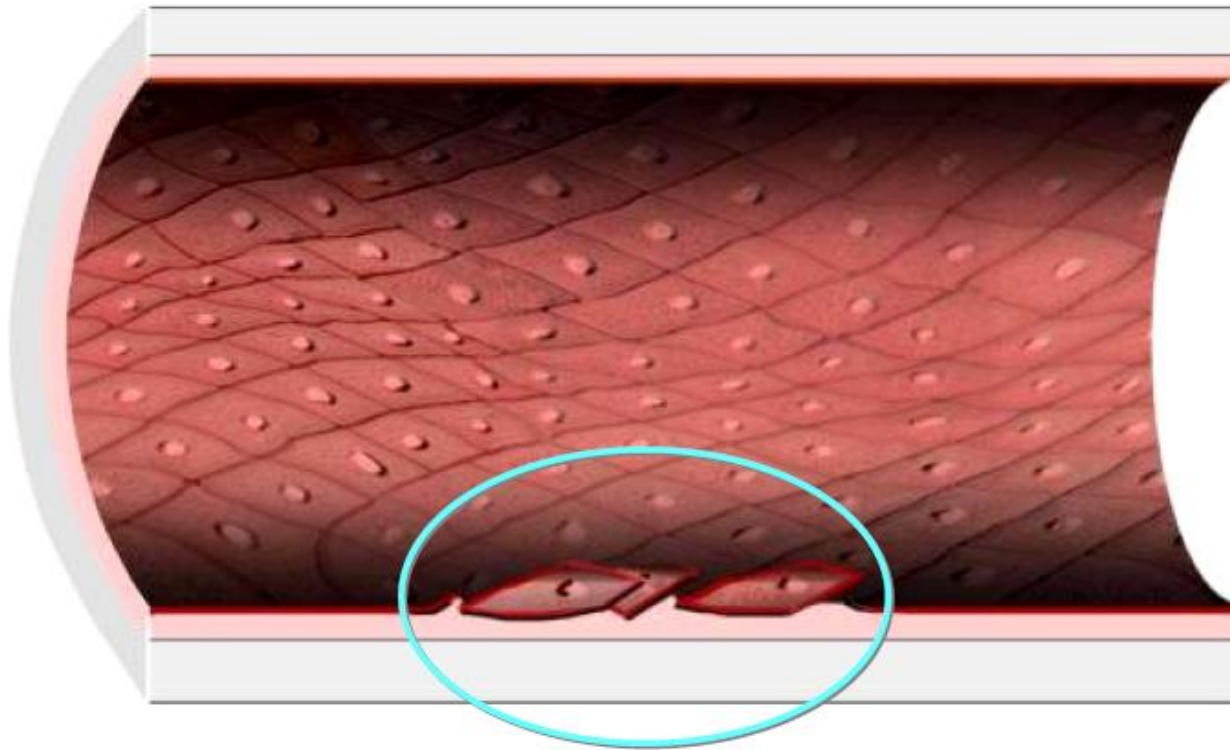
Bitterfeld, June 19, 2008



Aspirin® Update

International Press Workshop 2008

The way to myocardial infarction: An initially insidious process...



Endothelial injury

Injury to and inflammation of the epithelium
as a result of hypertension, diabetes,
smoking, etc.



Aspirin® Update

International Press Workshop 2008

The way to myocardial infarction: An initially insidious process...



Endothelial injury



**Inflammation and
deposition processes
(over years)**

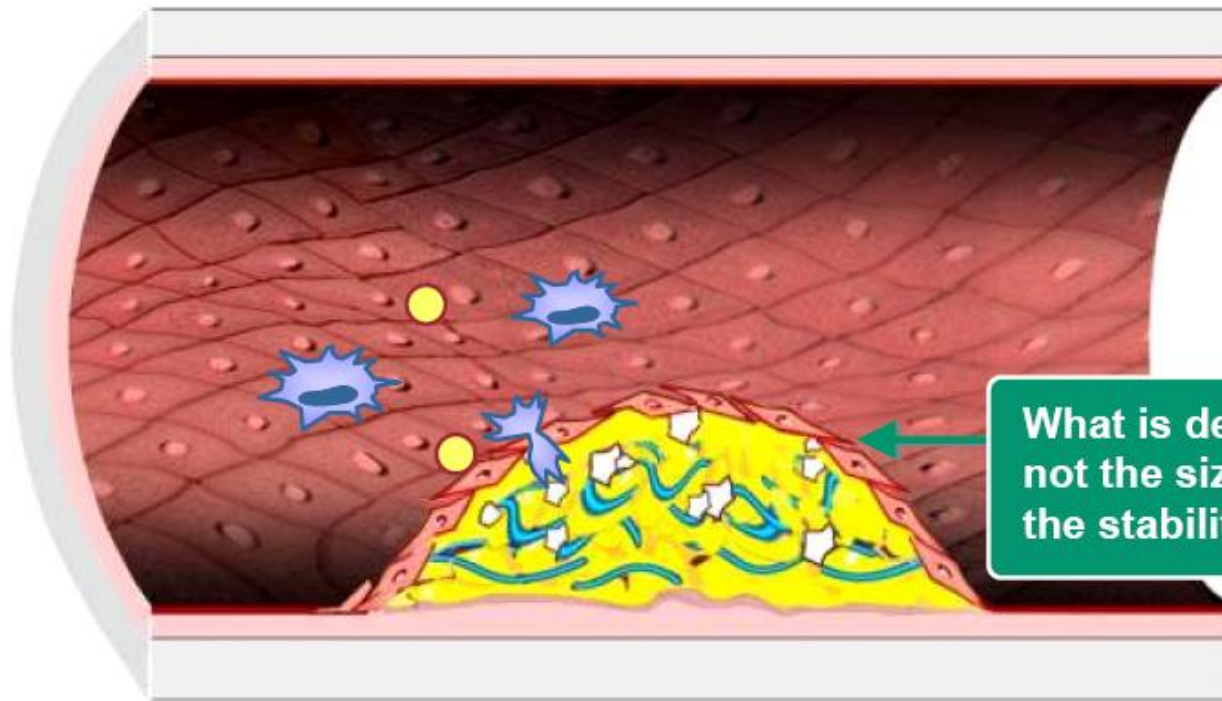
First deposition of fat ("fatty streak").
Attraction of defence cells, which take up LDL
particles, die and become deposited.



Aspirin® Update

International Press Workshop 2008

The way to myocardial infarction: An initially insidious process...



Endothelial injury



**Inflammation and
deposition processes
(over years)**

**What is decisive for the risk is
not the size of the plaque but
the stability of its cap**

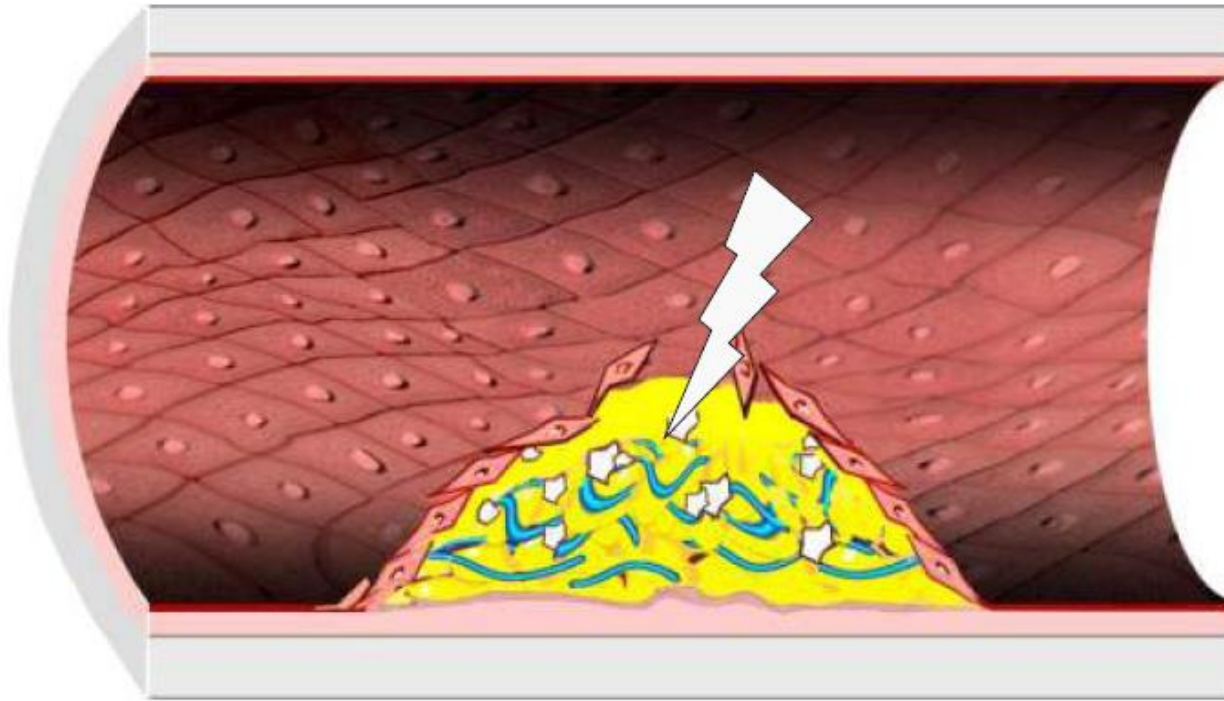
Under the influence of growth factors, smooth muscle cells migrate into the vascular endothelium.
A connective tissue cap is formed.



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International Press Workshop 2008

...that suddenly picks up speed...



Endothelial injury
↓
Inflammation and
deposition processes
(over years)
↓
Plaque rupture

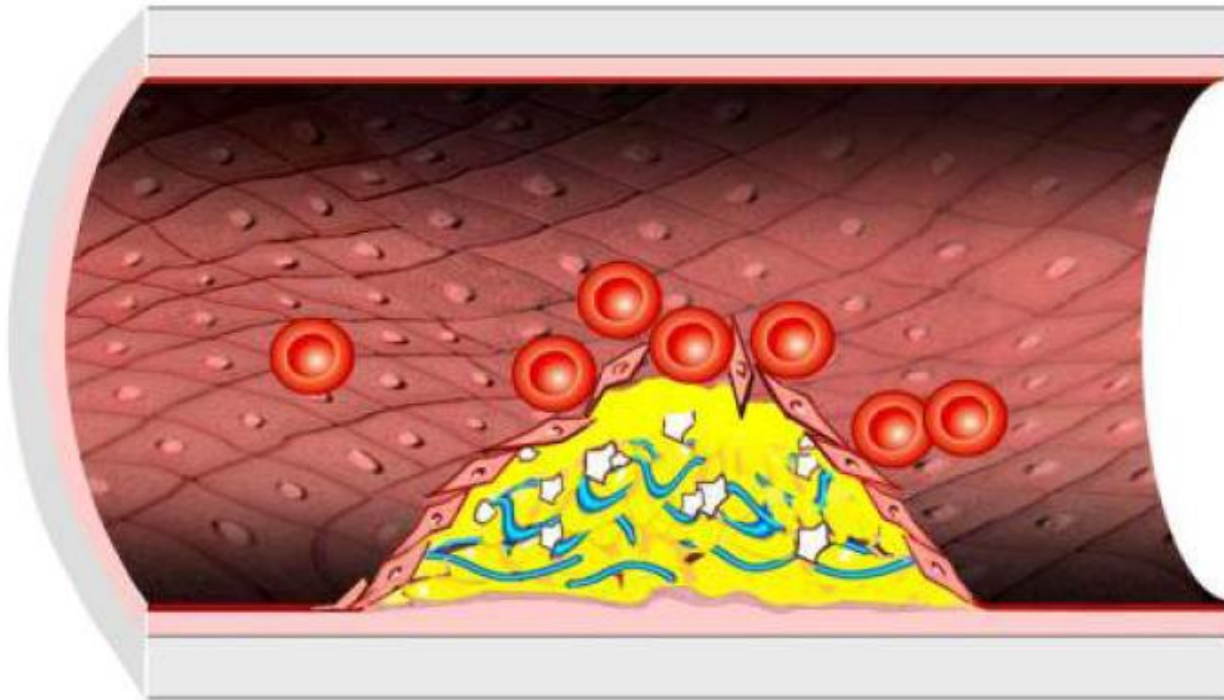
The deposit may suddenly rupture due to mechanical effects (e.g. increase of blood pressure) or to processes in the vascular wall = plaque rupture



Aspirin[®] Update

International Press Workshop 2008

...that suddenly picks up speed...



Endothelial injury



Inflammation and
deposition processes
(over years)



Plaque rupture



**Rapid activation of
platelets**

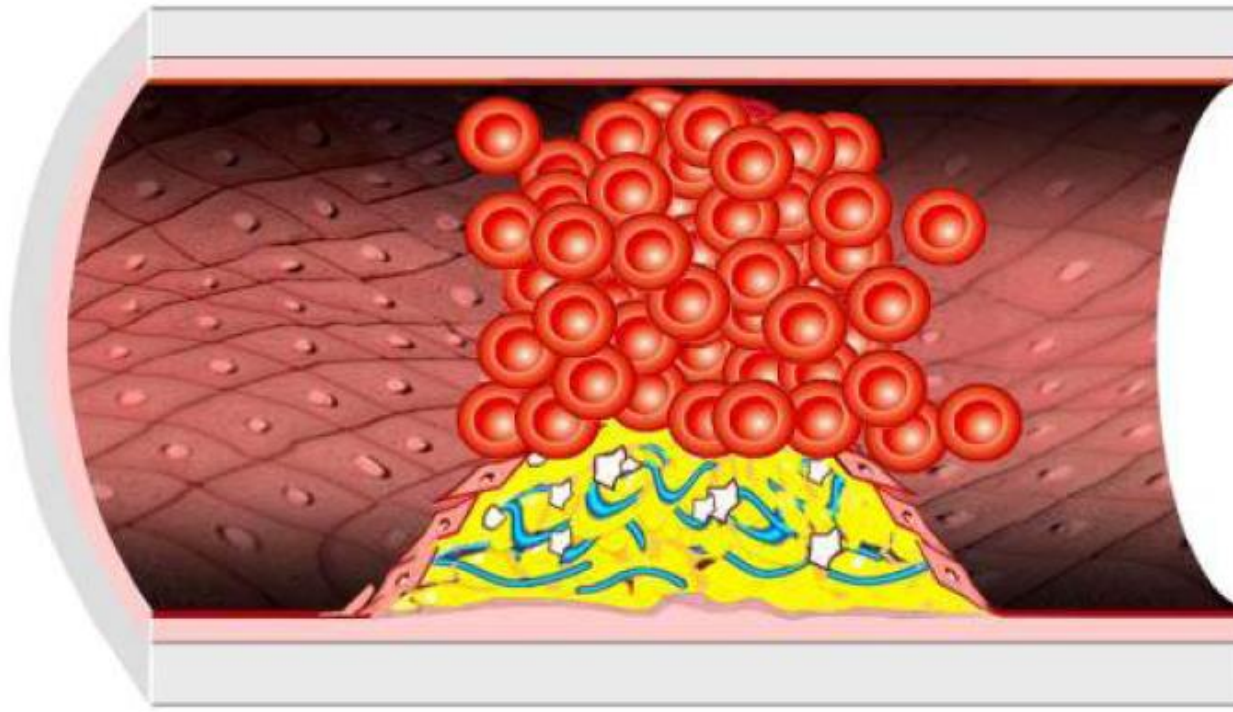
Blood platelets immediately migrate to the site
of the event in order to seal the leak.
More platelets are attracted.



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International Press Workshop 2008

...and peaks dramatically!



Endothelial injury



Inflammation and
deposition processes
(over years)



Plaque rupture



Immediate activation
of platelets



**Thrombus formation
with vascular occlusion:
myocardial infarction!**

By clumping together, the platelets form a blood clot (thrombus). The vessel is blocked.

A serious emergency for the heart because the unsupplied heart muscle tissue dies very quickly.



Aspirin® Update

International Press Workshop 2008

After surviving infarction: Long-term treatment to protect the heart

Basic antiplatelet/ anticoagulant therapy

- Acetylsalicylic acid (e.g. Aspirin® Protect/Aspirin Cardio®)
- Clopidogrel
- Marcumar

Treatment of the underlying disease (some examples)

Drugs

- ACE inhibitors
- AT₁ blockers
- Beta-blockers
- Cholesterol reducers
- Calcium-antagonists
- Diuretics
- Nitrates
- Diabetes drugs

General measures

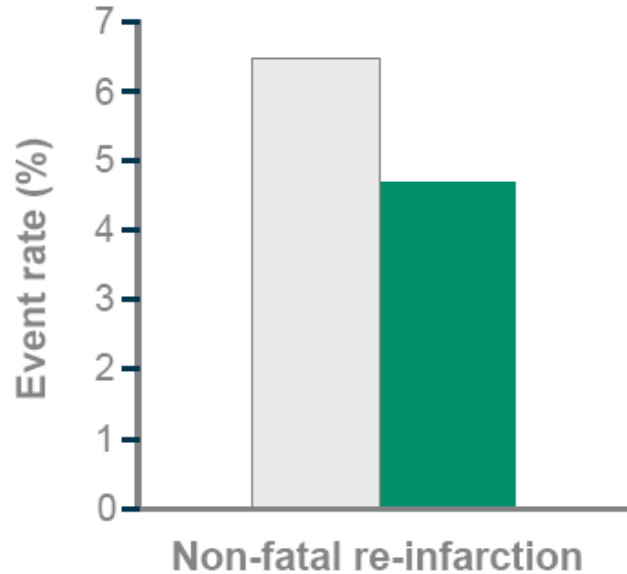
- Heart sports group
- Mediterranean diet



Aspirin® Update

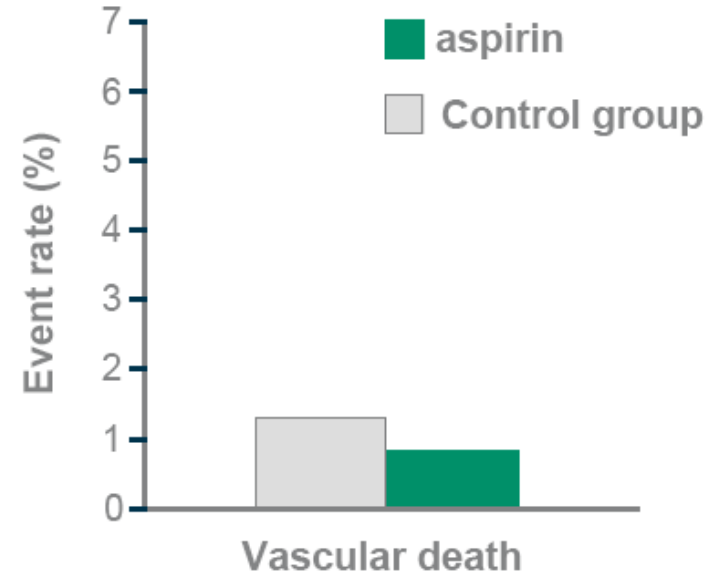
International Press Workshop 2008

Low dose Aspirin: significant reduction of non-fatal re-infarction and mortality



28%

**Reduction of non-fatal re-infarction
($p < 0.0001$)**



15%

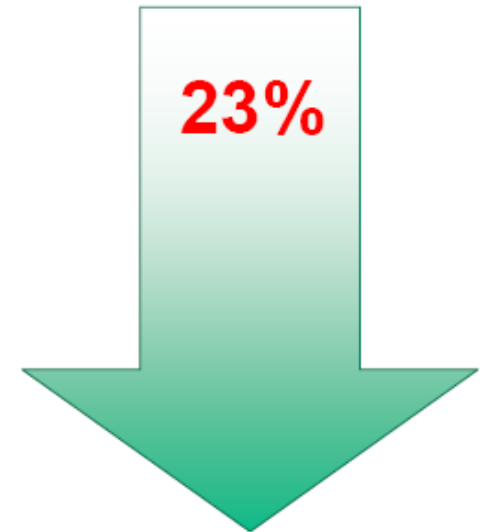
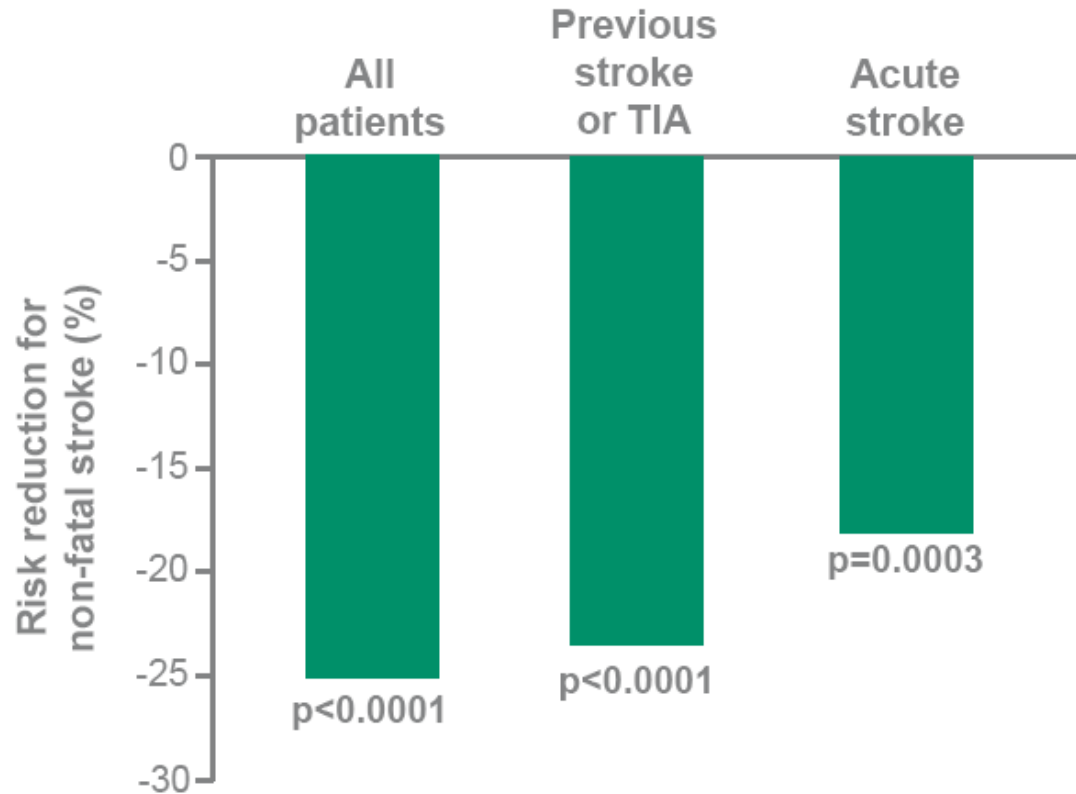
**Reduction of vascular death
($p < 0.0006$)**



Aspirin® Update

International Press Workshop 2008

Risk reduction for non-fatal stroke by platelet inhibition



**Risk reduction
for non-fatal
stroke
($p < 0.0001$)**

*versus placebo
TIA= Transient ischemic attack



Aspirin[®] Update

International Press Workshop 2008

Prevention of myocardial infarction and strokes

A lot can be done to control underlying disease



- Hypertension
- Elevated cholesterol
- Diabetes mellitus
- Other underlying diseases

**Suitable therapy
protects the heart and
blood vessels**



Aspirin® Update

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Ongoing primary prevention studies with Aspirin

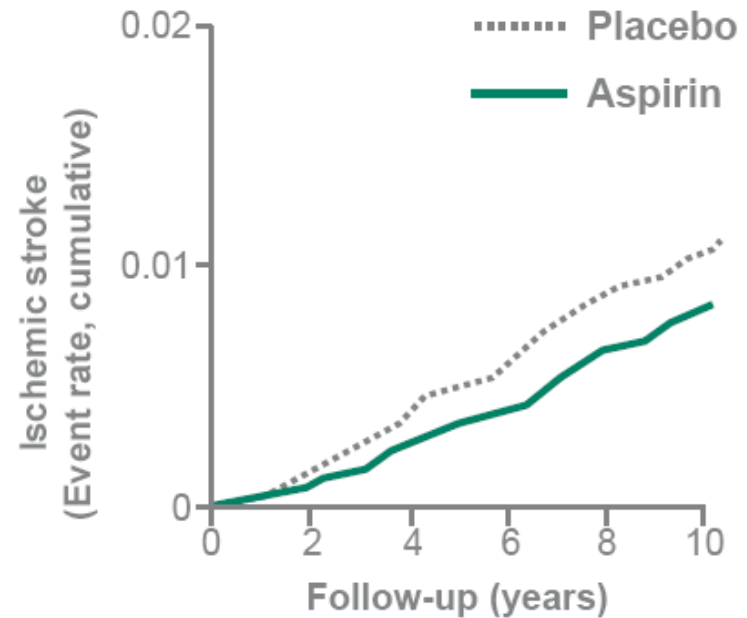
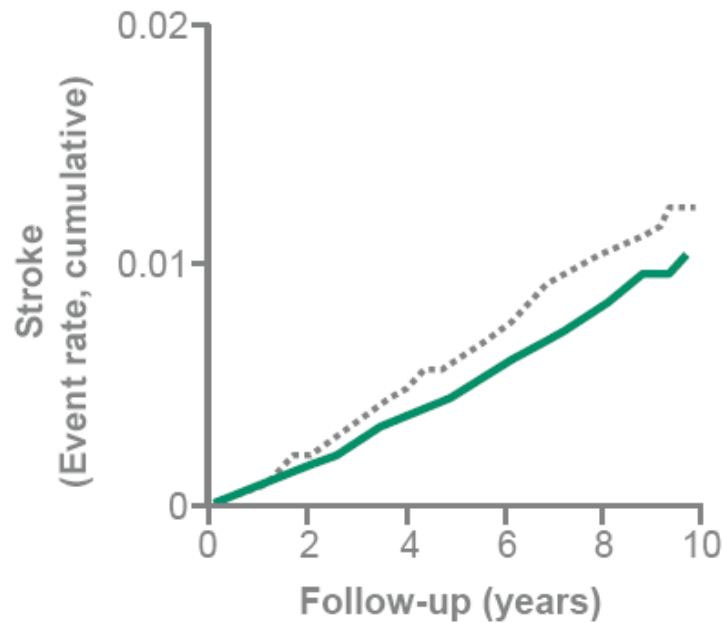
Study		n	Follow-up (years)	Planned to run until
J-PAD	<u>J</u> apanese <u>P</u> rimary prevention of atherosclerosis with <u>A</u> spirin for <u>D</u> iabetes	2,450	5	2008/9
POPADAD	<u>P</u> revention <u>O</u> f <u>P</u> rogression of <u>A</u> symptomatic Diabetic <u>A</u> rterial <u>D</u> isease	1,200	8	2009
AAAT	<u>A</u> spirin <u>A</u> symptomatic <u>A</u> therosclerosis <u>T</u> rial	3,300	8	2008
ASPREE	<u>A</u> SPirin in <u>R</u> educing <u>E</u> vents in the <u>E</u> lderly	20,500	5	2008
ASCEND	<u>A</u> Study of <u>C</u> ardiovascular <u>E</u> vents i <u>N</u> <u>D</u> iabetes	10,000	5	2009
JPPP	<u>J</u> apanese <u>P</u> rimary <u>P</u> revention <u>P</u> roject with Aspirin in elderly patients with one or more risk factors of vascular events	10,000	≥ 4	2010



Aspirin® Update

International Press Workshop 2008

Results of primary prevention with Aspirin in women (Women's Health Study)



17%

**Total reduction of strokes
(p=0.04)**

24%

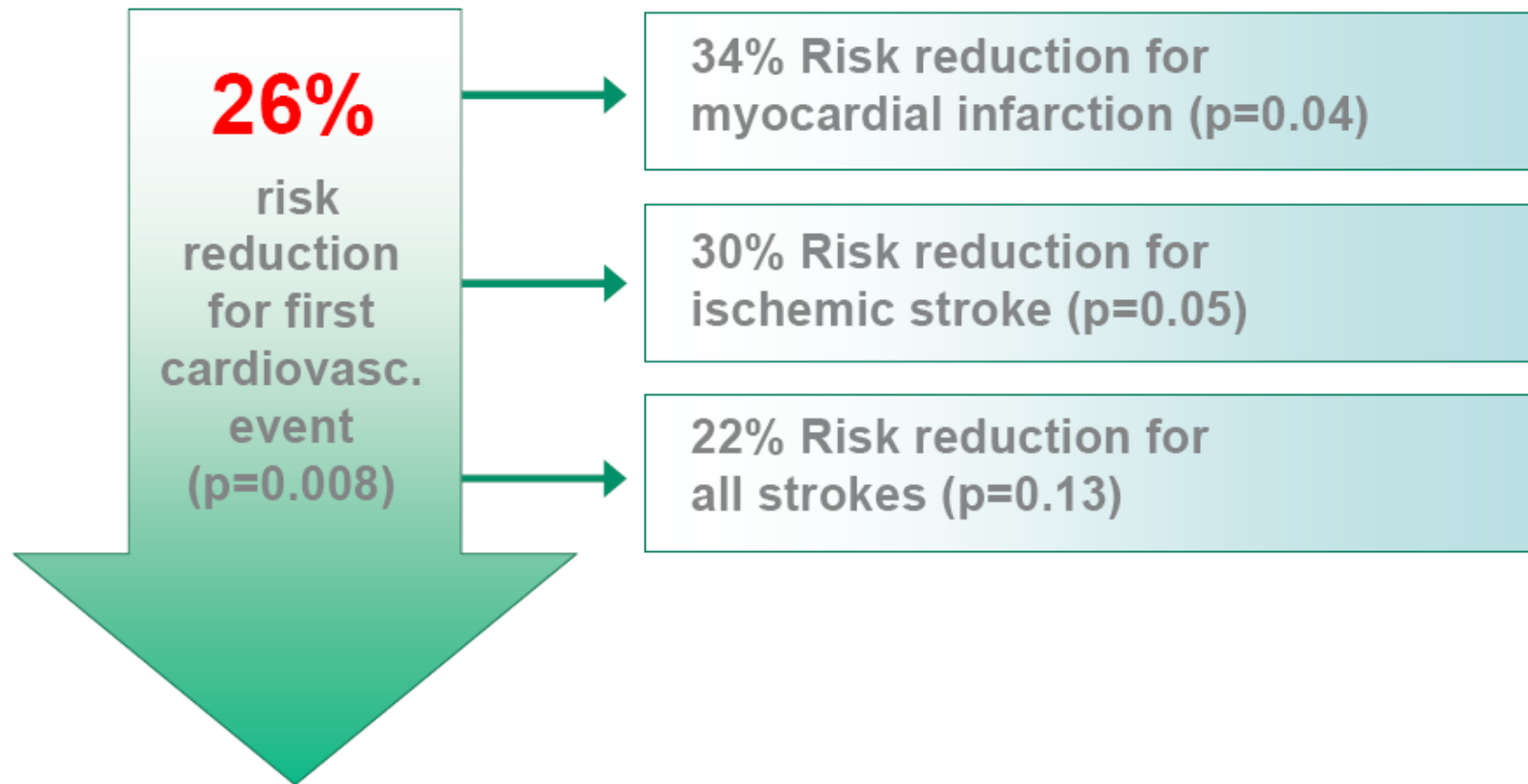
**Reduction of ischemic stroke
(p=0.009)**



Aspirin® Update

International Press Workshop 2008







Women's Health Study: Results in women ≥ 65 years



Aspirin[®] Update

International Press Workshop 2008

Six completed primary prevention studies with Aspirin

Study	n	Mean follow-up (years)*	Aspirin [®] dose per day (mg)	Control group	Patients		
					Age (years)	Risk factors	10-year risk for a first cardiovascular event
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BDT – British Doctors’ Trial: Peto R et al. BMJ 1988; 296: 313-6

TPT – Thrombosis Prevention Trial: Lancet 1998; 351: 233-41



Aspirin[®] Update

International Press Workshop 2008

ARRIVE™



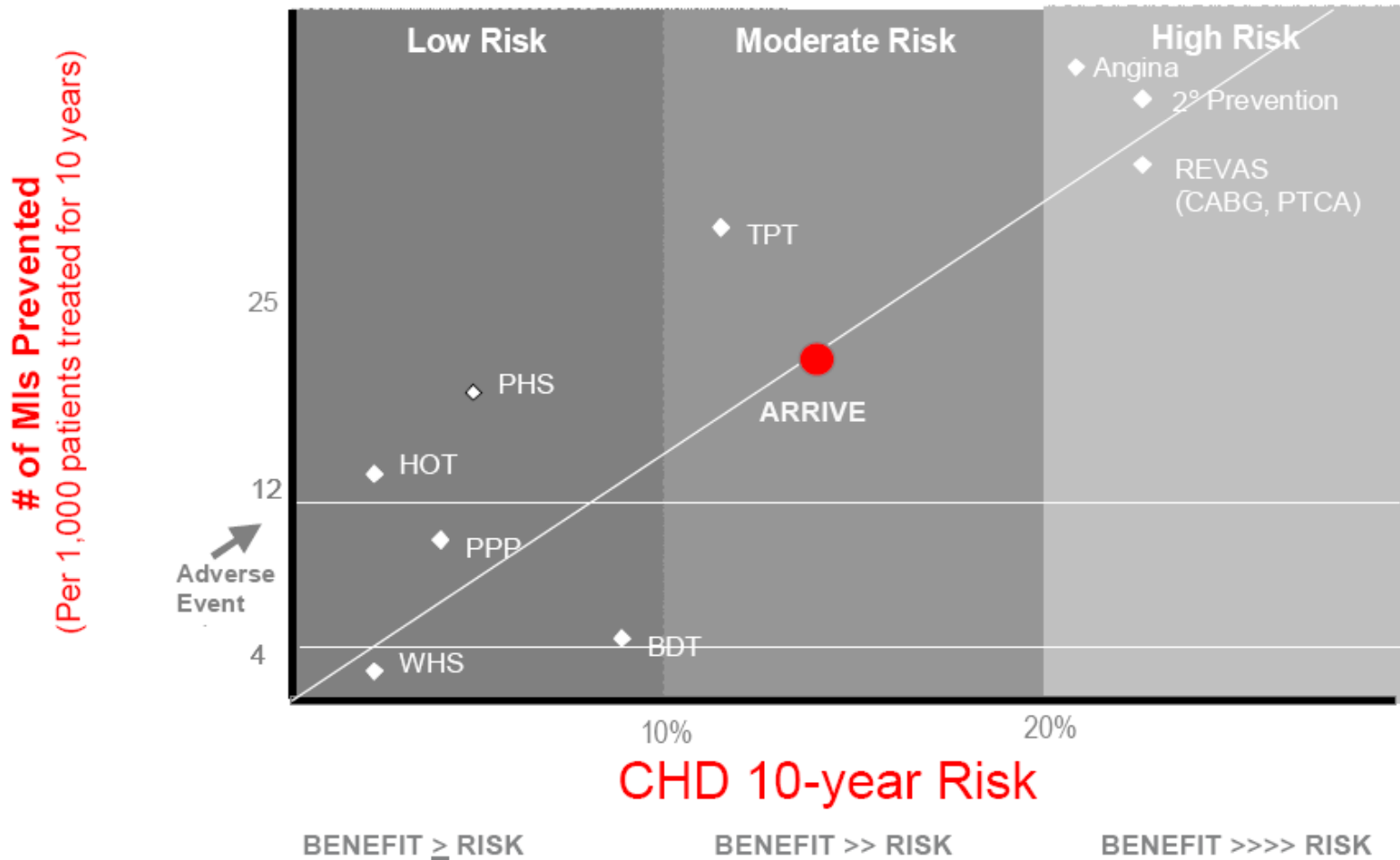
Aspirin to Reduce Risk of Initial Vascular Events



Aspirin® Update

International Press Workshop 2008

Coronary Heart Disease Risk Continuum



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International Press Workshop 2008

Aspirin[®] to Reduce Risk for Initial Vascular Events

Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Assess the Efficacy (Reduction of Cardiovascular Disease Events) and Safety of 100 mg Enteric-Coated Acetylsalicylic Acid in Patients at Moderate Risk of Cardiovascular Disease



Aspirin[®] Update

International Press Workshop 2008

Objective of the Study

Assessment of efficacy (reduction of CVD events) of 100 mg enteric-coated Aspirin[®] versus placebo in patients at moderate risk of CVD

Assessment of the safety and tolerability of 100 mg enteric-coated Aspirin[®] versus placebo in patients at moderate risk of CVD



Aspirin[®] Update

International Press Workshop 2008

General Study Parameters

Sample Size: N=12,000 patients (6,000 per group) enrolled to obtain at least 1488 adjudicated events over approximately 5 years (60 months)

Duration of Study: Event Driven - approximately 5 years (60 months)

Study Locations: International in five countries (Germany, Italy, Spain, UK and US)

Gender Distribution: 70% male/30% female



Aspirin[®] Update

International Press Workshop 2008

Primary Composite Endpoint

- Time to first event that qualifies as
 - MI
 - Stroke
 - Cardiovascular death
- Subsequent events will not be included in primary or secondary analyses



Aspirin[®] Update

International Press Workshop 2008

Secondary Efficacy Endpoints

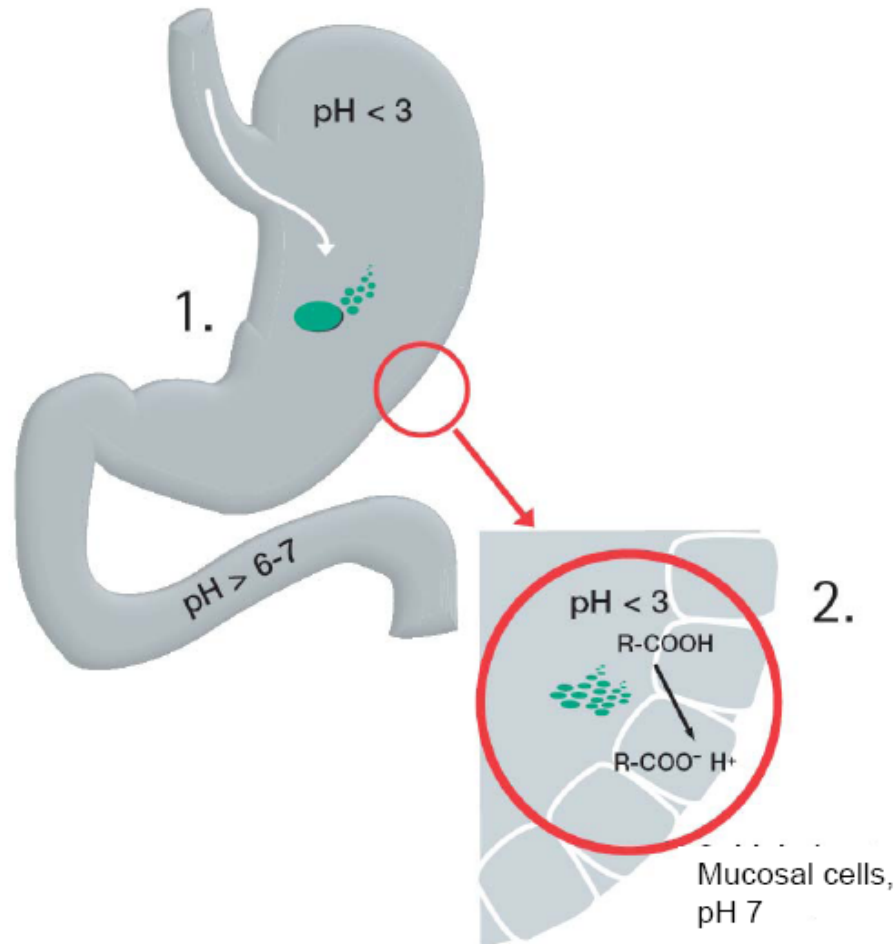
- Time to first occurrence of the composite outcome of cardiovascular death, ACS (Acute Coronary Syndrome), or stroke
- Time to first occurrence of the individual components of the primary: MI, stroke or cardiovascular death
- Time to first occurrence/ incidence of all cause mortality
- Time to first occurrence/ incidence of all cancers, excluding non melanoma skin cancer
- Time to first occurrence/ incidence of colon cancer
- Incidence of MI, stroke and CV death



Aspirin[®] Update

International Press Workshop 2008

Local irritation by ASA in long-term therapy



1. ASA is readily released in the stomach. In acidic medium, ASA is largely present in undissociated form. Due to its lipophilic nature, undissociated ASA penetrates into the gastric mucosa cells.

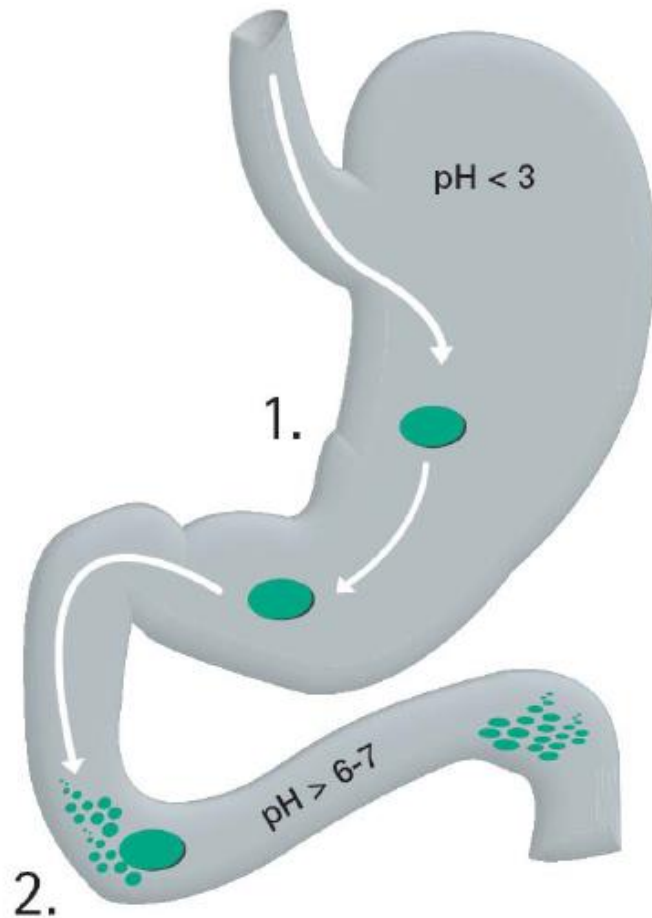
2. In the neutral medium of the gastric mucosal cells, ASA dissociates and can be stored in the cells (ion-trapping). The accumulation of free protons in the gastric mucosa can lead to injuries.



Aspirin® Update

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Better tolerated by the stomach: enteric coated Aspirin



1. Due to enteric coating, Aspirin Cardio® passes through the stomach and all the active substance is released only in the small intestine. Due to the neutral intestinal medium, the ASA is present here largely in dissociated form.

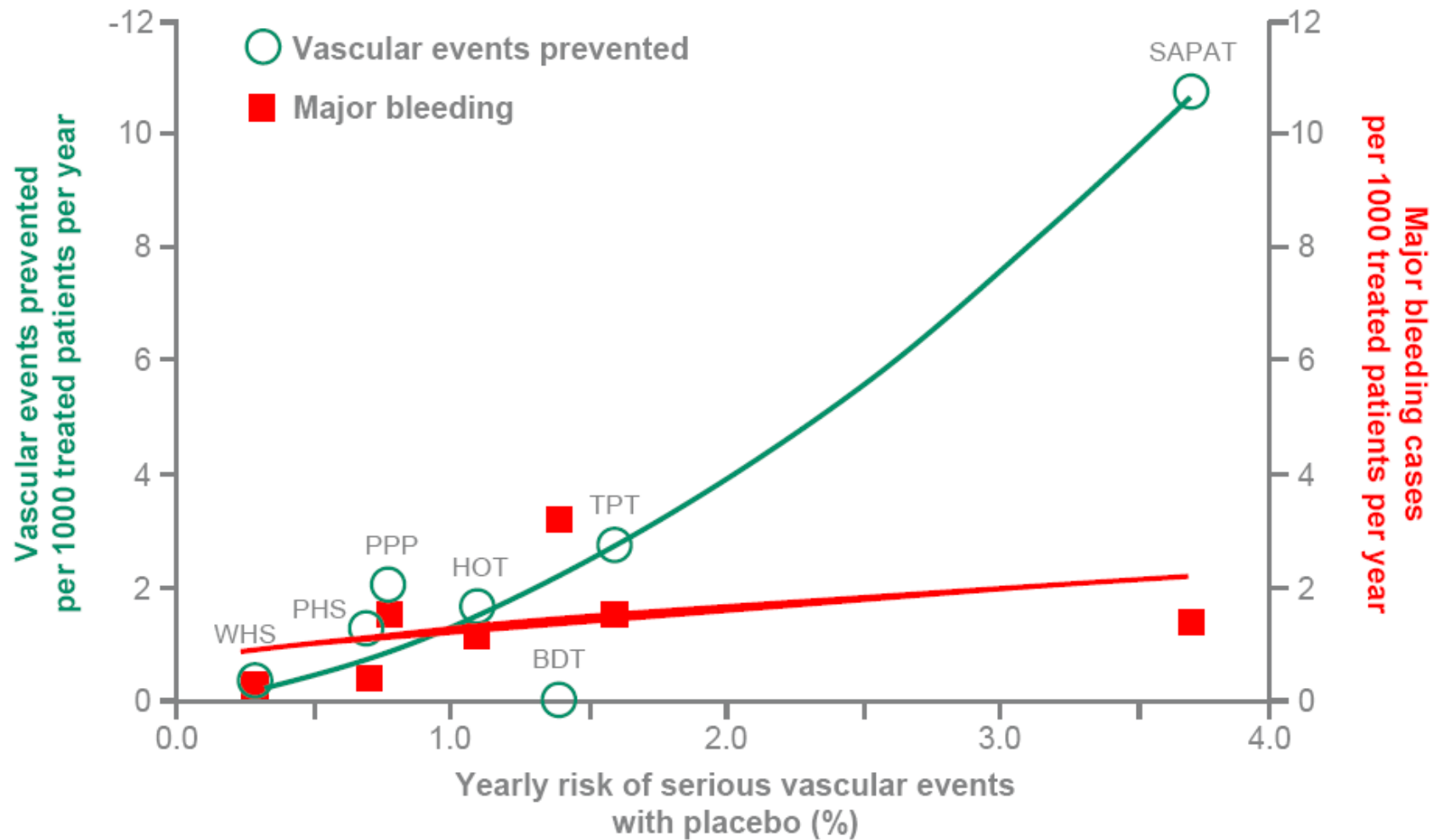
2. The large absorptive surface of the small intestine allows direct entry of the active substance into the blood stream.



Aspirin® Update

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Risk-benefit profile of Aspirin in the completed primary prevention studies



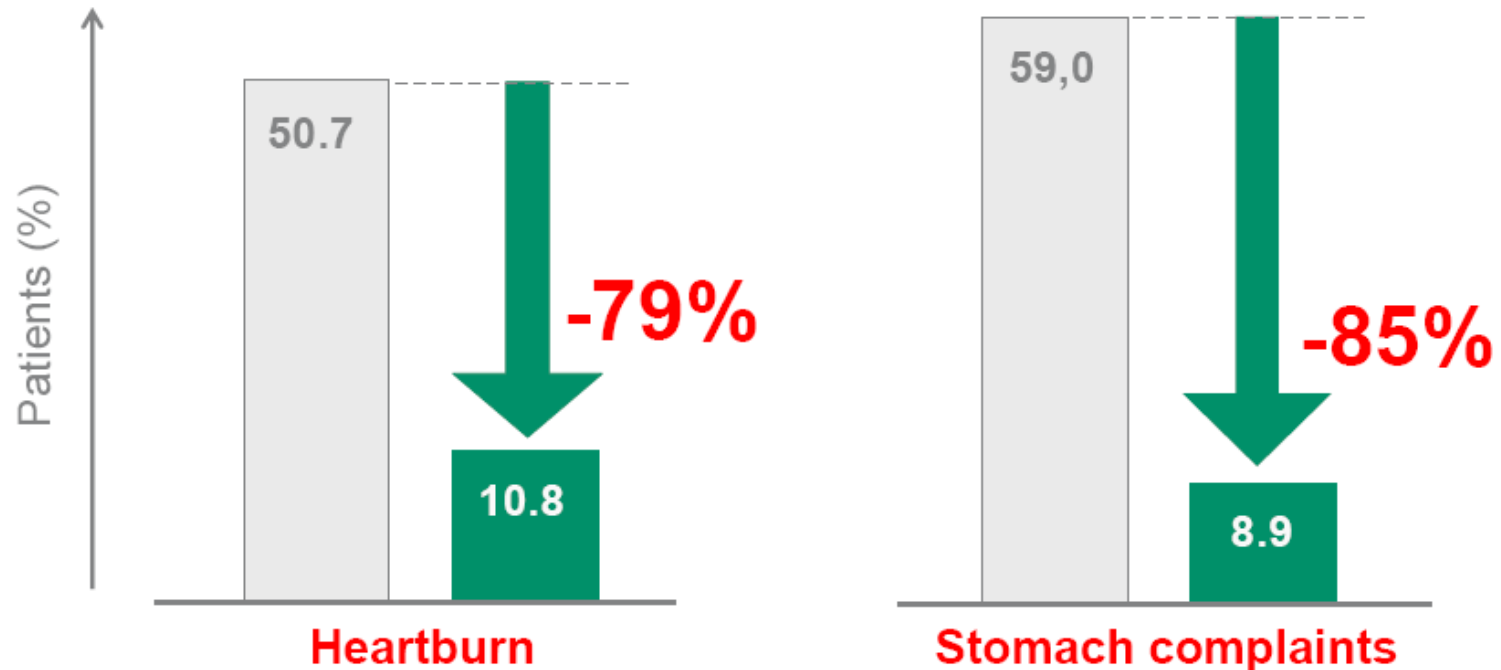
Aspirin® Update

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Aspirin[®] Protect/Aspirin Cardio[®]: The tolerable long-term therapy

□ At the start of the study

■ After 24 months of therapy with Aspirin[®] Protect 100/Aspirin Cardio[®] 100



Aspirin[®] Update

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A Quote Freddie Mercury (born Farrokh Bulsara)

(5Sep 1946 - 24Nov 1991)

- Mercury was born Farrokh Bulsara, on the island of Zanzibar, off the coast of Tanzania.
- His parents Bomi and Jer Bulsara were ethnic Parsis from the Gujarat region of the then province of Bombay Presidency in British India
- The family surname is derived from the town of Bulsar (also known as Valsad) in southern Gujarat.
- at the age of eight, Freddie was shipped to St. Peter's School, a boarding school for boys in Panchgani near Bombay (now Mumbai), India.
- At the age of 17, Mercury and his family fled from Zanzibar as a result of the 1964 Zanzibar Revolution. The family moved into a small house in Feltham, London
- Following graduation, Mercury joined a series of bands and sold second-hand clothes in the Kensington Market in London.
- He also held a job at Heathrow airport.
- In 1969 he formed the band Ibex, which was later renamed Wreckage. When this band failed to take off, he joined a second band called Sour Milk Sea. However, by early 1970, this group broke up as well.
- In April 1970, Mercury joined with guitarist Brian May and drummer Roger Taylor who had previously been in a band called Smile, and despite reservations from the other members, Mercury chose the name "Queen" for the new band.

Summary

- Apart from its analgesic effect, Aspirin also has a vascular preventive effect.
- In post-infarction treatment, this effect is utilized successfully throughout the world.
- The benefit of Aspirin for patients at high vascular risk has been scientifically demonstrated.
- Studies have shown that risk patients can also benefit from this in terms of the prevention of a first infarction.
- Opportunity exists to better define the moderate risk patient who benefit from an ASA regimen.
- Bayer is helping to answer this question with the ARRIVE-Study.
- For this, an Aspirin[®] formulation specially developed for long-term therapy is being used.



Aspirin[®] Update

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The Diabetes Polypill?

SAMTA: 21%

4 bits: 57%

3 bits: 92%

2 bits: 99%

Statin: 67%

Aspirin: 89.5%

Metformin: 65%

Thiazide: 73%

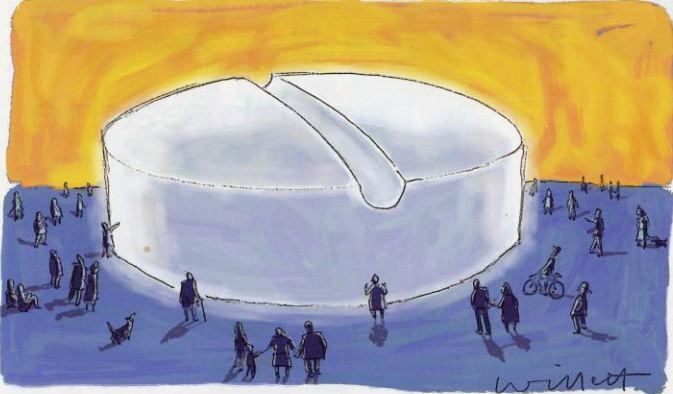
ACE-I or ARB: 79%

Indolinguistically: “equality” ie
in terms of reducing morbidity
and mortality esp. CVD

28 June 2003

BMJ

Aspostatinopitololazide Folate



326 1407-1468 No 704 28 JUNE 2003 Clinical research ISSN 0959-8138

A pill to prevent 80% of heart attacks

Polypill would contain a statin, three antihypertensives, folic acid, and aspirin [p1407, 1419, 1423, 1427]

↓ CM At+ PC an to PM pvan

Managing chronic pain in children p1408
Molecular epidemiology can help in Chagas' disease p1444
Positron emission tomography p1449
How consultants value aspects of their work p1432
The return of Questions and Answers p1412

bmj.com

A Quote from the Indian Philosopher

Farrokh Bulsara (1946 -1991)

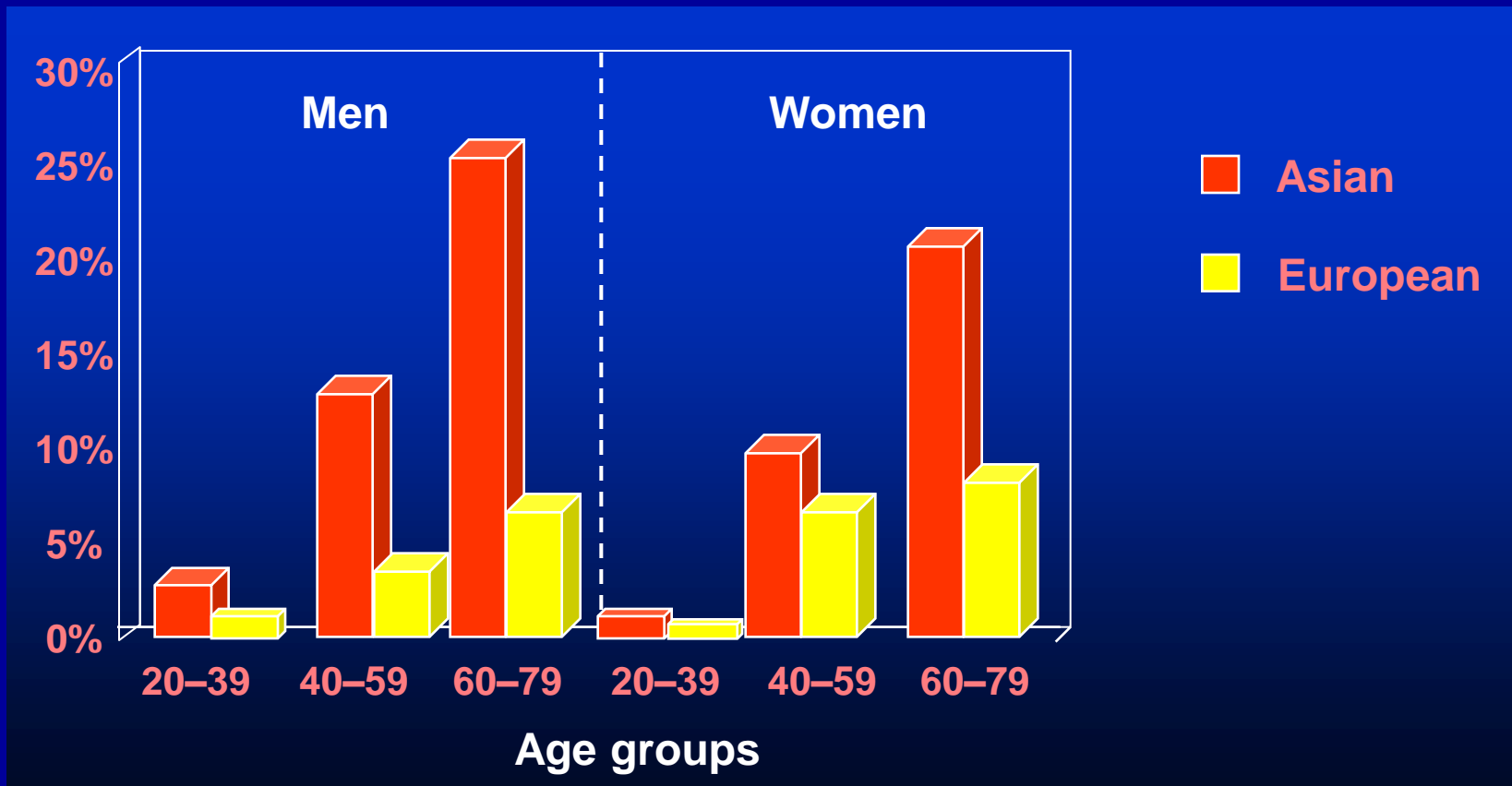
- Farrokh Bulsara, on the island of Zanziba
- Bomi and Jer Bulsara were ethnic Parsis from the Gujarat, India
- From the town of Bulsar (also known as Valsad) in southern Gujarat.
- At 8, he was shipped to St. Peter's School, a boarding school for boys in Panchgani near Bombay (now Mumbai), India.
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Prevalence of Diabetes in the UK Asian Population

More than one-quarter of people of Asian origin aged over 60 years suffer from diabetes

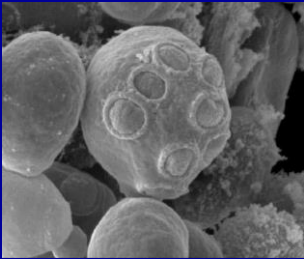


World's first evidence-based randomised control trial based Poem



Bring me the venom of the pit viper snake !

From bitter goat's rue a potion make



Ferment the juice that fat so hates!

Fetch the spit that shrinks the weight

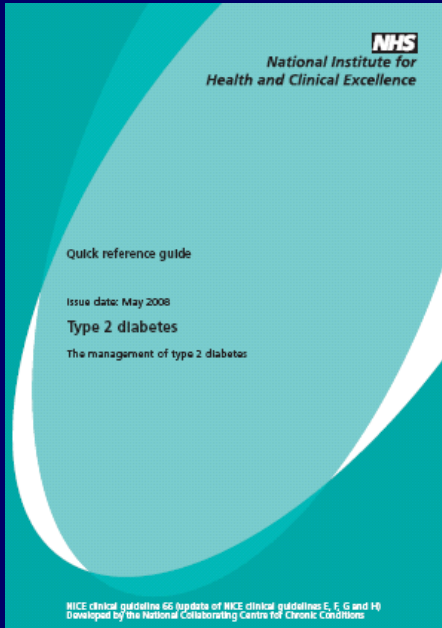


Dissolve in blood the bark that spatters!

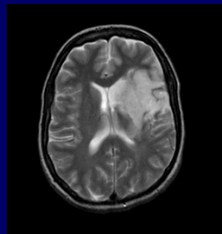
Extract from offal the magic that cures



Diabetes Mellitus



- **Advice:**
 - Education, self-management, smoking cessation, diet, physical activity, weight reduction
- **Blood Pressure:**
 - Target $<130/80$
 - Audit standard $<140/80$
- **Cholesterol:**
 - $TC \leq 4.0$ mmol/l, $LDL \leq 2$,
 - Consider $HDL \geq 1$ men, $HDL \geq 1.2$ women
- **Diabetes Control:**
 - Target HbA1c% $\leq 6.5\%$, audit $<7.5\%$
- **Eyes:**
 - check yearly and refer if needed
- **Feet:**
 - check yearly and refer if needed
- **Guardian Drugs:**
 - Aspirin 75mg, ACE-I or ARBs, Statins



Adverse Effects

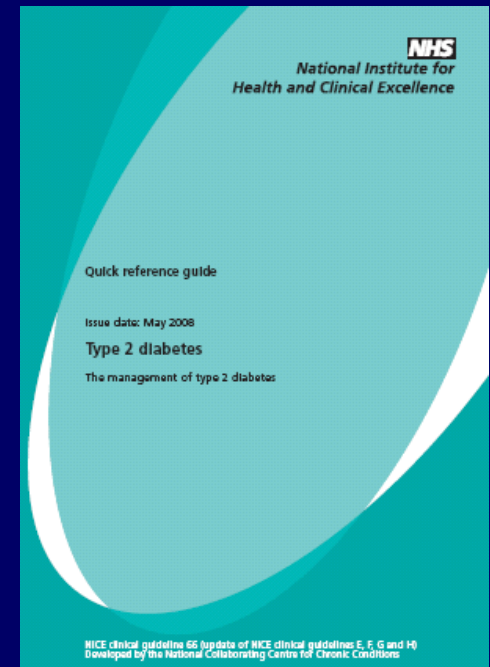
Table 3. Adverse Effects

	No.	
	Aspirin Group	Nonaspirin Group
Bleeding, gastrointestinal ^a		
Hemorrhagic gastric ulcer	5	3
Bleeding from esophageal varices	1	0
Bleeding from colon diverticula	2	0
Gastrointestinal bleeding due to cancer	2	0
Hemorrhoid bleeding	1	0
Gastrointestinal bleeding (cause unknown)	1	1
Bleeding, other		
Retinal bleeding	8	4
Bleeding after tooth extraction	1	0
Subcutaneous hemorrhage	3	0
Hematuria	2	1
Nose bleeding	6	1
Chronic subdural hematoma	2	0
Nonbleeding gastrointestinal event		
Nonhemorrhagic gastritis	3	0
Nonhemorrhagic gastric ulcer	17	3
Nonhemorrhagic duodenal ulcer	1	1
Only gastrointestinal symptom	26	0
Other		
Anemia	4	0
Asthma	1	0

^aIn the aspirin group, 4 cases of severe gastrointestinal bleeding required transfusion.

Anti-thrombotic therapy

- Offer low-dose aspirin, 75 mg daily, to a person who is 50 years old or over, if blood pressure is below 145/90 mmHg.
- Offer low-dose aspirin, 75 mg daily, to a person who is under 50 years old and has significant other cardiovascular risk factors (features of the metabolic syndrome, strong early family history of cardiovascular disease, smoking, hypertension, extant cardiovascular disease, microalbuminuria).
- Clopidogrel should be used instead of aspirin only in those with clear aspirin intolerance (except in the context of acute cardiovascular events and procedures). Follow the recommendations in 'Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events' (NICE technology appraisal guidance 90).



Aim

- To see whether the observed cardiac event reduction in the Steno-2 Study could have been predicted by the Polypill Concept.
- Our model incorporated Cardiac Event rate predicted by the UKPDS Cardiac Risk Engine (www.dtu.ox.ac.uk)

Conclusion

- “Aspostatinoprilololazide folate”

Aspirin, statin, ACE-I (‘opril’ drugs) , beta-blocker (‘lol’), thiazide diuretic and folate

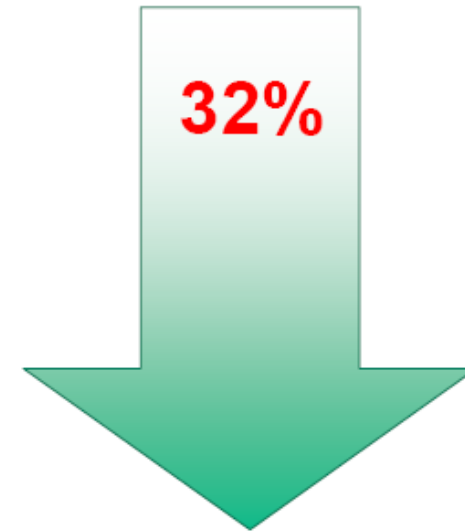
The Polypill appears likely to be not only a robust theoretical construct but also a practical instrument to reduce real CVD events

- To achieve this an aggressive multi-factorial strategy as adopted in the intensive arm of the Steno-2 needs to be advocated and implemented in clinical practice

Results of primary prevention with Aspirin in men (meta-analysis)

- Meta-analysis of the six primary prevention studies (HOT, PPP, PHS, BDT, TPT, WHS)
- > 44,000 male patients
- No significant risk reduction for a first ischemic stroke
- Significant risk reduction for a first non-fatal myocardial infarction

HOT – Hypertension Optimal Treatment trial
PPP – Primary Prevention Project
PHS – Physicians' Health Study
BDT – British Doctors' Trial
TPT – Thrombosis Prevention Trial
WHS – Women's Health Study



**Risk reduction for a first non-fatal myocardial infarction
(p=0.001)**



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